OECS

HIV/STI

Guidelines

2013

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1 PREFATORY MATERIALS

1.1 COMMONLY USED ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ABG	arterial blood gas [test]
AFB	acid-fast bacilli
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral medication
ASC	atypical squamous cells
ASC-US	atypical squamous cell of undetermined significance
ATV	atazanavir
AUC	area under the curve
AZT	azidothymidine (zidovudine)
BAL	bronchoalveolar lavage
BCA	bichloroacetic acid
BID	twice a day
BIW	twice weekly
CAREC	Caribbean Epidemiology Centre
CBC	complete blood count
CDC	US Centers for Disease Control and Prevention
Cmax	maximum concentration
Cmin	minimum concentration
CMV	cytomegalovirus
CNS	central nervous system
CrAG	cryptococcal antigen
CRP	C-reactive protein
CSF	cerebro-spinal fluid
CT	computed tomography [scan]
CXR	chest X-ray
DBS	dried blood spot test
ddI	didanosine (Videx, Videx EC)
DGI	disseminated gonococcal infection
DOT	directly observed therapy
DS	double-strength
DTP	diphtheria, tetanus, pertussis [vaccination]
EFV	efavirenz
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EMB	ethambutol
ESR	erythrocyte sedimentation rate
FDA	US Food and Drug Administration
FTA-ABS	fluorescent treponemal antibody absorbed test
FTC	emtricitabine

HAART	highly active antiretroviral therapy
HAM	human T-lymphotropic virus-1 associated myleopathy
HAPU	HIV/AIDS Project Unit of the OECS
HAV	hepatitis A virus
HBeAg	hepatitis B e antigen
HBIG	hepatitis B virus immune globulin
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV-8	human herpes virus-8
Hib	*Haemophilus influenzae*
HPV	human papilloma virus
HRSA	US Health Resources and Services Administration
HSIL	high-grade squamous intraepithelial lesion
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
HZV	herpes zoster virus
I-TECH	International Training and Education Center for Health
ICP	increased intracranial pressure
IgG	immunoglobulin G
IHPS	infantile hypertrophic pyloric stenosis
IM	intramuscularly
IPV	inactivated poliovirus
IRIS	immune reconstitution inflammatory syndrome
IRU	immune recovery uveitis
IU	international units
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulin
KOH	potassium hydroxide
LAIV	live attenuated influenza vaccine
LDH	lactate dehydrogenase
LGV	lymphogranuloma venereum
LPV	lopinavir
LSIL	low-grade squamous intraepithelial lesion
LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MARP	most-at-risk-populations
MCD	multi-centric Castleman's disease
MCV	meningococcal conjugate vaccine
MDR-TB	multi-drug-resistant tuberculosis
MMR	measles-mumps-rubella [vaccine]
MMRV	measles-mumps-rubella-varicella [vaccine]
MPSV	meningococcal polysaccharide vaccine
MRI	magnetic resonance imaging
MSM	men who have sex with men
MTB	mycobacterium tuberculosis

NAAT	nucleic acid amplification test
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NVP	nevirapine
OECS	Organisation of Eastern Caribbean States
OI	opportunistic infection
OPV	oral polio vaccine
PAHO	Pan American Health Organization
PCP	*Pneumocystis jiroveci* pneumonia
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PEL	Primary effusion lymphoma
PHDP	Positive Health, Dignity and Prevention
PI	protease inhibitor
PID	pelvic inflammatory disease
PITC	provider-initiated testing and counselling
PLHIV	people living with HIV
PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother-to-child transmission of HIV
PO	by mouth, oral
PPS	OECS's Pharmaceutical Procurement Service
PPSV	pneumococcal polysaccharide vaccine
Q[#]H	every [amount] hour
QD	daily
QHS	every bedtime
QID	four times a day
QM	monthly
QOD	every other day
QW	once a week
rPI	ritonavir-boosted protease inhibitor
RPR	rapid plasma reagin
RSV	respiratory syncytial virus
RTV	ritonavir
SD-NVP	single dose nevirapine
SQ	subcutaneous
SQV	saquinavir
SS	single-strength
STI	sexually transmitted infection
TB	tuberculosis
TCA	trichloroacetic acid
Td	diphtheria and tetanus toxoids
Tdap	diphtheria and tetanus toxoids and acellular pertussis
TDF	tenofovir disoproxil fumarate (tenofovir)
TE	toxoplasmic encephalitis
TID	three times daily

TIV	trivalent inactivated influenza vaccine
TIW	three times weekly
TMP-SMX	trimethoprim-sulfamethoxazole (co-trimoxazole)
TP-PA	*T. pallidum* passive particle agglutination
TST	tuberculin skin test
UWI	University of the West Indies
VCT	voluntary counselling and testing
VDRL	venereal disease research laboratory test
VIA	visual inspection with acetic acid
VL	viral load
VZV	varicella-zoster virus
WBC	white blood cells
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

1.2 FOREWORD

The changing and dynamic nature of innovations and their associated technologies against the background of evolutionary mutations in the HIV virus as well as in the population of both infected and affected persons demands careful monitoring, so as to identify trends and to adjust and prepare appropriate interventions.

Importantly, among these interventions is the adoption of care and treatment guidelines—as well as their timely reviews and updates—to ensure the effectiveness and efficiency in our management of HIV-infected clients. For us in the Organisation of Eastern Caribbean States (OECS), these tasks have a special significance. Although territorially separate, we share many interdependent links: We have common social services policies, including health; we all use the OECS's Pharmaceutical Procurement Service (PPS); and we all look to the Pan American Health Organization (PAHO) and other regional health institutions for technical guidance and assistance, research and development, and public health references.

Much of what binds us together is our rich and varied history, marked by the realities of interstate collaboration, imposed subservience, a political commitment to an OECS Economic Union, a lack of resources in our small economic markets, the active migration of our peoples, and the inadequacy of individual member states' capacity to implement high quality health care, without which our productive sectors, especially tourism, is hindered.

It is in this context that these guidelines aim to foster:

- Standardized protocols and procedures, including the type of technologies to be acquired;
- Economies of scale through conducting multi-country training, pooling the procurement of goods and services, and providing access to/sharing high-cost technology; and
- Collected and shared best practices, inter alia, to create new guidelines.

In addition, we strove to ensure that the output-reflected items were feasible and contributed to the improvement and sustainability of existing programs. Thusly, this document was prepared through a consultative process with key stakeholders from the national implementing authorities, lead by experts in the fields of pharmacology and pharmacy, clinical/health care delivery and facilities management, laboratory, counselling and mentoring services, and monitoring and evaluation. For ease of reference, it has been organized along the lines of existing and familiar treatment guidelines documents, while maintaining scientific content and perspective.

It is therefore with pleasure that we welcome this initiative, which is consistent with the goals and ambitions of the peoples of the OECS. We express our profound appreciation to the Human Resource and Services Administration (HRSA), the International Training and Education Center for Health (I-TECH), the University of the West Indies (UWI), and PAHO for their contributions to the development of these revised HIV care and treatment guidelines. Special thanks are also due to my colleagues at the OECS PPS, the OECS HIV/AIDS Project Unit (HAPU), the ministries of health of the OECS member states, and representatives from the community of persons living with HIV and AIDS (PLHIV) for their foresight and commitment to the development of these guidelines. I anticipate that together we will ensure the successful implementation of these guidelines, so that clients will be properly managed and all those in need

of care will receive it, as per their basic human rights, consistent with our public policy obligations.

James St Catherine
Head, OECS HIV/AIDS Project Unit (HAPU)

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Dr Marie Grandison-Didier, former Clinical Care Coordinator, St Lucia
Mr Francis Burnett, Managing Director, Pharmaceutical Procurement Services, Organisation of Eastern Caribbean States Secretariat, St Lucia
Ms Kala Dowlath, Senior Programme Officer, HIV/AIDS Project Unit, Organisation of Eastern Caribbean States Secretariat, St Lucia
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In addition to relevant publications from the medical literature, the following resources were used to support the technical recommendations of these guidelines:

- Selected guidelines from the World Health Organization (WHO) on HIV, tuberculosis, and sexually transmitted infections (STI)
- Guidelines from the US Centers for Disease Control and Prevention on HIV, opportunistic infections, and STIs
- HIV care and treatment guidelines for the Caribbean region

- Caribbean *Guidelines for the Prevention, Treatment, Care and Control of Tuberculosis and TB/HIV*
- National HIV care and treatment guidelines from Belize
- *HIV Web Study*
- FANTA Project's *Nutrition and HIV/AIDS: A Training Manual*

Please refer to the works cited section for complete references on these resources.

2 CLINICAL GUIDELINES FOR THE PREVENTION, DIAGNOSIS AND MANAGEMENT OF HIV IN THE OECS

2.1 SCREENING FOR AND DIAGNOSING HIV INFECTION

Identifying HIV disease in a timely manner is vitally important to the health of infected individuals as well as to public health, so that disease progression and transmission can be moderated. This is best accomplished through a combination of voluntary counselling and testing (VCT) and provider-initiated testing and counselling (PITC).

VCT relies upon individuals to seek HIV testing and requires being counselled by trained counsellors prior to the test. VCT was implemented first in the Organisation of Eastern Caribbean States (OECS) and then in the wider Caribbean region. However, VCT alone has proved insufficient—a large proportion of people living with HIV and AIDS (PLHIV) in the OECS are not aware that they are infected with HIV. The World Health Organization (WHO) in conjunction with the Pan American Health Organization (PAHO) and other stakeholders therefore recommend that VCT be supplemented by PITC.

The PITC approach acknowledges that any contact with the health care system represents an opportunity to offer HIV testing to that individual. Extensive pre-test counselling is not required with PITC, as counselling is provided along with the test results. In other parts of the world, PITC has dramatically increased the number of PLHIV who are aware of their HIV status. Thus, clinicians in the OECS are encouraged to adopt the PITC strategy as a supplement to existing VCT services in order to increase the number of PLHIV who know their status.

It is important to remember that all testing, whether client- or provider-initiated, should be conducted under the conditions of the **'three Cs': informed consent, confidentiality** and **counselling** (whether brief or extended).

2.1.1 Voluntary Counselling and Testing

Again, this form of testing is client-initiated, with a focus on pre- and post-test counselling, including risk-reduction counselling. VCT may be accompanied by group educational sessions. Appropriate referral is critically important for those who test positive for HIV infection.

2.1.2 Provider-initiated Testing and Counselling

2.1.2.1 Routine Offer of HIV Testing

HIV testing should be considered a routine component of primary health care and offered by health care providers to all clients/patients who present for medical services. General group education sessions are encouraged (e.g., a video presentation about HIV continually playing in a waiting room).

Such services include but are not limited to:

- Routine primary care encounters
- Sexually transmitted infections (STI) and tuberculosis (TB) clinics
- Cervical cancer screening clinics

- Reproductive and maternal and child health services
- Clinical as well as community-based health services
- Post-exposure testing and counselling in occupational and non-occupational setting for prophylaxis
- Communities and vulnerable groups who are at high risk for infection (youth; sex workers; men who have sex with men; persons identifying as gay, lesbian, bisexual,or transgender; drug users; prison inmates; migrant workers; physically and mentally challenged; and victims of domestic violence).

2.1.2.2 Diagnostic HIV Testing

This form of PITC is indicated whenever a person shows signs and symptoms that are consistent with HIV-related disease or AIDS to assist in clinical diagnosis and management.

2.1.2.3 Steps for PITC Intervention

The steps for carrying out PITC are listed below:

1. Address the patient's chief complaint first.
2. **Counselling:** Advise the patient that you are recommending an HIV test today.
    a. Ask what the patient already knows about HIV.
    b. Explain the benefits of knowing one's HIV status, using simple, non-technical language:
        i. If the test is negative, the patient can learn how to stay disease-free.
        ii. If the test is positive, the patient can access care and stay healthy.
    c. Ask the patient about any questions or concerns and if they are ready to do the test.
3. **Consent:** Obtain verbal consent for testing (written consent is not required).
4. **Testing:** Explain the testing procedure and timing of results (office-based or laboratory). Advise the patient that there may be a need for a confirmatory test if the initial result is positive or indeterminate; reassure them that test results are confidential.
    a. HIV testing for persons older than 18 months is performed using enzyme-linked immunosorbent assay (ELISA)-based HIV antibody (serologic) assays. Testing of infants younger than 18 months is reviewed in section 2.8. Use of HIV viral load assays to test for HIV infection is discouraged, except in special circumstances and in consultation with an expert in clinical HIV care.

Table1. Interpretation of test results

Test result	Interpretation
Negative	Because these tests are highly sensitive, a negative test does not require an additional confirmatory test. However, if a patient reports possible exposure to HIV within the past month, HIV testing should be repeated in 1–3 months, as the patient could be in the 'window period' of acute HIV infection. During this time, the patient is infected with HIV but has not yet developed antibodies to the virus which can be detected by conventional antibody tests.
Positive	A positive HIV antibody test requires confirmation before being considered truly positive. The confirmatory test can be performed using a different ELISA-based antibody test. 'Reflexive' confirmatory testing is typically automatically performed by the laboratory, bypassing the need for the provider to order confirmatory testing. Only if the confirmatory test is also positive is the patient considered to be HIV infected.
Indeterminate	If the initial test is positive but the confirmatory test is negative, then another sample should be obtained from the patient for a third and different test, based on laboratory protocol. Consultation with an expert HIV clinician is recommended in this situation.

2.1.3 Issuing the Results: Post-test Counselling

1. **Verify** the patient's identity and assess their readiness to receive the results. It is inadvisable to issue results over the telephone, especially when they are positive. Giving results in a face-to-face clinical situation allows for discussion of their significance.
    a. In the case of a negative test, ask the patient about the time of last exposure to HIV and explain about the window period; indicate the possible need for a second test after that period has elapsed.
2. **Give results** and allow the patient time to react. Depending on the results, be prepared to spend more time with the patient.
    a. Possible language to use in delivering **positive** results:
        i. Delivering the results: 'You tested positive, which means you have HIV infection.'
        ii. Coping with the results: Ask about concerns and respond appropriately. Reassure the patient that knowing their HIV status and getting care can extend their life.
        iii. Living positively: Explain the importance of knowing their CD4 count and HIV stage. Emphasise that this information guides care and treatment (e.g., when to start highly active antiretroviral therapy [HAART]).
        iv. Protecting the patient and their partner: Explain how to avoid reinfection with HIV and new STIs. Encourage condom use at EVERY sexual encounter. Encourage disclosure and partner notification. Encourage asking partner(s) to be tested and to use condoms. Obtain a sample or refer for CD4 count testing. Assess further counselling needs and needs for referrals. Make follow-up appointment arrangements.
    b. Possible language to use in delivering **negative** results:
        i. Delivering the results: 'You tested HIV negative.'
        ii. Discussing prevention options: 'What will you do to remain HIV negative?' Options may include abstaining from sexual intercourse, being faithful to one partner, reducing the number of sexual partners, using a new latex condom at EVERY sexual encounter, encouraging asking partner(s) to be tested and to use condoms, encouraging disclosure and partner notification, and getting tested again in a year's time or sooner if the patient gets an STI, has a new partner, has unsafe sex, becomes pregnant, or becomes sick.

3. Review key elements of the consultation with patient and give them a pamphlet or other patient educational materials on HIV prevention.

2.1.4 Special Populations: Pregnant Women and HIV-exposed Infants

2.1.4.1 HIV Testing of Pregnant Women

All pregnant women should be tested for HIV immediately upon enrolment into antenatal care, and (at a minimum) again during the third trimester of pregnancy (as recommended in the national protocol for the prevention of mother-to-child transmission of HIV [PMTCT]). For more information on how to manage pregnant women infected with HIV, refer to section 2.7.

2.1.4.1.1 HIV Testing of Infants <18 Months of Age

Infants less than 18 months of age require specialized testing for HIV DNA or RNA. Traditional HIV antibody tests do not provide accurate results for this age group because any HIV antibodies found in infants could actually be maternal HIV antibodies that crossed the placenta. Dried blood spot (DBS) testing is the preferred approach for this age group. With DBS, a small sample of blood is collected on special filter paper, typically from a heel prick—phlebotomy is not required. The blood dries on the filter paper and is sent to the Ladymeade Reference Unit in Barbados for HIV DNA testing. Results are typically available within 4–6 weeks.

For more information on how to manage HIV-exposed infants before the DBS test results are known, refer to section 2.8.

2.1.5 Immediate Management of a Newly-diagnosed Patient

Individuals who test positive for HIV infection should be immediately referred to a health care facility or provider experienced in the care and treatment of PLHIV (see also section 2.3). All patients should be followed up with to ensure that they are engaged in HIV care and treatment, as many patients become ‘lost to follow-up’ after being diagnosed.

Pregnant women who test HIV positive should immediately be referred to a PMTCT programme; PMTCT recommendations are presented in section 2.7.

2.2 ACUTE (PRIMARY) HIV INFECTION

Acute HIV infection (also referred to as ‘primary HIV infection’, or ‘acute retroviral syndrome’) is a non-specific flu-like syndrome exhibited by most patients when initially infected with HIV. The syndrome is characterized by fever, sore throat, lymphadenopathy, arthralgia/myalgia, and/or rash, among other symptoms. The mean time from exposure to development of illness is generally 2–4 weeks.

2.2.1 Diagnosis

As other illnesses have similar clinical presentations, having a high index of suspicion is helpful before initiating evaluation (i.e., a history of high-risk exposure like unprotected sexual encounters, shared needles, etc.).

Negative or indeterminate HIV serology (antibody testing) along with positive serum HIV RNA viral load (often in the millions) confirms the diagnosis. HIV antibody testing should be repeated after 1–3 months, to document seroconversion.

2.2.2 Management

Follow-up—including standard HIV testing and HIV primary care—should be arranged for the patient. In addition, they should be counselled regarding the **increased risk of HIV transmission** during the first few months after infection.

In pregnant women, once their diagnosis is confirmed, they should be treated immediately with antiretroviral therapy (ART), in order to reduce the risk of in utero transmission. Refer to section 2.7 for more information on PMTCT.

Theoretically, there may be clinical benefit to initiating HAART in acute HIV infection. However, there is insufficient evidence to support this practice routinely. **Early treatment of persons with acute HIV infection other than pregnant women cannot be recommended at this time**.

2.3 INITIAL MANAGEMENT OF THE NEWLY-DIAGNOSED ADULT OR ADOLESCENT

The following should be performed at the patient's first visit:

1. **Take a thorough history and physical examination**:
   a. Identify any current or past complications of HIV disease (such as opportunistic infections [OI]/diseases), to establish the patient's WHO clinical stage of HIV (see table 2 and appendix 4.4). Patients who present with one or more active OI at the time of HIV diagnosis merit careful management and their OIs should be treated immediately.
   b. Identify co-morbid acute and chronic diseases/conditions that need management along with the HIV.
   c. Identify partners who should be notified and tested for HIV.
2. **Conduct appropriate laboratory investigations** (see table 3):
   a. Establish the patient's degree of immunodeficiency (CD4 count).
   b. Screen for renal, hepatic, or hematologic disorders.
   c. Screen for other STIs.
   d. Screen for TB infection and/or disease.
   e. Screen for pregnancy in women.
3. **Assess the patient's psychological state**. Many individuals experience severe emotional distress upon learning that they are infected with HIV. Intensive counselling and/or referral for psychiatric care may be warranted.
4. **Initiate appropriate therapy for any active OI**. Many PLHIV in the Caribbean are diagnosed at a relatively late stage of the disease. HIV testing is often prompted due to a diagnosis of an associated OI or an OI might be diagnosed during clinical staging for a recently diagnosed HIV infection. In these situations, initiating therapy for the OI takes precident over initating HAART. HAART is typically started shortly thereafter, although the exact timing of its initiation varies depending upon the OI being treated. For detailed information on specific OIs, their treatment, and the timing of HAART initiation, refer to sections 2.4, 2.5, and 2.6.
5. **Initiate appropriate chemoprophylaxis against OIs** (reviewed in detail in section 2.5), where indicated. For example, co-trimoxazole should be prescribed to patients with a CD4 count <200 cells/mm^3, thrush, or WHO stage 3 or 4 disease. Desensitization to co-trimoxazole should be attempted for patients who describe a history of non-severe allergic reactions to co-trimoxazole or other sulfa-based drugs, as described in appendix 4.11.
6. **Assess the patient's eligibility for HAART**, as described in section 2.4. Patients who are HAART eligible should be scheduled for intensive adherence counselling as part of their preparation for starting therapy.
7. **Arrange for a clinician experienced in the care and treatment of PLHIV to follow up with the patient**. Measures should be implemented to ensure that the patient is not lost to follow-up.

Table 2. WHO clinical staging of HIV disease in adults and adolescents (see appendix 4.4 for presumptive and definitive diagnostic criteria for the conditions listed below)

Clinical stage I
• Asymptomatic • Persistent generalised lymphadenopathy ***Performance scale 1: Asymptomatic, normal activity***
Clinical stage II
• Weight loss of <10% of body weight • Minor mucocoetaneous manifestations (e.g., seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis) • Herpes zoster (HZV) within the last 5 years • Recurrent upper respiratory tract infections (e.g., bacterial sinusitis) ***Performance scale 2: Symptomatic, normal activity***
Clinical stage III
• Weight loss of >10% of body weight • Unexplained chronic diarrhoea for >1 month • Unexplained prolonged fever (intermittent or constant) for >1 month • Oral candidiasis (thrush) • Oral hairy leukoplakia • Pulmonary TB within the past year • Severe bacterial infections (e.g., pneumonia, pyomyositis) ***Performance scale 3: Bedridden <50% of the day during the last month***
Clinical stage IV
• HIV wasting syndrome, as defined by the US Centers for Disease Control and Prevention (CDC) • *Pneumocystis jiroveci* pneumonia (PCP) • Toxoplasmosis of the brain • Cryptosporidiosis with diarrhoea for >1 month • Cryptococcosis, extrapulmonary • Cytomegalovirus (CMV) disease of an organ other than liver, spleen, or lymph nodes • Herpes simplex viral (HSV) infection mucocoetaneous for >1 month or visceral any duration • Progressive multifocal leukoencephalopathy (PML) • Any disseminated endemic mycosis (e.g., histoplasmosis, coccidioidomycosis) • Candidiasis of the oesophagus, trachea, bronchi, or lungs • *Mycobacterium avium* complex (MAC), disseminated • Non-typhoid *Salmonella* septicaemia • Extrapulmonary TB • Lymphoma • Kaposi's sarcoma • HIV encephalopathy as defined by the CDC ***Performance scale 4: Bedridden for >50% of the day during the last month***

Table 3. Recommended laboratory tests for patients initially presenting for HIV care[1]

Test	Strength of recommendation
HIV disease tests	
Confirm positive HIV antibody status records review or serology testing)	Mandatory
CD4 count and percentage	Mandatory
Plasma HIV RNA level (viral load)	Recommended
Safety laboratory tests	
Urine or serum pregnancy test	Mandatory
Complete blood count (CBC) with differential	Mandatory
Fasting lipid profile	Recommended
Serum chemistry	
Liver function tests	Mandatory
Electrolytes, blood urea nitrogen, creatinine levels	Mandatory
Fasting blood glucose level	Recommended
Urinalysis	Recommended
Co-infection and comorbidity laboratory tests	
Chest radiography[a]	Optional
Screening for other STIs (syphilis, chlamydia, gonorrhoea, trichomoniasis)	Mandatory for syphilis; recommended for chlamydia, gonorrhoea, trichomoniasis
Serologic testing for *Toxoplasma gondii*	Optional
TB screening[b]	Mandatory
Viral hepatitis screening (hepatitis B [HBV], hepatitis C [HCV])[c]	Mandatory for HBV; recommended for HCV
Human T-lymphotropic virus (HTLV) (I/II)	Mandatory

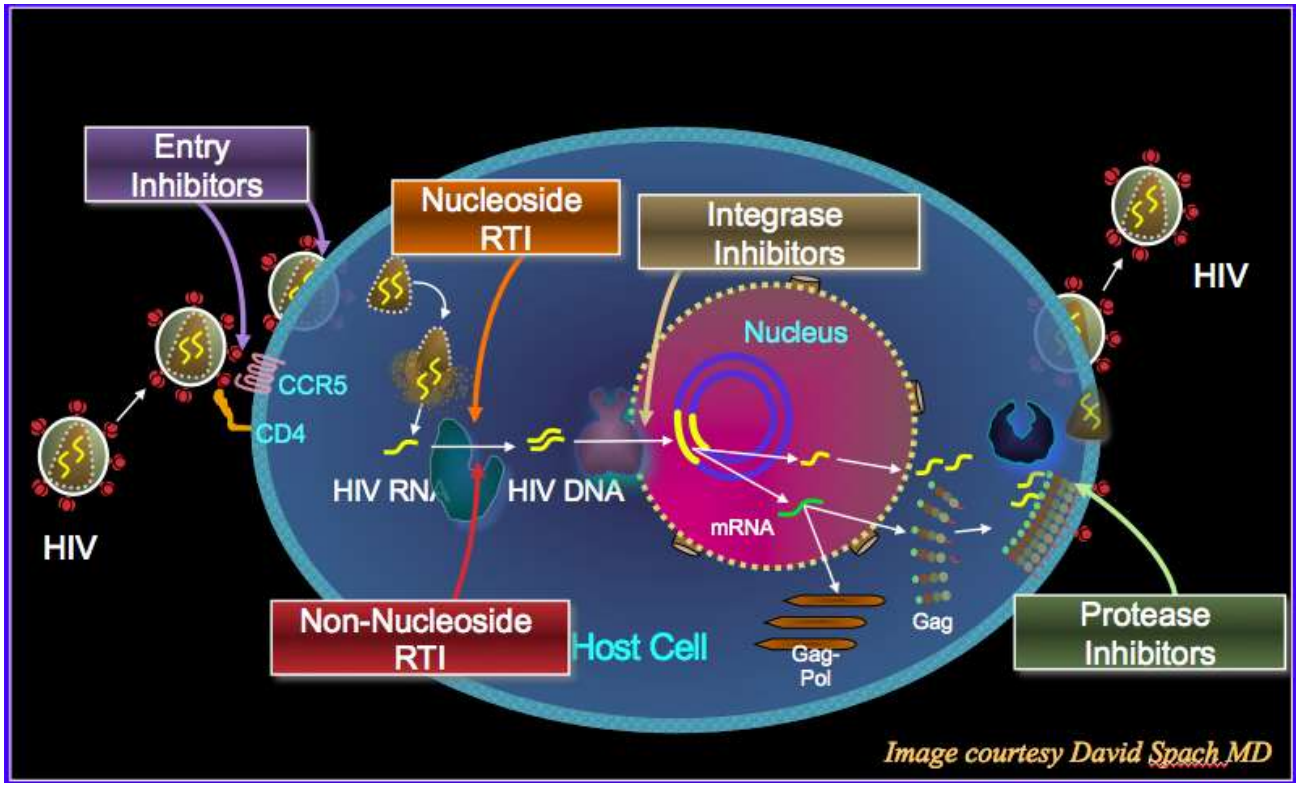
[a] *For patients with a positive TB test result; consider in patients with underlying lung disease for comparison in evaluating future respiratory illness.*
[b] *Tuberculin skin test (TST)*
[c] *HBV surface antigen (HBsAg), antibody to HBV surface antigen (HBsAb) or to HBV core antigen (HBcAb), antibody to HCV (HCV Ab).*

[1] Adapted from Aberg et al (2009); see works cited.

2.4 ANTIRETROVIRAL THERAPY FOR ADULTS AND ADOLESCENTS

The term **'antiretroviral therapy'** (ART) refers broadly to the use of antiretroviral medications (ARV)—either as individual drugs or in combination with each other—to treat or prevent HIV infection. **'Highly active antiretroviral therapy'** (HAART) refers specifically to the combination of three or more ARVs taken concurrently to suppress HIV replication in persons with chronic HIV infection by blocking key steps in the HIV life cycle (see figure 1).

Figure 1: HIV life cycle and drug classes for treating HIV infection



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HAART represents the current standard of care of ART for individuals infected with HIV. This strategy evolved from the recognition that treatment of chronic HIV infection with only one or two ARVs typically results in rapid treatment failure and facilitates the development of drug resistance, thereby compromising future therapeutic options. With standard first-line HAART, two ARVs from the nucleoside reverse transcriptase inhibitor (NRTI) class (e.g., tenofovir [TDF] plus lamivudine [3TC] or emtricitabine [FTC]) are combined with another drug from the non-nucleoside reverse transcriptase inhibitor (NNRTI) class (e.g., efavirenz [EFV] or nevirapine [NVP]). The development of inexpensive, fixed-dose combination tablets has greatly simplified HAART regimens—most PLHIV can now take a single pill once daily to control their HIV disease.

Ultimately, the goal of HAART is to prevent HIV-associated morbidity and mortality. This is most effectively achieved by suppressing HIV replication to a level below the limit of detection by viral load assays (generally less than 50 copies/mL). Suppression of HIV replication with

HAART is typically associated with a significant rise in CD4 count, reflecting partial reconstitution of the immune system that results in reduced HIV-related morbidity and mortality.

Factors influencing the initiation of HAART include CD4 count, viral load, WHO clinical stage, and presence of other medical conditions. WHO clinical staging in adults and adolescents is detailed in appendix 4.4.

2.4.1 Adherence to HAART

Medication adherence is defined as the extent to which a patient takes a medication in the manner intended by a health care provider. Adherence to HAART is critically important, as sub-optimal adherence is associated with treatment failure and the evolution of resistance to ARVs.

2.4.1.1 Predictors of Adherence

A number of factors have been associated with non-adherence to HAART, such as depression, substance abuse, homelessness, and the therapeutic relationship between patient and provider. These should be addressed in a proactive and ongoing manner, both before and after the initiation of HAART.

2.4.1.2 Role of the Health Care Provider

Providers should dedicate time to their patients throughout the course of treatment for education and collaborative planning on taking ARVs. Every member of the health care team should regularly ask about adherence in an open, non-judgmental, and collaborative manner. Providers may give their patients devices to prompt them to take their medication at the appropriate times. Devices might include medication organisers, alarms, pagers, or a visual medication schedule placed on a calendar in a prominent place at home.

2.4.1.3 Monitoring Adherence

Improving adherence requires a combination of methods appropriate to the patient and clinical setting. It is key to ask about adherence regularly and to do so in an open and inquisitive manner. Specific monitoring strategies are explained below.

- ***Patient self-report.*** This is a relatively simple and efficient method of assessing adherence in clinical practice. Using visual aids and reviewing the patient's understanding of the prescribed regimen prior to assessing adherence helps to increase the sensitivity of this method. An example of an adherence assessment tool that relies on patient self-report can be found in figure 2.
- ***Counting pills.*** This method requires the patient to bring their medication to each visit and to count the remaining pills to determine whether any doses were missed. The pharmacist can verify adherence as stated by sharing the patient's refill patterns.

Figure 2. Example of adherence assessment tool[2]

1. **Make an introductory statement.** Make a statement acknowledging that many PLHIV have difficulties taking ARVs—it is common and inevitable at some point in treatment. State that you are there to help identify these difficulties and to try to make it easier to take the medication. Consider the following language:
   'Taking pills every day is really hard. Most people have problems taking their pills at some point during treatment. I am going to ask you about problems that you may have taking your pills. Please feel comfortable telling me about pills you may have missed or taken late. I am asking because I want to make it easier for you to take them.'

2. **Confirm the patient's understanding of their HAART.** Using a visual aid, such as a chart that shows colour images of the available pills, ask the patient which medications they are taking. This is not always useful in situations with white, generic preparations that look similar. For each of the indicated pills, ask the patient how many and exactly how often they take them. Ask if they have special instructions for any of the pills, such as dietary restrictions or extra fluid requirements. If any answers are incorrect, clarify the regimen prior to completing the adherence assessment.

3. **Assess the patient's adherence.** Ask the patient about their adherence over the past 3 days, on a day-by-day basis. Start with yesterday and ask them how many of their pills they had missed or taken late that day. Then ask about the 2 days prior to that, addressing each day separately. Next, ask about how many doses they missed or took late over the past 7 days and the past 30 days. If they report no missing doses, ask them how long it has been since a dose was missed.

4. **Ask the patient about reasons for missing doses.** For patients who report missing any doses, ask if they know the reasons why. Prompt them if they cannot offer an explanation: Common reasons include forgetting, being away from home, being too busy with other things, having a schedule change, experiencing too many side effects, feeling sick or depressed, and running out of pills.

5. **Ask the patient about medication side effects or other problems.** Ask the patient about medication side effects or other problems that they may be experiencing. Prompts can be offered: Common problems include nausea, diarrhoea, difficulty swallowing the pills, headaches, fatigue, depression, or any other physical or emotional complaints.

6. **Collaborate with the patient to facilitate adherence.** Reassure the patient again that problems with adherence are common. Explain that your concern is based on the fact that missing more than 5% of doses in a month (i.e., more than three doses in a month, given a twice daily regimen) can lead to the medications not working well anymore, and that missing less than this would be a good goal. Take all complaints about side effects or other physical or emotional problems seriously and address them concretely. Offer suggestions to overcome specific obstacles the patient may have mentioned. Depending on their concerns, suggestions could include using a watch alarm, storing pills in a medication organiser, keeping extra packages of pills at work or in the car, or storing pills an unmarked bottle for enhanced privacy. Ask the patient if they have any ideas to make taking their medication easier. Finally, do not worry if the problem cannot be solved immediately; uncovering a problem with adherence is an important accomplishment and solutions can emerge in subsequent visits.

2.4.2 Initiating HAART

As described in the above section, providers need to prepare all patients initiating HAART by counselling them on adherence, including exploring potential barriers.

[2] **(Adapted from Chesney et al, 2000; see Works Cited)**

2.4.2.1 When to Start HAART: Key Recommendations

1. HAART is recommended for PLHIV with the following conditions, regardless of CD4 count[3]:
   - Significant symptoms attributable to HIV infection (WHO clinical stages 3 or 4)*
   - Pregnancy
   - Active TB*
   - HBV disease requiring treatment
   - HTLV-1 co-infection
   - Serodiscordant sexual relationship
   - HIV nephropathy
2. HAART is recommended for PLHIV with minimal or no symptoms attributable to HIV (WHO clinical stages 1 or 2) and CD4 counts ≤500 cells/mm^3, with priority given to PLHIV with CD4 counts ≤350 cells/mm^3.

Table 4. When to initiate HAART

Target population	Clinical condition	Recommendation
Non-pregnant PLHIV with minimal or no symptoms attributable to HIV	WHO clinical stage 1 or 2	Start HAART if CD4 count is ≤500
PLHIV with significant symptoms attributable to HIV	WHO clinical stage 3 or 4	Start HAART regardless of CD4 count
Pregnant women[a]	Any	
TB, HTLV-1, HBV co-infections	Active TB	
	HBV infection requiring treatment[b]	
	HTLV-1 coinfection	
HIV nephropathy	Any	
PLHIV in serodiscordant relationship[c]	Any	

[a] *See PMTCT section 2.7.*

[b] *HBV infection requires treatment if any of the following conditions are met:*
- *HBV e antigen (HBeAg) negative AND alanine aminotransferase (ALT) > 2x ULN AND HBV DNA viral load (VL) >20K IU/mL; OR*
- *HBeAg positive AND ALT (greater than 2x ULN); OR*
- *Jaundice or any evidence of decompensated liver disease.*

[c] *The infected partner has a regular sexual partner who is not HIV-infected.*

2.4.2.2 What to Start: Key Recommendations

- **In the absence of any contra-indications, a fixed-dose combination tablet of once-daily TDF + (3TC or FTC) + EFV is preferred** due to its potency, tolerability, and ease of administration.
- Azidothymidine (zidovudine) (AZT) should be substituted for TDF in patients with pre-existing renal disease. However, if AZT is contra-indicated (e.g., in the case of severe anaemia), then TDF should be used with close monitoring of renal function.
- NVP should be substituted for EFV in patients with poorly controlled psychiatric disease and low CD4 counts (less than 250 cells/mm^3 for women, less than 400 cells/mm^3 for men).

[3] Many patients qualify for HAART because they have an active OI or TB at the time their HIV is diagnosed. In these situations, initiating treatment for the OI is the first priority. HAART is typically started shortly thereafter, although the exact timing of HAART initiation varies depending upon which OI is being treated. Detailed guidance on this issue can be found in section 2.6.

Patients with higher CD4 counts and poorly controlled psychiatric disease should receive a ritonavir-boosted protease inhibitor (rPI) instead of NVP or EFV.

- Substitution of rPI for EFV may be indicated in patients with high CD4 counts and inadequately controlled psychiatric disease.
- EFV is no longer contra-indicated in pregnancy (including in the first trimester), and a fixed-dose combination of TDF + (3TC or FTC) + EFV is the preferred first-line agent for pregnant women.
- Substitution of rPI for EFV may be indicated in women who have received single-dose NVP (SD-NVP) in the past twelve months for PMTCT purposes. EFV may be used if a two-NRTI 'tail' was administered with the SD-NVP. See section 2.7 for more details.
- AZT should be substituted for TDF in patients with HTLV-1 co-infection, unless the patient has contra-indications for receiving AZT (e.g., severe anaemia).
- EFV can lower the seizure threshold. It should be avoided in patients with poorly controlled seizure disorders and used with caution in patients with well-controlled seizure disorders.

Table 5. Preferred 1st-line HAART regimens for PLHIV in the OECS

Target population	Preferred 1st line regimen	Comments
Adults and adolescents	TDF + (3TC or FTC) + EFV	Use once-daily fixed-dose combination whenever possible.
Pregnant women		EFV no longer contra-indicated in pregnancy.
HIV/TB co-infection		Initiate HAART within 2–8 weeks after starting TB therapy[a].
HIV/HBV co-infection		Use two agents with anti-HBV activity.
Renal disease	AZT + (3TC or FTC) + EFV	TDF can worsen pre-existing renal dysfunction, but can be used with close monitoring if AZT is contra-indicated.
HTLV-1 coinfection		AZT may have anti-HTLV-1 activity. Use TDF instead if AZT is contra-indicated.
Psychiatric disease	TDF + (3TC or FTC) + (NVP or r/PI)	EFV may worsen psychiatric disease, but is reasonable to use with close monitoring in patients whose psychiatric disease is adequately treated. Avoid using NVP in women with CD4 counts >250 cells/mm^3 and in men with CD4 counts >400 cells/mm^3.
Women with recent (<12 months ago) exposure to SD-NVP for PMTCT	TDF + (3TC or FTC) + r/PI	If SD-NVP was given within past 12 months with a 'tail' of two NRTIs, can use standard 1st-line EFV-based regimen.

[a] *Patients with absolute CD4 counts <50 cells/mm^3 should initiate HAART within two weeks of starting anti-TB therapy. See section 2.6.2.2 for details on HAART for patients with HIV and active TB.*

2.4.2.3 Drug Interactions

Drug interactions between ARVs and medications used to treat other conditions are common (see Appendix 4.8). Potential drug interactions must be investigated and appropriate modifications made prior to initiating HAART. Appendix 4.9 lists drugs that should not be used in patients on HAART due to potentially severe drug-drug interactions. Drug-drug interactions

between antiretrovirals and other medications can also be checked at the following website: http://hiv-druginteractions.org[4].

2.4.2.4 Laboratory Monitoring Prior to Initiation of HAART

Prior to initiating HAART, it is useful to check haematologic and chemistry indices as well CD4 count and (where available) HIV viral load so that the immunologic (and virologic) response to HAART may be measured against pre-therapy baseline levels. If primary drug resistence is a possibility, a resistance assay may be considered. **However, scarce resources or a lack of laboratory facilities for measuring baseline values should not delay the timely initiation of HAART in patients for whom HAART is clinically indicated.**

Pregnancy testing prior to initiation of HAART is strongly recommended for women of childbearing potential. Recommendations for baseline (and follow-up) laboratory monitoring are presented in Table 6.

2.4.3 Patient Follow-up and Monitoring after Initiation of Therapy

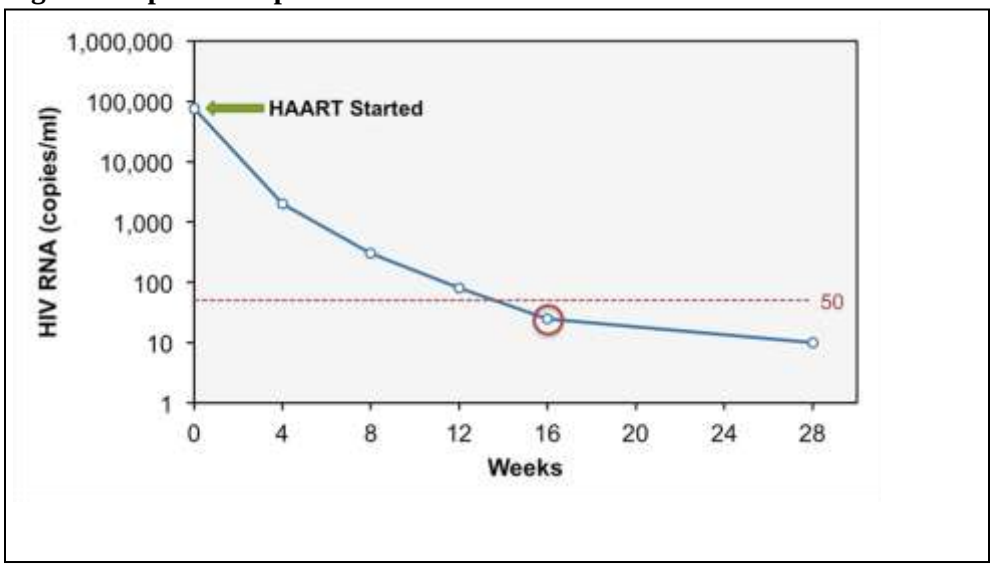
After HAART is initiated, close monitoring of the patient is warranted; the first six months are a critical time for them. During this period:

- The HIV viral load should decline rapidly, by at least 1.0 log per month, and be undetectable by 24 weeks of therapy (see figure 3).
- Medication toxicity is most likely to manifest.
- Problems with adherence are most likely to manifest.
- The potential for developing ARV resistance is highest.
- Patients may paradoxically worsen clinically due to immune reconstitution inflammatory syndrome (IRIS).
- Mortality is higher than at any other period while on HAART.

[4] See works cited.

The following is an example of a robust virologic response to HAART. The viral load should become undetectable by 24 weeks of therapy. Many patients, such as the one associated with this graph, experience a more rapid decline in viremia.

Figure 3. Optimal response to HAART



Source: www.hivwebstudy.org; see works cited.

2.4.3.1 Timing of Follow-up

A follow-up visit with the prescribing clinician or an associated community health care professional is recommended within two weeks of HAART initiation. This will reinforce the importance of adherence and provide an opportunity to assess whether there are any adverse medication reactions or IRIS. In addition, supplemental assessments by community health workers will be helpful.

2.4.3.2 Laboratory Monitoring

Periodic laboratory monitoring is recommended to screen for ARV toxicities and to assess the patient's immunologic and (where available) virologic response to the medication.

Virologic monitoring is indicated for PLHIV co-infected with HTLV-1. In such cases, CD4 count is not a reliable marker of immunological status or response to HAART. Recommended laboratory tests for patients on HAART can be found in Table 6.

Table 6. Basic laboratory monitoring for recommended first-line regimens

This table is meant to serve as a general guide and should not replace clinical judgment on an individual patient-basis. *Laboratory monitoring is warranted outside of this schedule for any signs or symptoms that suggest medication-related toxicity. Tolerance of a HAART regimen may reasonably lead to a decreased frequency of laboratory monitoring. HAART should not be withheld in circumstances where scarce resources do not permit laboratory monitoring, as suggested below. Detection of abnormalities on laboratory testing should not necessarily lead to automatic discontinuation or modification of a HAART regimen; rather, the results should be interpreted in the context of the patient's clinical signs and symptoms. Consultation with an expert HIV clinician is suggested.*

Key: BL = baseline

HAART regimen	Laboratory test	Frequency	Strength of recommendation
TDF + (3TC or FTC) + (EFV or NVP)	• CD4 count	• BL; Q3–6M	• Highly recommended
	• Pregnancy	• BL; clinician discretion	• Highly recommended
	• AST/ALT	• BL; Q3–6M; symptom-directed	• Recommended
	• HIV viral load	• BL; Q3–6M	• Optional, but recommended for patients with HTLV-1 infection or suspected treatment failure
	• Glucose	• BL; Q3–6M	• Recommended
	• Cholesterol	• BL; Q6–12M	• Recommended for patients with other risk factors for coronary artery disease
	• BUN/creatinine	• BL; 3–6M after initiation of treatment; clinician discretion	• Recommended
AZT + (3TC or FTC) + (EFV or NVP)	• CD4 count	• BL; Q4–6M	• Highly recommended
	• Hgb/CBC	• BL; 4W after initiation;	• Highly recommended
	• Pregnancy	• BL; clinician discretion	• Highly recommended
	• AST/ALT	• BL; Q3–6M; symptom-directed	• Recommended
	• HIV viral load	• BL; Q3–6M	• Optional, but recommended for patients with HTLV-1 infection or suspected treatment failure
	• Glucose	• BL; Q6–12M	• Recommended
	• Cholesterol	• BL; 3–6 months after initiation of treatment; clinician discretion	• Recommended for patients with other risk factors for coronary artery disease
	• BUN/Creatinine	• BL; Q6–12M	• Recommended

2.4.3.3 Adherence Assessment

Adherence should be measured at each patient encounter. If adherence is sub-optimal, counselling is warranted, including an investigation of adherence barriers. See section 2.4.1 for information on potential adherence interventions prior to and after initiation of HAART.

2.4.4 Treatment Toxicity

Adverse effects from HAART are common and can usually be managed symptomatically without interrupting the regimen; most resolve within 1–3 months of HAART initiation. A clinical toxicity grading system is outlined in Table 7, with more information in appendix 4.10. Table 8 provides guidance on managing drug toxicity. If the adverse effect is severe enough to require modification of the regimen, a different ARV can be substituted for the offending drug, assuming the agent responsible for the side effect in question can be reasonably determined. Table 9 presents options for managing selected common adverse reactions. Consulting an expert HIV clinician is strongly recommended when a regimen change is necessary. It is also important to report clinically significant adverse drug reactions to the OECS/PPS using the prescribed form in appendix 4.14.

Table 7. Estimating toxicity severity (see appendix 4.10 for more details)

Grade 1	**Mild reaction:** Transient or mild discomfort, no limitation in activity, no medical intervention/therapy required.
Grade 2	**Moderate reaction:** Limitation in activity, some assistance may be needed, no or minimal medical intervention/therapy required.
Grade 3	**Severe reaction:** Marked limitation in activity, some assistance usually required, medical intervention/therapy required, hospitalization possible.
Grade 4	**Severe/life-threatening reaction:** Extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization or hospice care.

Table 8. Managing ARV drug toxicity (see also Table 9)

1. Determine the seriousness of the toxicity.
2. Evaluate concurrent medications and establish whether the toxicity is attributable to one or more ARVs or to a non-ARV medication taken at the same time.
3. Consider other disease processes (e.g., viral hepatitis in a patient on ARVs who develops jaundice)—not all problems that arise during treatment are caused by ARVs.
4. Manage the adverse event according to severity. In general:
   a. ***Grade 4—severe life-threatening reaction:*** Immediately discontinue all ARVs, manage the medical event (i.e., symptomatic and supportive therapy) and reintroduce ARVs using a modified regimen (i.e., with an ARV substitution for the offending drug) when the patient has stabilized[a].
   b. ***Grade 3—severe reaction:*** Substitute the offending ARV without stopping HAART.
   c. ***Grade 2—moderate reaction:*** Consider continuing HAART as long as feasible. If the patient does not improve on symptomatic therapy, consider single-ARV substitutions.
   d. ***Grade 1—mild reactions:*** These are bothersome but do not require changes in therapy.
5. In grades 1 and 2 reactions, stress the importance of adherence.
6. If there is a need to discontinue HAART because of life-threatening toxicity, all ARVs should be stopped until the patient has stabilized.

Table 9. Symptom-directed toxicity management[5]

Adverse events	Major first-line ARVs	Recommendations
Acute pancreatitis	d4T	Discontinue HAART. Give supportive treatment with laboratory monitoring. Resume HAART with an NRTI with low pancreatic toxicity risk, such as AZT or TDF.
Drug eruptions (mild-to-severe, including Stevens-Johnson syndrome or toxic epidermal necrolysis)	NVP, EFV (less commonly)	In mild cases, provide symptomatic care. EFV rash often stops spontaneously after 3–5 days without need to change HAART. If moderate rash, non-progressing and without mucosal involvement or systemic signs, consider a single NNRTI substitution (i.e., from NVP to EFV). In moderate and severe cases, discontinue HAART and give supportive treatment. After resolution, resume HAART with a boosted protease inhibitor (rPI)-based regimen or triple NRTI if no other choice.
Dyslipidaemia	All NRTIs (particularly d4T) EFV	Consider replacing the suspected ARV.
Anaemia and neutropaenia	AZT	If severe (Hb <7.0g/dl and/or Absolute Neutrophil Count [ANC] <750 cells/mm^3), replace with an ARV with minimal or no bone marrow toxicity (e.g., d4T or TDF) and consider a blood transfusion.
Hepatits	All ARVs (particularly NVP)	If ALT is more than five times the basal level, discontinue HAART and monitor. After resolution, restart HAART, replacing the suspected causative drug (e.g., EFV replaces NVP).
Lactic acidosis	All NRTIs (particularly d4T)	Discontinue HAART and give supportive treatment. After resolution, resume HAART with TDF.
Lipoatrophy and lipodystrophy	All NRTIs (particularly d4T)	Replace the suspected ARV early on (e.g., d4T for TDF or AZT).
Neuropsychiatric changes	EFV	Usually self-limited, without the need to discontinue HAART. If intolerable to the patient, replace NVP with EFV or bPI. Single substitution recommended without cessation of HAART.
Renal toxicity (renal tubular dysfunction)	TDF	Consider substitution with AZT.
Peripheral neuropathy	d4T	Replace d4T with AZT, TDF. Symptomatic treatment (amitriptyline, vitamin B6).

[5] Adapted from: World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach, 2010 revision. Geneva: WHO; 2010. Available from: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf.

Occasionally, severe HAART-related toxicity requires the patient to discontinue all ARVs. In such circumstances, it is best to stop all of them simultaneously, because continuing therapy with only one or two ARVs is associated with the development of drug resistance. If the HAART regimen contains an NNRTI (e.g., NVP or EFV), some expert clinicians recommend discontinuing the NNRTI 3–7 days prior to discontinuing the NRTIs, given the prolonged plasma half-life of NNRTIs. HAART should be withheld until the patient recovers, at which time reinitiation of therapy with a different regimen can be considered, in consultation with an HIV expert clinician.

2.4.5 Immune Reconstitution Inflammatory Syndrome

IRIS is a strong inflammatory response to a pre-existing infection or condition by an immune system that has been invigorated by the recent initiation of HAART. Often, the OI was diagnosed prior to the initiation of HAART, and the patient is on appropriate treatment. However, sometimes the OI responsible for IRIS represents a new diagnosis; it may have remained clinically 'silent' prior to the initiation of HAART, due to the patient's severely debilitated immune system. Studies have suggested that roughly one-quarter to one-third of patients with advanced HIV disease who initiate HAART experience one or more IRIS reaction.

2.4.5.1 Clinical Presentation of IRIS

Clinically, IRIS typically presents as fevers, sweats, lymphadenopathy, fatigue, and other features characteristic of the underlying OI. These signs and symptoms typically develop within the first several weeks after initiating HAART, and can be severe enough to cause considerable morbidity and even mortality. While the majority of IRIS events occur in the first 3 months, late IRIS events (>4 months on HAART) have been reported.

A wide range of conditions have been associated with IRIS. The most common involve mycobacterial disease (especially TB), cryptococcal disease, or viral diseases from the herpesvirus family. Table 9 lists some of the pathogens and conditions that have been implicated in IRIS reactions.

Table 10. Pathogens and conditions that may present as IRIS

• *Bartonella henselae*	• Histoplasmosis	• *Mycobacterium tuberculosis* (MTB)
• *Chlamydia trachomatis*	• HTLV-1 and -2	
• CMV	• Kaposi's sarcoma	• Parvovirus B19
• *Cryptococcus*	• Leprosy	• PCP
• Graves' disease	• Lymphoma	• PML
• Guillain-Barré syndrome	• MAC	• Sarcoidosis
• HBV and HCV	• Microsporidia	• VZV, HPV, HSV

2.4.5.2 Risk Factors for IRIS

The following risk factors have been associated with IRIS:

- Active or sub-clinical infection by pathogens (or antigens of non-viable micro-organisms).
- Low CD4 count prior to HAART (e.g., less than 50 cells/mm^3).
- Robust virologic and immunologic response to HAART.

It should be noted that some patients with IRIS lack any of these risk factors. MTB IRIS, for example, often develops in patients whose CD4 counts prior to HAART are >50 cells/mm^3.

2.4.5.3 Differential Diagnosis

Some medication toxicities (e.g., hepatitis, allergic hypersensitivity) present with signs and symptoms suggestive of IRIS. Additionally, the timing typical of IRIS reactions overlaps with that of ARV-associated toxicities.

In patients with suspected IRIS, failure of therapy of a pre-existing OI should also be considered. Efforts should be made to diagnose as accurately as possible the pathogen(s) responsible (e.g., aspirating and culturing enlarged lymph nodes).

Key elements that would implicate IRIS include:
- Low pre-treatment CD4 count and/or advanced HIV disease.
- Robust immunologic (and virologic) response to HAART.
- Temporal association between initiation of HAART and onset of illness.
- Presence of clinical signs and symptoms of inflammation.
- Absence of evidence for other causes.

No widely accepted case definition exists yet, though diagnostic criteria have been proposed.

2.4.5.4 Management of the Patient with Suspected IRIS

Data from clinical trials are limited for determining the appropriate management of IRIS. However, the following steps represent a reasonable general guide for management.

1. Consider other possible aetiologies:
   a. Persistent active infection (e.g., OI treatment failure).
   b. Adverse drug reaction(s).
2. Continue HAART.
3. Attempt to diagnose the infection or condition responsible for IRIS:
   a. Aspirate and culture any easily accessible abscesses or lymphadenopathy.
   b. Obtain bacterial, mycobacterial, and (if available) fungal cultures.
4. Initiate pathogen-specific therapy, if not already in place, noting:
   a. The development of IRIS does not require reinitiating antimicrobial therapy or changing maintenance therapy for the responsible infection if the patient is already on appropriate therapy
   b. Initiating empiric therapy is reasonable for highly suspected conditions when the diagnosis is not immediately apparent.
5. Provide anti-inflammatory therapy:
   a. Nonsteroidal anti-inflammatory drugs (NSAID) for mild-to-moderate cases (e.g., ibuprofen, naproxen, acetylsalicylic acid).
   b. Corticosteroids for moderate-to-severe cases (e.g., prednisone dosed at 0.5–1.0 mg/kg/day while the patient is acutely ill with IRIS, then tapered gradually as he or she improves clinically).
6. Drain abscesses and infected lymph nodes as necessary; emergency surgical decompression may be indicated for the patient with tracheal or intestinal obstruction.

7. Consider interrupting HAART in patients with life-threatening IRIS reactions or who do not clinically stabilize with the above measures.

2.4.6 Metabolic Complications of HAART and HIV

A number of metabolic disturbances have been described in HIV-infected patients on HAART. Patients who have initiated HAART should be monitored carefully for signs of complications and managed appropriately, as outlined below. The exact aetiology of these complications is not clearly understood, and may reflect a multi-factorial process involving ARVs, HIV itself, and host factors.

2.4.6.1 Lactic Acidosis Syndrome and Hepatic Steatosis

Lactic acidosis syndrome represents a rare but potentially fatal complication of HAART, linked to NRTIs and to HIV infection. NRTIs can inhibit human mitochondrial DNA polymerase gamma, an enzyme crucial for normal mitochondrial DNA replication. This results in a depletion of the mitochondrial DNA, compromising cellular oxidative phosphorylation. Evidence of mitochondrial DNA depletion can also be found in HIV-infected persons who have never received HAART, suggesting that HIV itself may contribute to mitochondrial dysfunction.

Clinically, this syndrome can range from asymptomatic hyperlactataemia to fatal lactic acidosis. The development of lactic acidosis appears to depend on the duration of NRTI exposure and on the specific ARVs used. For example, d4T appears to be most commonly associated with lactic acidosis, followed by didanosine (ddI) and AZT, followed by 3TC and abacavir (ABC). TDF appears to carry a low risk of mitochondrial toxicity as well. Pregnant women appear to be at greater risk for developing lactic acidosis, and deaths have been reported in pregnant women taking the combination of d4T plus ddI.

Physicians should maintain a high clinical suspicion for this syndrome, as symptoms are usually non-specific. They may include nausea, vomiting, abdominal pain and distension, diarrhoea, fatigue, myalgias, weight loss, and dyspnoea. An elevated lactic acid level establishes the diagnosis but a proper diagnosis requires sampling without a tourniquet, rapid transportation to a laboratory on ice, and processing within a few hours. Other laboratory indicators include elevated CPK, LDH, amylase, and aminotransferases, and low serum bicarbonate.

Lactic acidosis is treated by discontinuing the ARVs and providing supportive care until the syndrome is resolved. Case reports have suggested that giving high doses of vitamins involved in oxidative phosphorylation, such as riboflavin or L-carnitine, may hasten the recovery process. Consulting an HIV expert is strongly recommended.

Following resolution of the syndrome, HAART should be reinitiated cautiously and in consultation with an HIV expert. NRTIs such as d4T and ddI—which are strongly associated with mitochondrial toxicity—should be avoided.

2.4.6.2 Lipodystrophy

Lipodystrophy refers to changes in the distribution of fat and is associated with HIV and HAART. Two distinct lipodystrophic syndromes have been characterised: subcutaneous fat wasting (‘lipoatrophy’) and central fat deposition (‘lipohypertrophy’). Lipoatrophy is typically

most apparent in the face and extremities, and has been associated with advanced HIV and with NRTIs, especially d4T. With lipohypertrophy, central fat deposition in the viscera, breasts, and dorsocervical fat pad ('buffalo hump') have been described; its pathophysiology remains unclear.

These changes in the distribution of fat are often, though not always, associated with dyslipidaemia and insulin resistance. A universally accepted case definition of lipodystrophy has not yet been established.

The optimal management of lipodystrophy is not known. Lipoatrophy appears to improve, though very slowly, in patients who remove d4T from their ARV regimens and substitute NRTIs like TDF or ABC, which have less potential for mitochondrial toxicity. Similar ARV-switch strategies have failed to consistently demonstrate a clinical benefit for patients with lipohypertrophy, though improvements have been documented following dietary and exercise modifications. Cosmetic plastic surgery options—such as facial injections with polylactic acid or surgical excision of dorsocervical fat pads—exist but are expensive and not widely available.

2.4.6.3 Hyperlipidaemia

In the absence of HAART, HIV infection can lead to dyslipidaemia, including lower HDL levels. HAART has been associated with elevated total cholesterol, LDL, and triglycerides. several (though not all) PIs have been strongly associated with lipid abnormalities, though dyslipidaemia has also been documented in patients on NNRTI-based regimens. Recent data suggest that these abnormalities can lead to accelerated atherosclerosis and cardiovascular complications in PLHIV. In general, patients with HIV/HAART-associated dyslipidaemia should be managed in a similar fashion to patients who are not infected with HIV. Low-fat diets, regular exercise, and smoking cessation represent first-line interventions. Fibrates and HMG-CoA reductase inhibitors (statins) can be helpful, but certain statins (e.g., simvastatin and lovastatin) should be avoided due to dangerous drug interactions with PIs. Pravastatin is the preferred agent; atovarstatin may also be used at reduced doses.

2.4.6.4 Insulin Resistance

Hyperglycaemia, new onset diabetes, exacerbation of pre-existing diabetes, and diabetic ketoacidosis have all been reported in PLHIV receiving HAART, especially in those receiving PIs. EFV has also been associated with insulin resistance. Routine fasting blood glucose measurements should be performed every 3–4 months for patients who are receiving PIs or EFV and have no previous history of diabetes. Pregnant women receiving PIs should have their glucose levels monitored closely. All patients should be counselled to recognise symptoms of hyperglycaemia, such as polyuria, polydipsia, and polyphagia.

Insulin resistance is usually treated by either switching to a non-PI-/non-EFV-based regimen (if possible), or by adding oral hypoglycaemic agents or insulin to the HAART regimen.

2.4.6.5 Metabolic Bone Disorders

Avascular necrosis and decreased bone density have been documented in HIV-infected adults and children. Although TDF has been associated with decreases in bone mineral density, the degree to which most ARVs contribute to these disorders is unclear. Some studies have linked

PIs to osteopaenia and osteoporosis, while other data suggest that PIs have a possible protective effect on bone mineralisation.

Recommended prevention and treatment measures for osteopaenia include modifying other risk factors (e.g., smoking cessation, weight-bearing exercise) and ensuring an adequate intake of calcium and vitamin D. Hormone replacement therapy may be considered in postmenopausal women. Bisphosphonates, such as alendronate, have demonstrated clinical efficacy for PLHIV who have osteoporosis.

Avascular necrosis most commonly involves the femoral or humeral head, leading to hip or shoulder pain. Risk factors for osteonecrosis include corticosteroid therapy, alcohol abuse, hyperlipidaemia, and hypercoagulable states. The diagnosis is typically made by X-ray or CT scan, but may miss early stages of disease; MRI is the most sensitive test. There is no accepted medical therapy, and surgery may be needed to treat severe disabling symptoms.

2.4.7 Treatment Failure

Treatment failure refers to the absence of a sustained favourable response to HAART. Treatment failure can be suspected on the basis of clinical, immunologic, or virologic criteria (summarized in Table 11). Treatment failure that is suspected on the basis of clinical progression or CD4 count decline should always be confirmed with HIV viral load testing before a patient's HAART regimen is changed. Suspected treatment failure should be confirmed as rapidly as possible to prevent HIV disease progression and the development of further resistance to ARVs. An expert HIV clinician should be consulted.

In the event of treatment failure, reassessment of adherence is indicated. After adherence issues have been adequately addressed, a change in the HAART regimen to second-line therapy is usually warranted. Resistance testing (where available) should be used to guide a change in HAART regimen.

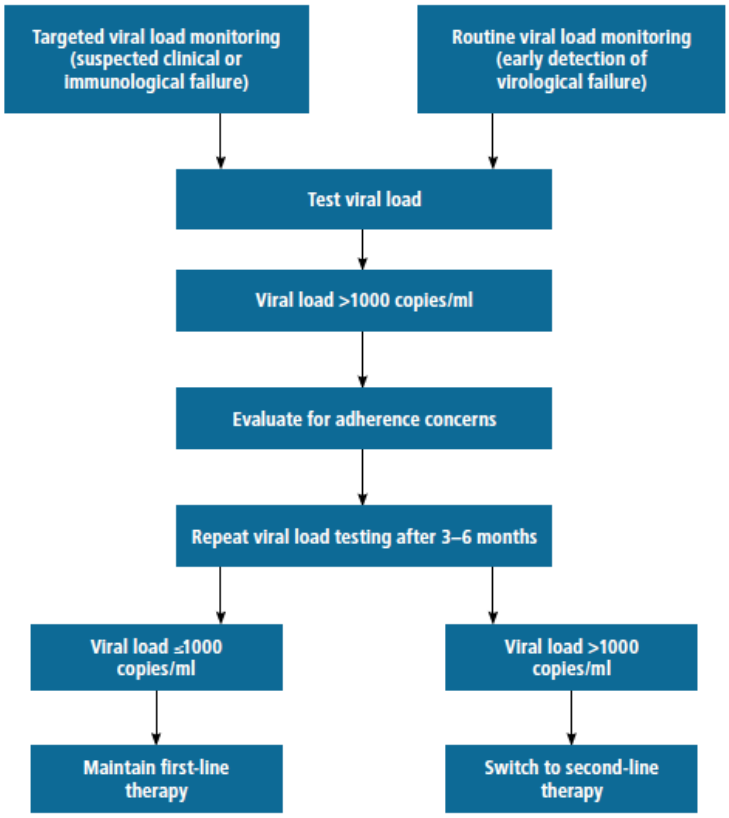
2.4.7.1 Key Recommendations: When to Switch First-Line HAART

- Use viral load (VL) to confirm treatment failure, as immunological and clinical criteria for treatment failure are not reliable. When VL is not available, use immunological criteria to confirm clinical failure.
- Where routinely available, use VL every 6 months to detect viral replication.
- A VL of >1,000 copies/mL should prompt the clinician to reinforce adherence with the patient, and repeat VL testing in 3 months, as shown in Figure 4
- A persistent VL of >1,000 copies/ml confirms treatment failure and should prompt change to second line therapy.

Table 11. HAART Switching Criteria

Failure	Definition	Comments
Virological failure	Persistent plasma viral load above 1,000 copies/ml	The optimal VL threshold for defining virological failure has not been determined. A single VL > 1,000 copies/mL should prompt reinforcement of adherence measures with the client and repeat VL testing 3-6 months later. A persistent VL > 1,000 copies/mL should prompt change to second line therapy (see text and Figure 4)
Immunological failure	Fall of CD4 count to baseline (or below) OR persistent CD4 count below 100 cells/mm^3	Verify no concomitant infection is causing transient CD4 count decrease.
Clinical failure	New recurrent WHO stage 4 condition	Condition must be differentiated from IRIS. Certain WHO clinical stage 3 conditions (e.g., pulmonary TB, severe bacterial infections), may be an indication of treatment failure.

Figure 4. Viral Load Testing algorithm to detect or confirm treatment failure in adults, adolescents, and children.[6]



[6] Source: WHO 2013 Consolidated Antiretroviral Therapy Guidelines. World Health Organization, Geneva, 2013.

2.4.7.2 HIV Resistance to HAART

Treatment failure may occur because a patient's strain of HIV has developed resistance to one or more ARV. The manner by which HIV develops resistance to ARVs is similar to the way bacteria or mycobacteria (e.g., TB) develop resistance to antibiotics: insufficiently potent drug therapy selects for mutant strains that are resistant to the medications administered to the patient. These mutant strains then replace the wild-type strain due to their selective replication advantage in the face of drug pressure, thus leading to treatment failure. Resistance to ARVs most commonly develops in cases of suboptimal adherence but it can occur in patients who maintain very high levels of adherence to their medications. For example, severe diarrhoea can result in the malabsorption of ARVs, potentially leading to treatment failure and ARV resistance.

Laboratory assays have been developed to estimate the patterns of resistance that have developed in a given patient's strain of HIV. Though imperfect, these assays have demonstrated clinical efficacy in aiding the design of second-line treatment regimens following treatment failure. Hence, where resources permit, a resistance assay is recommended in cases of treatment failure.

Even in the absence of resistance testing, however, knowledge of the patterns of resistance and cross-resistance that commonly develop in patients failing specific regimens allows for reasonably accurate empiric decision-making in designing a second-line regimen. For example, patients failing an NNRTI-based initial treatment regimen commonly develop one or more mutations that confer high-level resistance to all available NNRTI medications. Therefore, a second-line regimen for these patients should be PI-based rather than NNRTI-based. These concepts are discussed more fully below and summarised in Table 12.

2.4.7.3 Second-Line HAART Regimens

Second-line HAART regimens are indicated for patients who are forced to discontinue their initial (first-line) treatment regimen as a consequence of treatment failure, and must be constructed carefully to account for potential ARV resistance. Where available, ARV resistance testing is strongly recommended to help guide the design of the second-line regimen. If resistance testing is not available, empiric reasoning of the likelihood of resistance to agents in the initial regimen, as well as considerations of cross-resistance, can be used to design a second-line regimen with the highest likelihood of efficacy. Because the exact nature and extent of resistance is difficult to estimate empirically, these guidelines suggest trying to replace as many of the agents in the initial regimen as possible.

See table 12 for suggested second-line regimens for patients who have experienced treatment failure on their initial regimens, in situations where resistance testing is not available to help guide decision-making.

2.4.7.4 Second-line Therapy: Key Recommendations

- A ritonavir-boosted PI (PI/r) plus two NRTIs are recommended for second-line HAART.
- ATV/r and lopinavir (LPV)/r are the preferred boosted PIs for second-line HAART.
- Simplification of second NRTI options is recommended:
    - If d4T or AZT has been used in first-line therapy, use TDF + (3TC or FTC) as the NRTI backbone in second-line therapy.
    - If TDF has been used in first-line therapy, use AZT + 3TC as the NRTI backbone in

second-line therapy.

Table 12. Preferred second-line therapy options

Target population		Preferred options	Comments
Adults and adolescents (including pregnant women)	If d4T or AZT used in first-line therapy	TDF + 3TC or FTC + ATV/r or LPV/r	NRTI sequencing based on availability of FDCs and potential for retained antiviral activity, and considering early and late switch scenarios. ATV/r and LPV/r are comparable and available as heat-stable FDCs or co-package formulations.
	If TDF used in first-line therapy	AZT + 3TC + ATV/r or LPV/r	
TB/HIV co-infection	If rifabutin available	Same regimens as recommended above for adults and adolescents	No difference in efficacy between rifabutin and rifampicin. Rifabutin has significantly less drug interaction with boosted PIs, permitting standard boosted PI dosing.
	If rifabutin not available	Same NRTI backbones as recommended for adults and adolescents PLUS LPV/r or SQV/r with super-boosted dosing of RTV (LPV/r 400 mg/400 mg twice daily or LPV/r 800 mg/200 mg twice daily or SQV/r 400 mg/400 mg twice daily)	Rifampicin significantly reduces the levels of bPIs, limiting the effective options. Use of extra doses of RTV with selected PIs (LPV and SQV) overcome this effect but with increased rates of toxicity.
HBV co-infection		AZT + TDF +3TC or FTC + ATV/r or LPV/r	In case of treatmet failure, TDF + 3TC or FTC should be maintained for anti-HBV activity and the second-line regimen should include other drugs with anti-HIV activity.

2.4.7.5 Third-line (Salvage) Therapy

Following failure of two or more ARV regimens, complete and durable virologic suppression is unlikely. However, preventing further immunologic deterioration is possible even in the absence of full virologic suppression. Studies have demonstrated that highly treatment-experienced patients, including those with demonstrably high levels of ARV resistance, generally fare better clinically if they remain on HAART than if they discontinue it altogether. While full virologic suppression may not be a realistic goal for highly treatment-experienced patients, attempts should be made to construct a regimen that will maintain some efficacy and prevent or slow further progression of HIV. The design of salvage therapy regimens is exceedingly complex and should be carried out in consultation with an expert HIV clinician.

2.4.7.6 Third-line Regimens: Key Recommendations

- Consult with an expert HIV clinician.

- Include new drugs likely to have anti-HIV activity, such as an integrase inhibitor (e.g., raltegravir), a second-generation NNRTI (e.g., etravirine), and/or a second-line PI (e.g., darunavir).
- Have patients on a failing second-line regimen with no new ARV options continue with a tolerated regimen.

2.5 ADULT AND ADOLESCENT OPPORTUNISTIC INFECTION PROPHYLAXIS

This section provides detailed guidance on the prevention of selected OIs commonly seen in PLHIV in the Caribbean region. Sources for these recommendations include the website HIV Web Study[7] and the CDC's OI guidelines[8], which have been adapted for the Eastern Caribbean region. Not all treatments listed may be available in the OECS but are included in case referral outside the region is an option. For management of OIs not listed below, please consult the CDC OI Guidelines.

Preferred and alternative treatment options are presented; each recommendation includes a rating of its strength as well as the quality of the evidence supporting it, coded as follows.

Strength of recommendation:

A. Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B. Moderate evidence for efficacy, or strong evidence for efficacy but only limited clinical benefit, supports recommendation for use. Should generally be offered.
C. Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of treatment or alternative approaches. Optional.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

Quality of the evidence supporting the recommendation

I. Evidence from at least one properly-designed randomized, controlled trial.
II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one centre), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

[7] HIV Web Study. Seattle: University of Washington; c2004–13 [updated 7 Mar 2013]. Available from: www.hivwebstudy.org.

[8] Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR. 2009 Apr 10; 58(4). Available from: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf

2.5.1 Primary Prophylaxis

Table 13. Prophylaxis to prevent first episode of OIs[9]

Pathogen	Indication	Preferred	Alternative
Pneumocystis jirovecii pneumonia (PCP)	• CD4 count <200 cells/μL **(AI)** or oropharyngeal candidiasis **(AII)** • CD4 count <14% or history of AIDS-defining illness **(BII)** • CD4 count >200 but <250 cells/μL if monitoring CD4 count every 1–3 months is not possible **(BII)**	• Co-trimoxazole[10] 1 double strength (DS) PO (orally) QD (daily) **(AI)**; OR • 1 single strength (SS) QD **(AI)**	• Co-trimoxazole[9]: 1 DS PO TIW) **(BI)**; OR • Dapsone: 100 mg PO QD or 50 mg PO twice a day BID **(BI)**; OR • Dapsone: 50 mg PO QD + pyrimethamine: 50 mg PO QW + leucovorin 25 mg PO QW **(BI)**; OR • Aerosolized pentamidine: 300 mg via Respigard II™ nebulizer QM **(BI)**; OR • Atovaquone: 1,500 mg PO QD **(BI)**;
Toxoplasma gondii encephalitis	• Toxoplasma IgG positive patients with CD4 count <100 cells/μL **(AII)** • Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have toxoplasma serology retested if CD4 count decline to <100 cells/μL **(CIII)** • Prophylaxis should be initiated if seroconversion occurred **(AII)**	• Co-trimoxazole[9]: 1 DS PO QD **(AII)**	• Co-trimoxazole[9]: 1 DS PO TIW **(BIII)**; OR • Co-trimoxazole[9]: 1 SS PO QD **(BIII)**; OR • Dapsone: 50 mg PO QD + pyrimethamine: 50 mg PO weekly + leucovorin: 25 mg PO weekly **(BI)**; OR • Dapsone: 200 mg PO weekly + pyrimethamine: 75 mg PO weekly + leucovorin: 25 mg PO weekly **(BI)**; OR • Atovaquone: 1,500 mg PO QD , with or without pyrimethamine: 25 mg PO QD + leucovorin: 10 mg PO QD **(CIII)**

[9] For recommendations regarding secondary prophylaxis (also known as 'maintenance therapy') for OIs, see table 21 in section 2.6.7.

[10] Desensitization to co-trimoxazole should be attempted for patients who describe a history of non-severe allergic reactions to co-trimoxazole or other sulfa-based drugs. See appendix 4.11.

Mycobacterium tuberculosis infection (treatment of latent TB [LTBI])	• Positive diagnostic test for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB **(AI)** • Negative diagnostic test for LTBI, but close contact with a person with infectious pulmonary TB and no evidence of active TB **(AII)** • A history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions) regardless of diagnostic tests for LTBI and no evidence of active TB **(AII)**	• Isoniazid: 300 mg PO QD **(AII)** or 900 mg PO twice weekly (BIW) **(BII)** for 9 months—both PLUS pyridoxine: 50 mg PO QD **(BIII)**; OR • For persons exposed to drug-resistant TB, select drugs after consultation with public health authorities **(AII)**	• Rifampicin: 600 mg PO QD x 4 months **(BIII)**; OR • Rifabutin: (dose adjusted based on concomitant HAART) x 4 months **(BIII)**
Disseminated *Mycobacterium avium* complex (MAC)	• CD4 count <50 cells/μL—after ruling out active MAC infection **(AI)**	• Azithromycin: 1,200 mg PO once weekly **(AI)**	• Clarithromycin: 500 mg PO BID **(AI)**; OR • Rifabutin: 300 mg PO QD **(BI)** (dosage adjustment based on drug-drug interactions with HAART); rule out active TB before starting rifabutin
Streptococcus pneumoniae	• CD4 count >200 cells/μL and no receipt of pneumococcal vaccine in the past 5 years **(AII)** • CD4 count <200 cells/μL—vaccination can be offered **(CIII)** • In patients who received pneumococcal vaccination when CD4 count <200 cells/μL, but has increased to >200 cells/μL in response to HAART **(CIII)**	• 23-valent PPV: 0.5 mL intramuscularly (IM) x 1 **(BII)** • Revaccination every 5 years may be considered **(CIII)**	
Influenza A and B	• All HIV-infected patients **(AIII)**	• Inactivated influenza vaccine: 0.5 mL IM annually **(AIII)**	
Histoplasma capsulatum	• CD4 count $\leq$150 cells/μL and at high risk because of occupational exposure or live in a community with a hyperendemic rate of histo-plasmosis (>10 cases/100 patient-years) **(CI)**	• Itraconazole: 200 mg PO QD **(CI)**	
Coccidioido-mycosis	• Positive IgM or IgG serologic test in a patient from a disease-endemic area; and CD4 count <250 cells/μL **(CIII)**	• Fluconazole: 400 mg PO QD **(CIII); OR** • Itraconazole: 200 mg PO BID **(CIII)**	

Varicella zoster virus (VZV)	Post-exposure—close contact with a person who has active varicella or herpes zoster: • For susceptible patients (those who have no history of vaccination or of either condition or are known to be VZV seronegative) **(AIII)**	Post-exposure therapy: • Varicella-zoster immune globulin (VariZIG™) 125 IU per 10 kg (maximum of 625 IU) IM, administered within 96 hours after exposure to a person with active VZV or HZV **(AIII)** *Note: As of June 2007, VariZIG can be obtained only under a treatment investigational new drug (IND): (1-800-843-7477, FFF Enterprises)*	• VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential VZV transmission **(BIII)** Alternative post-exposure therapy: • Post-exposure varicella vaccine (Varivax) 0.5 mL subcutaneous (SQ) x 2 doses, 3 months apart if CD4 count >200 cells/μL **(CIII)**; or • Pre-emptive acyclovir 800 mg PO 5 x/day for 5d **(CIII)** *Note: These two alternatives have not been studied in the HIV population*
Human papillomavirus (HPV)	• Women aged 15–26 years **(CIII)**	• HPV quadravalent vaccine 0.5 mL IM months 0, 2, and 6 **(CIII)**	
HAV	• HAV-susceptible patients who have chronic liver disease, are injection drug users, or are men who have sex with men **(AII)**; certain specialists might delay vaccination until CD4 count >200 cells/μL **(CIII)**	• HAV vaccine 1 mL IM x 2 doses—at 0 and 6–12 months **(AII)** • IgG antibody response should be assessed 1 month after vaccination; non-responders should be revaccinated **(BIII)**	

HBV	• All HIV patients without evidence of prior exposure to HBV should be vaccinated with HBV vaccine, including patients with CD4 count <200 cells/μL **(AII)** <u>Patients with isolated anti-HBc:</u> • Consider screening for HBV DNA before vaccination to rule out occult chronic HBV infection **(BII)** Vaccine non-responders (defined as anti-HBs <10 IU/mL 1 month after a vaccination series): • For patients with low CD4 count at the time of first vaccination series, certain specialists might delay revaccination until after a sustained increase in CD4 count with HAART	• HBV vaccine IM (Engerix-B® 20 μg/mL or Recombivax HB® 10 μg/mL) at 0, 1, and 6 months **(AII)** • Anti-HBs should be obtained one month after completion of the vaccine series **(BIII)** • Revaccinate with a second vaccine series **(BIII)**	• Some experts recommend vaccinating with 40 μg doses of either vaccine **(CIII)** • Some experts recommend revaccinating with 40 μg doses of either vaccine **(CIII)**
Malaria	• Travel to disease-endemic area	• Recommendations are the same for HIV-infected and uninfected patients • One of the following three drugs is usually recommended depending on location: atovaquone/proguanil, doxycycline, or mefloquine (refer to http://www.cdc.gov/malaria/ for the most recent recommendations based on region and drug susceptibility) **(AIII)**	

2.5.2 Discontinuing and Restarting Opportunistic Infection Prophylaxis

Table 14. Criteria for discontinuing and restarting OI prophylaxis for adults and adolescents with HIV

OI	Criteria for discontinuing primary prophylaxis	Criteria for restarting primary prophylaxis	Criteria for discontinuing secondary prophylaxis/chronic maintenance therapy	Criteria for restarting secondary prophylaxis/chronic maintenance
PCP	CD4 count >200 cells/μL for >3 months in response to HAART **(AI)**	CD4 count <200 cells/μL **(AIII)**	• ≥CD4 count increased from <200 cells/μL to >200 cells/μL for 3 months in response to HAART **(BII)** • If PCP is diagnosed when CD4 count >200 cells/μL, prophylaxis should probably be continued for life regardless of CD4 count rise in response to HAART **(CIII)**	CD4 count <200 cells/μL **(AIII)**, or if PCP recurred at a CD4 count >200 cells/μL **(CIII)**
Micro-sporidiosis	Not applicable	Not applicable	• No signs and symptoms of non-ocular microsporidiosis and CD4 count >200 cells/μL for >6 months in response to HAART **(BIII)** • Patients with ocular microsporidiosis should be on therapy indefinitely regardless of CD4 count **(BIII)**	No recommendation
Disseminated MAC	≥CD4 count >100 cells/μL for 3 months in response to HAART **(AI)**	CD4 count <50 cells/μL **(AIII)**	If the following criteria **(BII)** is fulfilled: • ≥Completed 12 months therapy; and • No signs and symptoms of MAC; and • ≥Have sustained (6 months) CD4 count >100 cells/μL in response to HAART	CD4 count <100 cells/μL **(AIII)**
Bartonellosis	Not applicable	Not applicable	If the following criteria is fulfilled **(CIII)**: • Received 3–4 months of treatment • ≥CD4 count >200 cells/μL for 6 months • Certain specialists would only discontinue therapy if *Bartonella* titres have also decreased by fourfold	No recommendation
Mucosal candidiasis	Not applicable	Not applicable	• If used, reasonable to discontinue when CD4 count >200 cells/μL **(CIII)**	No recommendation

Cryptococcal meningitis	Not applicable	Not applicable	If the following criteria is fulfilled **(BII)**: • Completed course of initial therapy • Remain asymptomatic of cryptococcosis • ≥CD4 count 200 cells/μL for >6 months in response to HAART • Certain specialists would perform a lumbar puncture to determine if cerebro-spinal fluid (CSF) is culture- and antigen-negative before stopping therapy **(CIII)**	CD4 count <200 cells/μL **(AIII)**
Histoplasma capsulatum	If used, CD4 count >150 cells/μL for 6 months on HAART **(BIII)**	For patients at high risk for acquiring histoplasmosis, restart at CD4 count 150 cells/μL **(CIII)**	If the following criteria is fulfilled **(AI)**: • ≥Received itraconazole for 1 year • Negative blood cultures • ≥CD4 count >150 cells/μL for 6 months in response to HAART • Serum *Histoplasma* antigen <2 units	≤CD4 count 150 cells/μL **(BIII)**
Coccidioido-mycosis	If used, CD4 count should be >250 cells/μL for 6 months **(CIII)**	If used, restart at CD4 count <250 cells/μL **(BIII)**	• Only for patients with focal coccidioidal pneumonia **(CIII)**: o Clinically responded to 12 months of antifungal therapy o CD4 count >250 cells/μL o Receiving HAART • Suppressive therapy should be continued indefinitely, even with increase in CD4 count on HAART for patients with diffuse pulmonary **(AIII)**, disseminated **(AIII)**, or meningeal diseases **(AII)**	No recommendation
CMV retinitis	Not applicable	Not applicable	• CD4 count >100 cells/μL for >3–6 months in response to HAART **(BII)** • Therapy should be discontinued only after consultating with an ophthalmologist, taking into account magnitude and duration of CD4 count increase, anatomic location of the lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring	CD4 count <100 cells/μL (AIII)

			(BII) • Routine (every 3 months) ophthalmologic follow-up is recommended for early detection of relapse or immune restoration uveitis **(AII)**	
Isospora belli	Not applicable	Not applicable	• Sustained increase in CD4 count to >200 cells/μL for >6 months in response to HAART and without evidence of *I. belli* infection **(BIII)**	No recommendation

2.5.3 Immunizations

Immunizations for HIV-infected adults in the OECS are the same as those for HIV-uninfected adults, with the following exceptions:

- MMR and varicella should not be administered to severely immunosuppressed persons (e.g., CD4 less than 200, or recent Opportunistic Infection), as MMR and varicella are live attenuated vaccines
- Pneumococcal vaccination (polysaccharide PPSV 23-valent vaccine, and/or conjugate PCV 7-valent vaccine) are recommended for HIV-infected adults, given the increased susceptibility of PLHIV to pneumococcal pneumonia.

The following immunization schedule[11] represents the ideal set of immunizations for adult PLHIV. Not all vaccines may be routinely available in the OECS but are included in case the patient is able to obtain vaccines overseas.

Vaccine	**Age group (years)**		
	19–49	**50–64**	**≥65**
Influenza	1 dose annually		
Pneumococcal (polysaccharide) (PPSV)	1 dose		
Hepatitus B	3 doses (0, 1–2, 4–6 mos)		
Tetanus, diphtheria, pertussis (Td/Tdap)	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years		1 dose Td booster every 10 years
HPV	3 doses		
Measles, mumps, rubella (MMR)	***Do not administer to severely immunosuppressed persons***		
Varicella	***Do not administer to severely immunosuppressed persons***		
Hepatitus A	2 doses		
Meningococcal	1 or more doses		

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack of documentation of vaccination or have no evidence of prior infection)

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indicatons)

Adapted from the Advisory Committee on Immunization Practices (ACIP) Adult Immunization Schedule. (www.cdc.gov/vaccines/pubs/ACIP-list.htm).

[11] Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR. 2009 Apr 10; 58(4). Available from: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf.

2.6 ADULT AND ADOLESCENT OPPORTUNISTIC INFECTION TREATMENT

This section provides detailed guidance on the management of selected OIs commonly seen in PLHIV in the Caribbean region. Sources for these recommendations include the website HIV Web Study[12] and the United States CDC's OI guidelines[13], which have been adapted for the Eastern Caribbean region. Not all treatments listed may be available in the OECS but are included in case referral outside the region is an option. For management of OIs not listed below, please consult the original CDC OI guidelines.

Preferred and alternative treatment options are presented; each recommendation includes a rating of its strength as well as the quality of the evidence supporting it, coded as follows.

Strength of recommendation:

A. Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B. Moderate evidence for efficacy, or strong evidence for efficacy but only limited clinical benefit, supports recommendation for use. Should generally be offered.
C. Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of treatment or alternative approaches. Optional.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

Quality of the evidence supporting the recommendation

I. Evidence from at least one properly-designed randomized, controlled trial.
II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one centre), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

2.6.1 Management of the Patient Newly Diagnosed with HIV and an Opportunistic Infection

Many patients with HIV in the Caribbean are diagnosed at a relatively late stage of HIV disease. HIV testing is often prompted by the diagnosis of an associated OI, or an OI might be diagnosed during clinical staging for a recently diagnosed HIV infection. In these situations, initiating

[12] HIV Web Study. Seattle: University of Washington; c2004–13 [updated 7 Mar 2013]. Available from: www.hivwebstudy.org.

[13] Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR. 2009 Apr 10; 58(4). Available from: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf

therapy for the OI is the first priority. HAART is typically started shortly thereafter, although the exact timing of initiation varies depending upon which OI is being treated. This section includes guidance on the timing of HAART initiation for patients presenting with a newly diagnosed HIV infection and selected common OIs. For less common OIs, consult an expert HIV clinician.

2.6.2 Tuberculosis

Patients co-infected with HIV and active TB present complex treatment issues. If possible, consult a clinician who is an expert in managing these diseases. HAART and co-trimoxazole prophylaxis are indicated for all PLHIV with active TB, although anti-TB therapy is the first priority. PLHIV with active TB who are already on HAART should continue it, though the regimen may need to be modified to minimize drug-drug interactions with anti-TB medications (see appendix 4.7). For PLHIV with active TB who are not yet on HAART, **anti-TB therapy should be started first**, and ideally accompanied by drug-susceptibility testing to identify drug-resistant strains of TB. Co-trimoxazole prophylaxis and HAART should be started shortly thereafter (within 2–8 weeks after initiating TB therapy).

2.6.2.1 Anti-TB Therapy for Patients with HIV and TB Disease

- **Drug susceptibility testing.** Patients with multi-drug-resistant tuberculosis (MDR-TB) or extensively drug-resistant tuberculosis (XDR-TB) require different treatment regimens than patients whose strains of TB are susceptible to all commonly available TB drugs. Very high mortality rates, particularly soon after diagnosis, have been documented among HIV-infected patients with co-morbid MDR- or XDR-TB. The WHO recommends that all HIV-infected persons with active TB be tested for drug-resistant TB at the start of anti-TB therapy to reduce the risk of death from unrecognized MDR or XDR-TB. TB drug resistance testing using the GeneXpert system can be obtained in the OECS by sending sputum samples to the Caribbean Epidemiology Centre (CAREC) in Trinidad and Tobago; results are typically returned within two weeks. If national resources do not permit drug-susceptibility testing for all HIV-infected persons with TB, then those with the highest mortality risk (i.e., CD4 counts less than 200 cells/mm^3) and those at highest risk of harboring a drug-resistant strain of TB (e.g., histories of treatment interruption, treatment failure, or relapse) should have priority for drug-susceptibility testing. Although drug-susceptibility testing is important, ***initiation of anti-TB therapy should not be delayed while waiting for results. Empiric treatment with a standard four-drug regimen should begin immediately;*** the regimen can be modified as needed if susceptibility testing reveals drug resistance.
- **Timing for initiating anti-TB therapy.** Four-drug therapy for active TB should be started as soon as possible. It is critically important to coordinate the TB and HIV treatment programs.
- **Anti-TB therapy regimen selection.** For HIV-infected persons with drug-susceptible pulmonary TB, the treatment course consists of a 2-month, four-drug intensive phase of treatment, followed by a 4-month, two-drug continuation phase of treatment (table 15). The four-drug intensive phase regimen consists of isoniazid, rifampicin, pyrazinamide, and ethambutol (commonly abbreviated as HRZE); the two-drug continuation phase typically consists of isoniazid plus rifampicin (commonly abbreviated as HR). The medications should be administered using weight-based dosing (table 16). Daily dosing of TB medication is preferred throughout the entire course of therapy for patients with HIV and TB disease, based on evidence of lower efficacy and higher risk of rifampicin resistance when TB therapy is dosed three times weekly.

- **Duration of anti-TB therapy.** In general, the recommended total duration of anti-TB therapy is 6 months. For some forms of extrapulmonary TB, extension of therapy is recommended, regardless of HIV status.
- **Extrapulmonary TB.** Extrapulmonary TB should be treated with the same regimens as pulmonary TB, but treatment duration should extend to 9–12 months for TB meningitis, and to 9 months for bone or joint involvement. Corticosteroids are also recommended in the setting of TB meningitis and pericarditis, unless drug resistance is suspected.
- **Drug interactions with ARVs**. Standard anti-TB regimens do not have significant interactions with EFV-based HAART regimens. Rifampicin, however, does have significant interactions with NVP and most PIs. Dosing adjustments required for use with these agents are reviewed in detail in appendix 4.8.
- **Drug-resistant TB.** The management of drug-resistant TB is beyond the scope of these guidelines. For information on the programmatic management of drug-resistant TB, particularly MDR-TB or XDR-TB, consult the Caribbean Regional TB Guidelines[14] and seek out expert advice, if available.

2.6.2.2 Co-trimoxazole Prophylaxis for PLHIV with Active TB

Multiple studies have established that co-trimoxazole prophylactic therapy significantly reduces mortality in HIV-infected persons with active TB. PLHIV with active TB, regardless of CD4 count or HIV disease stage, should receive daily co-trimoxazole prophylaxis, initiated as soon as possible following anti-TB therapy initiation. The recommended dose of co-trimoxazole for adults and adolescents is one double-strength tablet or two single-strength tablets once daily—the total daily dose is 800 mg of sulfamethoxazole and 160 mg of trimethoprim. Individuals with a history of severe (grade 4) adverse reaction to co-trimoxazole or other sulfa drugs should not be prescribed co-trimoxazole prophylaxis. Among adults and adolescents with a previous non-severe (grade 3 or less) reaction to co-trimoxazole or other sulfa drugs, desensitization should be attempted, as outlined in appendix 4.11.

[14] Caribbean HIV/AIDS Regional Training Network. Caribbean guidelines for the prevention, treatment, care and control of tuberculosis and TB/HIV. Washington, DC: Pan American Health Organization. Available from: http://www.chartcaribbean.org/images/stories/ctbg_guidelines_2010_web2.pdf.

Table 15. Standard anti-TB regimens for PLHIV with active TB (presumed or known to be drug-susceptible[15]

WHO treatment guidelines for standard regimens for new TB patients	
Intensive phase treatment	**Continuation phase**
2 months of HRZE[a] (H) Isoniazid (R) Rifampicin (Z) Pyrazinamide (E) Ethambutol	4 months of HR (H) Isoniazid (R) Rifampicin
[a] The WHO no longer recommends omitting ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative pulmonary TB or extrapulmonary TB who are know to be HIV-negative. In tuberculous meningitis, ethambutol should be replaced by streptomycin.	

Table 16. Recommended doses of first-line anti-TB drugs for adults[15]

	Recommended dose			
	Daily dosing		3 times per week dosing	
Drug	**Dose and range (mg/kg body weight)**	**Maximum (mg)**	**Dose and range (mg/kg body weight)**	**Maximum (mg)**
Isoniazid	5 (4–6)	300 mg	10 (8–12)	900 mg
Rifampicin	10 (8–12)	600 mg	10 (8–12)	600 mg
Pyrazinamide	25 (20–30)	–	35 (30–40)	–
Ethambutol	15 (15–20)	–	30 (25–35)	–
Streptomycin[b]	15 (12–18)		15 (12–18)	1,000 mg
[b] Patients aged over 60 years may not be able to tolerate more than 500–750 mg daily, so some guidelines recommend reducing the dose for patients in this age group to 10 mg/kg per day. Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily.				

2.6.2.3 HAART for PLHIV with Active TB

All HIV-infected persons with active TB should initiate HAART, regardless of CD4 count or HIV disease stage.

2.6.2.3.1 Timing for Initiating HAART in Patients with Newly Diagnosed TB

HAART should be started as soon as possible (and within the first 8 weeks) after starting anti-TB therapy. Patients should be tolerant of TB therapy before starting HAART, which ideally may be as early as 2 weeks after starting TB therapy. Prompt initiation of HAART is especially important for PLHIV with TB who have very low CD4 counts (less than 50 cells/mm^3).

2.6.2.3.2 Selecting Initial ARV Regimen for Patients with Active TB

A number of critical drug-drug interactions can occur between ARVs and anti-TB agents. Specifically, rifampicin has significant drug-drug interactions with NVP and most PIs, especially rPIs. The drug-drug interactions between EFV and rifampicin are not substantial enough to require replacement or dose-adjustment of either medication. ***These guidelines therefore recommend that HIV-infected persons with active TB receive an EFV-based ARV regimen*** (table 17).

[15] HIV Web Study. Seattle: University of Washington; c2004–13 [updated 7 Mar 2013]. Available from: www.hivwebstudy.org; and World Health Organization. Treatment of tuberculosis guidelines. 4th ed. Geneva: WHO; 2010. Available from: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf.

If EFV is not an option, a NVP- or triple NRTI-based regimen should be used. Although pharmacokinetic data suggest that standard dosing of NVP with rifampicin could result in sub-therapeutic serum NVP levels, this approach appears to be reasonably effective and well tolerated. Use of higher-dose NVP (300 mg twice daily) to compensate for lowered NVP drug levels is associated with an increased risk of NVP hypersensitivity and therefore is not recommended. If NVP is used, the typical NVP 14-day lead-in dosing is not required in the presence of rifampicin.

Although not as potent as traditional NNRTI- or PI-based ARV regimens, a triple NRTI regimen, such as (AZT + 3TC + ABC) or (AZT + 3TC + TDF), avoids problematic drug-drug interactions. A raltegravir-based ARV regimen is ideal, but raltegravir is not widely available in the Caribbean region. For PLHIV with TB who require a PI-based ARV regimen, rifabutin should be substituted for rifampicin, since rifabutin has less severe drug-drug interactions with PIs. If rifabutin is not available and rifampicin must be included in the anti-TB regimen, adjusted doses of RTV-LPV or RTV-boosted SQV may be used (specifically, LPV/RTV 400 mg/400 mg BID; LPV/RTV 800 mg/200 mg BID; or SQV 400 mg BID plus RTV 400 mg BID). These combinations, however, are associated with high levels of drug toxicity and require close clinical and laboratory monitoring.

Table 17. Recommended ARV regimens for PLHIV receiving TB therapy[16]

WHO recommended ARV regimens for persons co-infected with HIV and TB	
Regimen	**Comment**
Preferred regimens	
AZT + (3TC or FTC) + EFV or TDF + (3TC or FTC) + EFV	EFV dosing should not be altered since drug-drug interactions between EFV and rifampicin are not substantial enough to require replacement or dose-adjustment of either medication
Alternative regimens, if EFV contra-indicated	
AZT + (3TC or FTC) + ABC or AZT + (3TC or FTC) + TDF	Not as potent as traditional NNRTI- or PI-based regimens, but avoids problematic drug-drug interactions
2 NRTIs + RTV + PIs	If RTV-boosted PI regimen used, substitute rifabutin for rifampicin, if possible, to reduce drug-drug interactions If PI-based therapy ***must*** be used and rifabutin is not available, options include: • RTV/LPV: 400 mg/400 mg 2 x a day; OR • RTV/LPV: 200 mg/800 mg 2 x a day; OR • RTV/SQV: 400 mg/400 mg 2 x a day For patients receiving rifampicin and rPIs, options listed are associated with high rates of drug toxicity and therefore require close clinical and laboratory monitoring

[16] HIV Web Study. Seattle: University of Washington; c2004–13 [updated 7 Mar 2013]. Available from: www.hivwebstudy.org; and World Health Organization. Treatment of tuberculosis guidelines. 4th ed. Geneva: WHO; 2010. Available from: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf.

2.6.2.4 TB Immune Reconstitution Inflammatory Syndrome

IRIS is a common complication of HAART in patients co-infected with TB. It can be associated with significant morbidity and even mortality if not managed appropriately. TB-IRIS typically manifests as a paradoxical worsening of TB-related signs and symptoms (e.g., night sweats, fevers, lymphadenopathy, pulmonary findings) in the first several weeks after initiating HAART, and can be severe enough to require steroid therapy.

2.6.2.4.1 Risk Factors and Clinical Presentation

Specific risk factors for TB-IRIS include multiple prior OIs; advanced HIV disease and/or low CD4 count at HAART initiation; rapid rise in CD4 count following HAART initiation; and a rapid drop in HIV RNA levels following HAART initiation. Patients with pulmonary TB-IRIS typically present with fever, lymphadenopathy, and respiratory complaints, but other possible clinical manifestations include abdominal lymphadenopathy; cervical lymphadenitis; abscesses; pulmonary effusions and/or pulmonary infiltrates; pericardial effusions; meningitis; brain tuberculomas; and skeletal lesions (usually vertebral). In most cases, TB-IRIS typically manifests within 2 months of HAART initiation.

2.6.2.4.2 Diagnosis

The diagnosis of TB-IRIS is rarely straightforward—no single laboratory test can establish or rule out TB-IRIS. To establish a provisional diagnosis, clinicians rely upon a combination of clinical signs and symptoms, laboratory findings, the likelihood of other conditions, and clinical judgment. Consult an expert in HIV and TB when TB-IRIS is in the differential diagnosis.

2.6.2.4.3 Management

- Consider alternative diagnoses in patients with suspected TB-IRIS, especially if the severity of the condition warrants administering corticosteroids. Ideally, the patient should be evaluated for MDR-TB, as such cases have been identified in patients with TB-IRIS.
- Most cases of TB-IRIS have a self-limited course and will resolve by continuing treatment with little or no change in overall management. Use of NSAID agents may provide adequate relief of symptoms in mild cases, though the effectiveness of this approach remains unproven.
- Patients should continue anti-TB therapy without change unless there is a reason to suspect the current regimen is inadequate (e.g., MDR-TB is suspected, or drug-drug interactions are causing suboptimal serum anti-TB drug levels).
- In nearly all cases, HAART should be continued. Certain circumstances, however, may require temporary interruption, such as when life-threatening complications of IRIS develop (e.g., intracranial pressure in patients with TB meningitis, an expanding abscess compromising a patient's airway).
- Incision and drainage (with stains and cultures) should be performed for localized abscesses.
- Although criteria for initiating corticosteroids remain poorly defined, prednisone is recommended for patients with TB-IRIS who have persistent fever, abscesses, meningitis, or dyspnea. Patients with moderate-to-severe TB-IRIS may receive prednisone dosed at 1.5 mg/kg/day for 2 weeks, followed by a taper of 0.75 mg/kg/day over 2 additional weeks. Some patients, particularly those with very high mycobacterial loads or severe clinical deterioration, may require prolonged courses of corticosteroids. Patients receiving corticosteroids for TB-IRIS should be monitored carefully for response to therapy. If the

patient's clinical condition does not improve, consider an alternative diagnosis and possible termination of corticosteroids, since administering corticosteroids to a patient with a non-tuberculous OI could result in further clinical deterioration.

2.6.3 Mycobacterium-Avium Complex

2.6.3.1 Clinical Presentation and Diagnosis

Disseminated MAC is commonly found in patients with advanced HIV disease and very low CD4 counts (<50 cells/mm^3). Typical signs and symptoms include fever, night sweats, fatigue, weight loss, and abdominal pain from extensive mesenteric lymphadenopathy, which is sometimes accompanied by hepatosplenomegaly and/or diarrhoea. Laboratory findings may include anaemia, increased alkaline phosphatase (often with normal bilirubin and transaminases levels), and increased serum lactate dehydrogenase (LDH) levels. Definitive diagnosis is made by blood culture or tissue culture (e.g., lymph node biopsy); a positive stool or respiratory tract culture does NOT establish the diagnosis of disseminated MAC, however, as the organism can colonize these sites without necessarily causing disease.

2.6.3.2 Treatment

Most cases of disseminated MAC can be successfully treated, though therapy can be complicated by drug-drug interactions and by IRIS.

- **Acute therapy:** The ideal antibiotic regimen consists of ethambutol plus a macrolide, such as azithromycin or clarithromycin, with or without rifabutin.
  - **Ethambutol** is dosed at 15 mg/kg orally daily.
  - **Azithromycin** is dosed at 500 mg orally daily. While clarithromycin has had more clinical trials (dosed at 500 mg orally twice daily), azithromycin has fewer problematic drug-drug interactions with ARVs and is therefore recommended over clarithromycin, where available. Most patients with MAC not yet on HAART will be starting HAART in the near future (while still receiving therapy for MAC). If azithromycin cannot be used, clarithromycin dosed at 500 mg orally twice daily can be used instead.
  - **Rifabutin**, where available, may be added to the MAC regimen for patients with severe disease, dosed at 300 mg orally daily. Data from clinical trials are inconsistent regarding the benefits of including rifabutin.
- **Maintenance therapy:** Maintenance therapy (also known as secondary prophylaxis) to prevent recurrence of disseminated MAC consists of the same acute therapy regimen, given at the same doses. Maintenance therapy may be discontinued in patients on HAART who have a sustained (greater than 6 months) increase in CD4 count to >100 cells/mm^3, so long as they have completed 12 months of MAC therapy and have no ongoing symptoms or signs attributable to MAC.
- **HAART:** Patients already receiving HAART who develop disseminated MAC should continue their treatment regimen. In patients who have not yet begun HAART, disseminated MAC is an indication for initiation of HAART. The optimal timing of initiation for patients with acute disseminated MAC has not been established, although the available evidence suggests that worse outcomes are associated with delaying HAART. It is recommended that HAART should be initated within two weeks of MAC therapy initiation.

2.6.3.3 Mycobacterium-Avium Complex Immune Reconstitution Inflammatory Syndrome

MAC IRIS usually manifests as focal inflammatory lymphadenitis, osteomyelitis, pulmonary infection, or gastrointestinal disease. Biopsies typically show a marked localized inflammatory response with few organisms. The management of MAC IRIS is identical to that of TB-IRIS (see section 2.6.2.4). As with TB-IRIS, the use of corticosteroids is frequently indicated to control excessive inflammation, but evidence regarding the appropriate dosing and timing of steroids is lacking. For patients with moderate-to-severe MAC IRIS, prednisone dosed at 40–60 mg per day for 4–6 weeks is recommended, followed by a gradual taper over 2–4 weeks. Dose modification may be required if the taper is poorly tolerated due to a recurrence of IRIS symptoms.

2.6.4 Toxoplasmic Encephalitis

2.6.4.1 Clinical Manifestations and Diagnosis of Toxoplasmic Encephalitis

Toxoplasmic encephalitis (TE) is associated with advanced HIV. Most patients with TE and HIV will have a CD4 count less than 100 cells/mm^3. Other common signs and symptoms include headache, confusion, fever, and focal neurologic deficits. Severe TE can be associated with seizures and/or mental status changes, nausea, and vomiting.

The contrast CT scan of a TE patient's brain typically shows multiple ring-enhancing lesions, often involving the basal ganglia. In cases where the CT scan shows a solitary lesion, magnetic resonance imaging (MRI)—if available—should be performed because it is more sensitive. In the absence of contra-indications, a lumbar puncture should be done to help rule out other diseases.

2.6.4.2 Clinical Management of Suspected Toxoplasmic Encephalitis

The diagnosis of TE often is made based on a high index of suspicion and a favorable response to empiric therapy. A high index of suspicion would include compatible signs and symptoms, a positive IgG serology for *T. gondii*, non-use of *Toxoplasma* prophylaxis, and a CT or MRI showing multiple ring-enhancing brain lesions. Suspected patients should be empirically treated for TE; a positive response to therapy serves as a functional confirmation of the diagnosis (see below). Alternate diagnoses (such as CNS lymphoma) should be considered in patients who are seronegative for *T. gondii*, are taking effective TE prophylaxis, and have only a solitary lesion on MRI.

2.6.4.3 Initial Therapy for Toxoplasma Encephalitis

PLHIV for whom empiric TE therapy is indicated should be started immediately on a regimen of co-trimoxazole (5 mg/kg trimethoprim-sulfamethoxazole [TMP] and 25 mg/kg sulfamethoxazole [SMX]) intravenously (IV) or orally twice daily. The initial therapy's duration is at least 6 weeks, and should be prolonged if clinical or radiologic disease is extensive or if the patient's response is incomplete at 6 weeks. The use of adjunctive corticosteroids should generally be limited to patients who deteriorate clinically despite therapy or whose initial imaging shows evidence of a mass effect or midline shift. Historically, sulfadiazine/pyrimethamine/folinic acid has been used as first-line therapy for TE, but recent data suggest that co-trimoxazole is equally effective, less expensive, and may be associated with less toxicity.

2.6.4.4 Monitoring Response to Initial Therapy

Most patients with TE respond to initial therapy with clinical and radiographic improvement. Absence of any improvement by day 14 should prompt a workup for other diagnoses, such as primary CNS lymphoma. Patients who display clinical and/or radiographic improvement on initial therapy should continue acute treatment for a minimum of 6 weeks before switching to maintenance therapy. Where available, follow-up neuroimaging should be performed to document the resolution of active TE prior to switching to maintenance therapy.

2.6.4.5 Maintenance Therapy for Toxoplasmic Encephalitis

Maintenance therapy for TE consists of the same co-trimoxazole (5 mg/kg TMP and 25 mg/kg SMX) used in acute therapy, but administered orally just once daily. Maintenance therapy can be discontinued for patients who have completed initial TE therapy, have had no signs or symptoms suggestive of active TE, and have experienced a sustained (>6 months) increase in CD4 count to more than 200 cells/mm^3on HAART.

2.6.5 Cryptococcal Meningitis

2.6.5.1 Managing Cryptococcal Meningitis

The management of cryptococcal meningitis (as well as disseminated non-meningeal cryptococcal disease in HIV-infected individuals) consists of an initial 2-week induction phase, followed by an 8-week consolidation phase, and then a long-term maintenance phase. Increased intracranial pressure (ICP), if present, must also be carefully managed (see below).

2.6.5.2 Managing Increased Intracranial Pressure

Elevated ICP (defined as opening pressure greater than 200 mm H_20) in the setting of cryptococcal meningitis is common and is associated with significant morbidity and mortality. Every patient with suspected cryptococcal meningitis should have the opening pressure measured during lumbar puncture. Elevated ICP should be aggressively managed in the following ways.

- Patients with an opening pressure >250 mm H_20 on initial lumbar puncture should have sufficient CSF removed to achieve a closing pressure that is either <200 mm H_20 or <50% of the initial opening pressure.
- Lumbar punctures should be repeated daily, with removal of 20 to 30 cc of CSF with each procedure, until the opening pressure remains <200 cm H_20 for three consecutive days.
- If the elevated ICP persists after several daily lumbar punctures, insertion of a lumbar drain may be considered.
- Other approaches for reducing ICP, such as systemic acetazolamide, mannitol, or corticosteroids are not recommended.

2.6.5.3 Induction Therapy

The optimal induction therapy for cryptococcal meningitis is 2 weeks of IV amphotericin B (0.7–1.0 mg/kg/day) plus oral flucytosine (100 mg/kg/day, divided in four doses). Oral fluconazole (800 mg/day) should be substituted for flucytosine if flucytosine is not available. If amphotericin is unavailable or contra-indicated, then high-dose fluconazole (1,200 mg/day) plus flucytosine

(100 mg/kg/day divided in four doses) is the recommended therapy. In settings where neither amphotericin B nor flucytosine is available, high-dose oral fluconazole (1,200 mg/day) is recommended. If amphotericin B is administered, the patient should be closely monitored for potentially serious hypokalemia and nephrotoxicity, which are associated with this agent.

2.6.5.4 Consolidation and Maintenance Phases

After the initial 2-week induction phase, the optimal consolidation phase of treatment is an 8-week course of oral fluconazole (400–800 mg/day for adults; 6–12 mg/kg/day for children). After 8 weeks, patients should be switched to low-dose fluconazole (200 mg/day for adults; 6 mg/kg/day for children) to begin the long-term maintenance phase.

2.6.5.5 Treatment of Cryptococcal Infection without Evidence of Cryptococcal Meningitis

The optimal anti-fungal regimen in patients with isolated serum cryptococcal antigen (CrAG) positivity (where active cryptococcal meningitis has been excluded) remains to be determined. In this situation, the WHO recommends treating with fluconazole (800 mg/day) for 2 weeks followed by a reduced dose (400 mg/day) for 8 weeks.

2.6.5.6 HAART in Patients with Cryptococcal Meningitis

HAART is indicated for patients with cryptococcal meningitis, but immediate initiation of HAART in the context of acute cryptococcal meningitis has been associated with a higher risk of life-threatening IRIS. Therefore, based on limited evidence from clinical trials, ***HAART should be deferred until a sustained clinical response to antifungal therapy is evident, and after a minimum of 2–4 weeks following initiation of cryptococcal therapy with an amphotericin B-containing regimen. If the patient is receiving high-dose fluconazole monotherapy, HAART should be deferred until at least 4–6 weeks of treatment have been completed.***

2.6.5.7 Discontinuation of Maintenance Treatment

If the patient is clinically stable, has adhered to HAART and antifungal maintenance treatment for at least 1 year, and shows evidence of immune reconstitution, then maintenance treatment for cryptococcal meningitis can be discontinued. If viral load testing is not available, then 'immune reconstitution' in this context is defined as a CD4 count ≥200 cells/mm^3 measured twice at least 6 months apart. If viral load testing is available, immune reconstitution can be defined as a CD4 count ≥100 cells/mm^3, measured twice at least 6 months apart AND an undetectable HIV RNA level. Maintenance treatment should not be discontinued in children <2 years of age. Furthermore, maintenance therapy should be restarted if the CD4 count drops to <100 cells/mm^3 in adults or <25% (or 750 cells/mm^3) in children, or if a WHO stage 4 clinical event occurs, regardless of patient age or CD4 count.

2.6.6 *Pneumocystis jiroveci* Pneumonia (PCP)

2.6.6.1 Clinical Presentation

Most PLHIV who develop PCP have a CD4 count <200 cells/mm^3 and are not on effective PCP prophylaxis. Typical initial symptoms include fever, fatigue, and weight loss, followed by respiratory symptoms, such as a nonproductive cough, dyspnea on exertion, and shortness of

breath—sometimes severe. Rales may or may not be heard on lung auscultation. Extrapulmonary disease is rare.

2.6.6.2 Diagnosis

Typical chest radiographic features include bilateral, perihilar, interstitial infiltrates that appear as finely granular, reticular, or ground glass opacities. Many patients, however, will have a normal chest radiograph, particularly early on. Atypical chest radiographic findings include upper lobe predominance, cystic lesions, and/or focal infiltrates. Suspicion for PCP increases in patients who have abnormal oxygen saturation, especially with exertion. An arterial blood gas (ABG) test helps to evaluate the severity of the disease and to determine whether corticosteroids are indicated (paO_2 <70 mm Hg or a calculated p(A-a O_2) gradient >35—see table 19 for how to calculate the p(A-a O_2) gradient). An elevated serum LDH level suggests, but does not confirm, the diagnosis. A definitive diagnosis of PCP requires detecting the *Pneumocystis jiroveci* organism, typically by staining an induced sputum sample. Where available, bronchoscopy with bronchoalveolar lavage (BAL) can be used to confirm the diagnosis if induced sputum staining is negative. Though PCP can be treated empirically, confirmation of the diagnosis is preferred because other conditions—like TB—can mimic PCP and could be exacerbated by steroids, which are often indicated in PCP therapy.

2.6.6.3 Treatment

Outpatient management is reasonable for patients with mild-to-moderate PCP who appear non-toxic, have a documented paO_2 >70 mm Hg, and a calculated p(A-a O_2) gradient <35. Trimethoprim-sulfamethoxazole (co-trimoxazole) is the preferred first-line oral agent (see table 18). Trimethoprim plus dapsone is an alternative oral regimen for patients who cannot take sulfamethoxazole. Other oral alternatives include clindamycin (Cleocin) plus primaquine, or atovaquone, though this drug is less effective. IV trimethoprim-sulfamethoxazole is indicated for patients with more severe PCP and those who cannot take or absorb oral medications. Alternative IV regimens include IV pentamidine or IV clindamycin plus oral primaquine.

Table 18. Initial therapy for PCP

Therapy	Preferred therapy	Alternative choices
Oral therapy	Co-trimoxazole: 15 mg/kg/d (based on trimethoprim component) PO in 3–4 divided doses x 21D (typically 2 DS tablets 3 x a day [TID] to 4 x a day [QID])	Trimethoprim: 15 mg/kg/D PO in 3–4 divided doses; PLUS Dapsone: 100 mg PO QD x 21D
		Clindamycin: 450 mg PO Q6H x 21D; PLUS Primaquine: 15 mg base PO QD x 21D
		Atovaquone Suspension: 750 mg PO BID x 21D
IV therapy	Co-trimoxazole: 15 mg/kg/d (based on TMP component) IV divided Q6H to Q8H x 21D	Clindamycin: 600 mg IV Q6H x 21D; PLUS Primaquine: 15 mg base PO QD x 21D
		Petamidine: 3–4 mg/kg IV QD x 21D
		Trimetrexate: 45 mg/m^2 (1.2 mg/kg) IV QD x 21D; PLUS Leucovorin: 20 mg/m^2 IV (or PO) Q6H x 24D
Adjunctive therapy (if pO_2 < 70 mm Hg) and within 72 hours of starting therapy	Prednisone: 40 mg PO BID x 5D, then 40 mg QD x 5D, then 20 mg QD x 11D	Methylprednisolone: 30 mg IV BID x 5D;, then 30 mg IV QD x 5D;, then 15 mg IV QD x 11D

Source: HIV Web Study (http://depts.washington.edu/hivaids/oit/case2/discussion.html); see works cited.

2.6.6.4 HAART for Patients with Pneumocystis jiroveci Pneumonia

PCP is an indication for HAART, regardless of CD4 count. The best available evidence suggests that HAART should be initiated within 14 days of anti-PCP therapy, as deferral of HAART until later has been associated with worse clinical outcomes. Simultaneous initiation of PCP therapy and HAART is not recommended.

2.6.6.5 Corticosteroids for Pneumocystis jiroveci Pneumonia

Corticosteroids are indicated in patients who have a paO_2 <70 mm Hg or a calculated $p(A\text{-}a\ O_2)$ gradient >35 (table 19); these patients should receive a 21-day course of oral prednisone or intravenous (IV) prednisolone (see table 18). Ideally, patients should begin corticosteroids at the time they start taking antimicrobial therapy for PCP, even if the diagnosis has not been confirmed. If a different diagnosis is made, steroid therapy should be discontinued.

Table 19. How to calculate the alveolar-arterial oxygen difference (the 'A-a gradient')

Alveolar-arterial oxygen difference
$p(A–aO_2)$ difference = pAO_2 (calculated below) – paO_2 (from ABG)
$pAO_2 = 150 – (pCO_2$ [from ABG]/0.8)

Source: HIV Web Study (http://depts.washington.edu/hivaids/oit/case2/discussion.html); see works cited.

2.6.6.6 Secondary Prophylaxis to Prevent Recurrence of Disease

Patients who complete the initial 21-day course of therapy for PCP should receive secondary prophylaxis to prevent recurrence. The recommended prophylactic regimens (see table 20) are the same as those used for primary prophylaxis.

Table 20. Secondary PCP prophylaxis regimens

Preferred therapy	Alternative choices
Co-trimoxazole: 1 DS qd or Co-trimoxazole: 1 SS qd	Dapsone: 50 mg BID; OR Dapsone: 100 mg QD
	Dapsone: 50 mg QD PLUS Pyrimethamine: 50 mg QW; PLUS Leucovorin: 25 mg QW
	Pentamidine (aerosolized): 300 mg QM
	Atovaquone suspension: 1,500 mg QD
	Co-trimoxazole: 1 DS 3 x/week

Source: HIV Web Study (http://depts.washington.edu/hivaids/oit/case2/discussion.html); see works cited.

2.6.6.7 Discontinuation of Secondary Prophylaxis

Patients who have responded to HAART with a sustained (at least 3 months) rise in their CD4 count to >200 cells/mm^3 may safely discontinue secondary PCP prophylaxis. Patients who have discontinued secondary prophylaxis and whose CD4 count subsequently decreases to <200 cells/mm^3 should restart prophylaxis.

2.6.7 Other Opportunistic Infections: Treatment Summary Tables

Sources for these recommendations include the website HIV Web Study[17] and the United States CDC OI guidelines[18], which have been adapted for the Eastern Caribbean region. Not all treatments listed may be available in the OECS but are included in case referral outside the region is an option. For management of OIs not listed below, please consult the CDC OI Guidelines.

Preferred and alternative treatment options are presented; each recommendation includes a rating of its strength as well as the quality of the evidence supporting it, coded as follows.

Strength of recommendation:

A. Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B. Moderate evidence for efficacy, or strong evidence for efficacy but only limited clinical benefit, supports recommendation for use. Should generally be offered.
C. Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of treatment or alternative approaches. Optional.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

Quality of the evidence supporting the recommendation

I. Evidence from at least one properly-designed randomized, controlled trial.
II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one centre), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

[17] HIV Web Study. Seattle: University of Washington; c2004–13 [updated 7 Mar 2013]. Available from: www.hivwebstudy.org.

[18] Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR. 2009 Apr 10; 58(4). Available from: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf.

Table 21. Acute and chronic maintenance (secondary prophylaxis) therapy of HIV-associated opportunistic infections in adults and adolescents

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
PCP	Preferred acute therapy for moderate-to-severe PCP: • Co-trimoxazole (15–20 mg TMP and 75–100 mg SMX/kg/day IV administered Q6H or Q8H) **(AI)**; may switch to PO after clinical improvement **(AI)** • Duration of therapy: 21 days **(AII)** Preferred acute therapy for mild-to-moderate PCP: • Same QD dose of co-trimoxazole as above, administered PO in 3 divided doses **(AI)**; OR • Co-trimoxazole (160 mg/800 mg or DS 2 tablets) TID **(AI)** • Duration of therapy: 21 days **(AII)** Preferred chronic maintenance therapy: • Co-trimoxazole (160 mg/800 mg or DS tablet PO QD) **(AI)**; OR • Co-trimoxazole (80 mg/400 mg or SS tablet PO QD) **(AI)**	Alternative acute therapy for moderate-to-severe PCP: • Pentamidine (4 mg/kg IV QD infused over ≥60 minutes) **(AI)**; certain specialists reduce dose to 3 mg/kg IV QD because of toxicities **(BI)**; OR • Primaquine (15–30 mg [base] PO QD) + clindamycin (600–900 mg IV Q6H to Q8H) or clindamycin (300–450 mg PO Q6H to Q8H) **(AI)** Alternative acute therapy for mild-to-moderate PCP: • Dapsone (100 mg PO QD) and TMP (15 mg/kg/day PO [3 divided dose]) **(BI)**; OR • Primaquine (15–30 mg [base] PO QD) + clindamycin (300–450 mg PO Q6H to Q8H) **(BI)**; OR • Atovaquone (750 mg PO BID with food) **(BI)** Alternative chronic maintenance therapy: • Co-trimoxazole (160 mg/800 mg or DS PO 3 x week [TIW]) **(BI)**; OR • Dapsone (50 mg PO BID or 100 mg PO QD) **(BI)**; OR • Dapsone (50 mg PO QD) + pyrimethamine (50 mg PO QW) + leucovorin (25 mg PO QW) **(BI)**; OR • Dapsone (200 mg PO) + pyrimethamine (75 mg PO) + leucovorin (25 mg PO QW) **(BI)**; OR • Atovaquone (1,500 mg PO QD) **(BI)**; OR • Atovaquone (1,500 mg) + pyrimethamine (25 mg) + leucovorin (10 mg) PO QD **(CIII)**	Indications for corticosteroids **(AI)**: • PaO_2 <70 mmHg at room air or alveolar-arterial O_2 gradient >35 mmHg • Prednisone doses (beginning as early as possible and within 72 hours of PCP therapy) **(AI)**: o Days 1–5: 40 mg PO BID o Days 6–10: 40 mg PO QD o Days 11–21: 20 mg PO QD • IV methylprednisolone can be administered as 75% of prednisone dose • Benefits of corticosteroid if started after 72 hours of treatment is unknown, but a majority of clinicians will use it in patients with moderate-to-severe PCP **(BIII)** • Whenever possible, patients should be tested for G6PD deficiency before use of primaquine

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
TE	Preferred acute therapy: • Co-trimoxazole (5 mg/kg TMP and 25 mg/kg SMX) IV or PO BID **(BI)** Duration for acute therapy: • At least 6 weeks **(BII)**; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks Preferred chronic maintenance therapy/secondary prophylaxis: • Co-trimoxazole (5 mg of TMP/kg/day and 25 mg of SMP/kg/day) **(BI)**	Alternative acute therapy regimens: • Pyrimethamine 200 mg PO x 1, then 50 mg (<60 kg) to 75 mg (≥60 kg) PO QD; PLUS sulfadiazine 1,000 mg (<60 kg) to 1,500 mg (≥60 kg) PO Q6H; PLUS leucovorin 10–25 mg PO QD (can increase 50 mg) **(AI)**; or • Pyrimethamine (leucovorin)[a]; PLUS clindamycin 600 mg IV or PO Q6H **(AI)**; or • Atovaquone 1,500 mg PO BID with food (or nutritional supplement); PLUS pyrimethamine (leucovorin)* **(BII)**; or • Atovaquone 1,500 mg PO BID with food (or nutritional supplement); PLUS sulfadiazine 1,000–1,500 mg PO Q6H **(BII)**; or • Atovaquone 1,500 mg PO BID with food (**BII)**; or • Pyrimethamine (leucovorin)[a] PLUS azithromycin 900–1,200 mg PO QD **(BII)** Alternative chronic maintenance therapy/secondary prophylaxis: • Pyrimethamine 25–50 mg PO QD; PLUS sulfadiazine 2,000–4,000 mg PO QD (in 2–4 divided doses); PLUS leucovorin 10–25 mg PO QD **(AI)** • Clindamycin 600 mg PO every 8 hours; PLUS pyrimethamine 25–50 mg PO QD; PLUS leucovorin 10–25 PO QD (BI) (should add additional agent to prevent PCP) **(AII)**; or • Atovaquone 750 mg PO every 6–12 hours +/- (pyrimethamine 25 mg PO QD PLUS leucovorin 10 mg PO QD; or sulfadiazine 2,000–4,000 mg PO) QD **(BII)**	• Adjunctive corticosteroids (e.g., dexamethasone) should be administered when clinically indicated only for treatment of mass effect attributed to focal lesions or associated oedema (**BIII)**; discontinue as soon as clinically feasible • Anti-convulsants should be administered to patients with a history of seizures **(AIII)** and continued through the acute treatment, but should not be used prophylactically **(DIII)**

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
Cryptosporidiosis	Preferred therapy: • Initiate or optimize HAART for immune restoration **(AII)** • Symptomatic treatment of diarrhoea **(AIII)** • Aggressive oral or IV rehydration and replacement of electrolyte loss **(AIII)**	Alternative therapy for cryptosporidiosis: • A trial of nitazoxanide 500–1,000 mg PO BID with food for 14 days **(CIII)**; PLUS optimized HAART, symptomatic treatment and rehydration and electrolyte replacement	Use of anti-motility agents such as loperamide or tincture of opium might palliate symptoms **(BIII)**
Microsporidiosis	Initiate or optimize HAART; immune restoration to CD4 count >100 cells/μL is associated with resolution of symptoms of enteric microsporidiosis **(AII)** Preferred therapy for gastrointestinal infections caused by *Enterocytozoon bienuesi*: • Fumagillin 20 mg PO TID **(BII)** • TNP-470 (a synthetic analog of fumagillin) might also be effective **(BIII)** Preferred therapy for disseminated (not ocular) and intestinal infection attributed to microsporidia other than *E. bienuesi* and *Vittaforma corneae*: • Albendazole 400 mg PO BID **(AII)**; continue until CD4 count >200 cells/μL for >6 months after initiation of HAART **(BIII)**	Alternative therapy for gastrointestinal infections caused by *E. bienuesi*: • Nitazoxanide 1,000 mg BID with food for 60 days—effects might be minimal for patients with low CD4 count **(CIII)** Alternative therapy for disseminated disease: • Itraconazole 400 mg PO QD PLUS albendazole 400 mg PO BID for disseminated disease attributed to *Trachipleistophora* or *Anncaliia* **(CIII)**	• Severe dehydration, malnutrition, and wasting should be managed by fluid support and nutritional supplement **(AIII)** • Antimotility agents can be used for diarrhoea control if required **(BIII)**

MTB[19]	Empiric treatment should be initiated and continued in PLHIV with suspected TB until all diagnostic work-up is complete **(AII)**
	
	Treatment of drug-susceptible active TB disease:
	• Initial phase (2 months) **(AI)**:
	  ○ Isoniazid†; PLUS rifampicin or rifabutin; PLUS pyrazinamide; PLUS ethambutol; if drug susceptibility report
		Treatment for drug-resistant active TB:
		• Resistant to isoniazid:
		  ○ Discontinue isoniazid (and streptomycin, if used)
		  ○ Rifampicin or rifabutin; PLUS ethambutol; PLUS pyrazinamide for 6 months **(BII)**; or
		  ○ Rifampicin or rifabutin; PLUS ethambutol for 12 months (preferably with pyrazinamide during at
			• Directly observed therapy (DOT) is recommended for all HIV patients undergoing treatment for active TB **(AII)**
			• Initial phase of TB treatment may also be administered 5 days weekly (40 doses) **(AII)**, or tiw (24 doses) **(BII)** by DOT
			• For CNS disease, corticosteroid should be initiated as early as possible and continued for 6–8 weeks **(AII)**

[19] Caribbean HIV/AIDS Regional Training Network. Caribbean guidelines for the prevention, treatment, care and control of tuberculosis and TB/HIV. Washington, DC: Pan American Health Organization. Available from: http://www.chartcaribbean.org/images/stories/ctbg_guidelines_2010_web2.pdf.

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	shows sensitivity to isoniazid PLUS rifampicin and pyrazinamide, then ethambutol may be discontinued before 2 months of treatment is completed **(AI)** • Continuation phase: ○ Isoniazid PLUS rifampicin or rifabutin QD or TIW **(AIII)**; or BIW (if CD4 count >100/μL) **(CIII)** Duration of therapy: • Pulmonary TB: 6 months **(AI)** • Pulmonary TB with cavitary lung lesions and a positive culture after 2 months of TB treatment **(AII)**: 9 months • Extrapulmonary TB with CNS, bone, or joint infections: 9–12 months **(AII)** • Extrapulmonary TB in other sites: 6–9 months **(AII)**	least the first 2 months) **(BII)** ○ A fluoroquinolone may strengthen the regimen for patients with extensive disease **(CIII)** • Resistant to rifamycins: ○ Isoniazid; PLUS pyrazinamide; PLUS ethambutol; PLUS a fluoroquinolone for 2 months; followed by 10 to16 additional months with isoniazid; PLUS ethambutol; PLUS fluoroquinolone **(BIII)** ○ Amikacin or capreomycin may be included in the first 2–3 months for patients with rifamycin resistance and severe disease **(CIII)** • MDR-TB (isoniazid and rifampicin resistant) or XDR-TB (isoniazid PLUS rifampicin, fluoroquinolone, and at least one injectable agent): ○ Therapy should be individualized based on resistance patterns and in close consultation with an experienced specialist **(AIII)**	• Rifampicin is not recommended for patients receiving PIs because of its induction of PI metabolism **(EII)** • Rifabutin is a less potent CYP 3A4 inducer than rifampicin and is preferred in patients receiving PIs • Rifapentine administered once weekly can result in resistance in HIV-infected patients and is not recommended **(EI)** • Therapeutic drug monitoring should be considered in patients receiving a rifamycin and potentially interacting HAART • Paradoxical reaction that is not severe may be treated with NSAIDs without a change in anti-TB or HAART (**BIII**) • For severe paradoxical reaction, consider prednisone or methylprednisolone 1 mg/kg of body weight, gradually reduced after 1–2 weeks **(BIII)**
Disseminated MAC	Preferred therapy for disseminated MAC: • At least two drugs as initial therapy: clarithromycin 500 mg PO BID **(AI)** PLUS ethambutol 15 mg/kg PO QD **(AI)** • Addition of rifabutin may also be considered: rifabutin 300 mg PO QD (dosage adjusted may be necessary based on drug-drug interactions) **(CI)** Chronic maintenance therapy (secondary prophylaxis): • Same as treatment drugs and regimens	Alternative therapy for disseminated MAC (e.g., when drug interactions or intolerance precludes the use of clarithromycin): • Azithromycin 500–600 mg + ethambutol 15 mg/kg PO QD **(AII)** • Consider adding a third or fourth drug for patients with advanced immunosuppression (CD4 count <50 cells/μL), high mycobacterial loads (>2 log CFU/mL of blood), or in the absence of effective HAART **(CIII)**: • Amikacin 10–15 mg/kg IV	• Testing a patient's susceptibility to clarithromycin and azithromycin is recommended **(BIII)** • In HAART-naïve patients, consider withholding HAART initiation until after 2 weeks of MAC treatment to lessen drug interactions, reduce pill burden, and potentially lower the occurrence of IRIS **(CIII)** • NSAIDs may be used for patients who experience moderate-to-severe symptoms attributed to HAART-associated IRIS **(CIII)** • If IRIS symptoms persist,

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	• Duration: Lifelong therapy **(AII)**, except in patients with sustained immune recovery on HAART **(BII)**	QD (split into two doses per day), not to exceed 1,500 mg total per day; or ○ Streptomycin 1 gm IV or IM QD; OR ○ Ciprofloxacin 500–750 mg PO BID; OR ○ Levofloxacin 500 mg PO daily; OR ○ Moxifloxacin 400 mg PO QD	short-term (4–8 weeks) of systemic corticosteroid (equivalent to 20–40 mg of prednisone) can be used **(CIII)**
Bacterial respiratory diseases	Preferred empiric outpatient therapy (oral): • A beta-lactam PLUS a macrolide (azithromycin or clarithromycin) **(AII)** • Preferred beta-lactams: High-dose amoxicillin or amoxicillin/clavulanate • Alternative beta-lactams: Cefpodoxime or cefuroxime Preferred empiric therapy for non-ICU in-patient: • A beta-lactam (IV) PLUS a macrolide **(AII)** • Preferred beta-lactams: Cefotaxime, ceftriaxone, or ampicillin-sulbactam Preferred empiric ICU in-patient therapy: • A beta-lactam (IV) PLUS azithromycin IV **(AII)** or an IV respiratory fluoroquinolone (levofloxacin 750 mg or moxifloxacin) **(AII)** • Preferred beta-lactams: Cefotaxime, ceftriaxone, or ampicillin-sulbactam Preferred empiric *Pseudomonas* therapy (if risks present): • An anti-pneumococcal, anti-pseudomonal beta-lactam PLUS either ciprofloxacin or levofloxacin 750 mg/day **(BIII)** • Preferred beta-lactams: Piperacillin-tazobactam, cefepime, imipenem, or	Alternative empiric outpatient therapy (oral): • A beta-lactam PLUS doxycycline **(CIII)** • For penicillin-allergic patients or those with beta-lactam use in prior 3 months: A respiratory fluoroquinolone (levofloxacin 750 mg/day, gemifloxacin, or moxifloxacin) **(AII)** Alternative empiric therapy for non-ICU in-patient: • A beta-lactam (IV) PLUS doxycycline **(CIII)** • For penicillin-allergic patients or those with beta-lactam use in prior 3 months: An IV respiratory fluoroquinolone (levofloxacin 750 mg or moxifloxacin) **(AII)** Alternative empiric ICU in-patient therapy: • For penicillin-allergic patients or those with beta-lactam use in prior 3 months: Aztreonam IV PLUS an IV respiratory fluoroquinolone **(BIII)** Alternative empiric *Pseudomonas* therapy: • An anti-pneumococcal, anti-pseudomonal beta-lactam PLUS an aminoglycoside PLUS azithromycin **(BIII)** • Above beta-lactam PLUS an	• Patients receiving macrolide for MAC prophylaxis should not receive macrolide monotherapy for empiric treatment of bacterial pneumonia • Fluoroquinolones should be used with caution in patients where TB is suspected but is not being treated • Empiric therapy with a macrolide alone is not routinely recommended, because of increasing pneumococcal resistance **(DIII)** • Once the pathogen has been identified by a reliable microbiologic method, antibiotics should be directed at the pathogen **(BIII)** • For patients begun on IV antibiotic therapy, switching to PO should be considered when patient is clinically improved and able to tolerate oral medications • Chemoprophylaxis may be considered for patients with frequent recurrences of serious bacterial respiratory infections **(CIII)** • Clinicians should be cautious of using antibiotics to prevent recurrences because of the potential for drug resistance and toxicities

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	meropenem Preferred empiric methicillin-resistant *Staphylococcus aureus* (if risks present): • Add vancomycin (possibly PLUS clindamycin) or linezolid alone to above **(BIII)**	aminoglycoside PLUS an anti-pneumococcal fluoroquinolone* **(BIII)** • For penicillin-allergic patients or those with beta-lactam use in prior 3 months: Replace the beta-lactam with aztreonam **(BIII)**	
Bacterial enteric infections: Salmonellosis	Most specialists recommend treatment for all HIV-infected patients with salmonellosis due to the high risk of bacteremia in these patients **(BIII)** Preferred therapy for salmonellosis with or without symptomatic bacteremia: • Ciprofloxacin 500–750 mg PO BID (or 400 mg IV BID) **(AIII)** Duration for mild gastroenteritis with or without bacteremia: • If CD4 count ≥200/μL: 7–14 days **(BIII)** • If CD4 count <200/μL: 2–6 weeks **(CIII)** • If recurrent symptomatic septicaemia, may need 6 months or more **(CIII)**	Alternative therapy for salmonellosis with or without symptomatic bacteremia: • Levofloxacin 750 mg; or moxifloxacin **(BIII)** • Co-trimoxazole PO or IV, if susceptible **(BIII)** • Third generation cephalosporin, such as ceftriaxone (IV) or cefotaxime (IV), if susceptible **(BIII)**	The role of long-term secondary prophylaxis for patients with recurrent bacteremia is not well established; the benefit must be weighed against the risks of long-term antibiotic exposure
Bacterial enteric infections: Shigellosis	Preferred therapy for shigellosis: • Fluoroquinolone IV or PO **(AIII)** Duration of therapy: • For gastroenteritis: 3–7 days **(AIII)** • For bacteremia: 14 days **(BIII)**	Alternative therapy, depending on antibiotic susceptibility: • For gastroenteritis: ○ Co-trimoxazole DS 1 tab PO BID for 3–7 days **(BIII)**; or ○ Azithromycin 500 mg PO on day 1, then 250 mg PO QD for 4 days **(BIII)**	• Therapy is indicated both to shorten the duration of illness and to prevent the spread of infection **(AIII)** • *Shigella* infections acquired outside of the US have high rates of co-trimoxazole resistance
Bacterial enteric infections: Campylo-bacteriosis	For mild disease: • Might withhold therapy unless symptoms persist for several days For mild-to-moderate disease: • Ciprofloxacin 500 mg PO bid **(BIII)**; or • Azithromycin 500 mg PO QD **(BIII)** • Consider adding an		• There is an increasing rate of fluoroquinolone resistance • Antimicrobial therapy should be modified based on susceptibility reports

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	aminoglycoside in bacteremic patients **(CIII)** Duration of therapy: • Mild-to-moderate disease: 7 days **(BIII)** • Bacteremia: at least 2 weeks **(BIII)**		
Bartonella infections	Preferred therapy for bacillary angiomatosis, peliosis hepatis, bacteremia, and osteomyelitis: • Erythromycin: 500 mg PO or IV QID **(AII)**; or • Doxycycline: 100 mg PO or IV Q12H **(AII)** Duration of therapy: At least 3 months **(AII)** CNS infections and severe infections: • Doxycycline: 100 mg PO or IV Q12H +/- rifampicin 300 mg PO or IV Q12H **(AIII)** Duration of therapy: 4 months **(AII)** Long-term suppression: • A macrolide or doxycycline for patients with relapse or reinfection, as long as the CD4 count remains <200 cells/μL **(AIII)**	Alternative therapy for bacillary angiomatosis infections, peliosis hepatis, bacteremia, and osteomyelitis: • Azithromycin: 500 mg PO QD **(BIII)** • Clarithromycin: 500 mg PO bid **(BIII)**	Severe Jarisch-Herxheimer-like reaction can occur in the first 48 hours of treatment
Syphilis	Preferred therapy for early stage (primary, secondary, and early latent): • Benzathine penicillin G 2.4 million units IM for 1 dose **(AII)** Preferred therapy for late-latent (>1year or of unknown duration, CSF examination ruled out neurosyphilis): • Benzathine penicillin G 2.4 million units IM weekly for 3 doses **(AIII)** Preferred therapy for late-stage (tertiary, cardiovascular or gummatous disease): • Rule out neurosyphilis before	Alternative therapy for early stage (primary, secondary, and early latent) **(BIII)**: • For penicillin-allergic patients: o Doxycycline 100 mg PO BID for 14 days **(BIII)**; or o Ceftriaxone 1 g IM or IV QD for 8–10 days **(BIII)**; or o Azithromycin 2 g PO for 1 dose **(CII)** Alternative therapy for late-latent (without CNS involvement): • For penicillin-allergic patients: o Doxycycline 100 mg PO	• The efficacy of non-penicillin alternatives has not been evaluated in HIV-infected patients and should be undertaken only with close clinical and serologic monitoring **(BIII)** • Combination of procaine penicillin and probenecid is not recommended for patients with history of sulfa allergy **(DIII)** • The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache and myalgias that might occur within the first 24 hours after syphilis treatment

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	therapy with 3 doses of benzathine penicillin and consult with an infectious diseases expert to guide management **(AIII)** Preferred therapy for neurosyphilis (including otic and ocular disease): • Aqueous crystalline penicillin G: 18–24 million units per day, administered as 3–4 million units IV Q4H or by continuous IV infusion for 10–14 days **(AII)** +/- benzathine penicillin G 2.4 million units IM weekly for 3 doses after completion of IV therapy **(CIII)**	BID for 28 days **(BIII)** Alternative therapy for neurosyphilis • Procaine penicillin: 2.4 million units IM QD; PLUS • Probenecid: 500 mg PO QID for 10–14 days **(BII)** +/- benzathine penicillin G 2.4 million units IM weekly for 3 doses after completion of above **(CIII)**; or • For penicillin-allergic patients: ○ Desensitization to penicillin is the preferred approach **(BIII)**; IF NOT FEASIBLE ○ Ceftriaxone: 2 g IM or IV QD for 10–14 days **(CIII)**	
Mucosal candidiasis	Preferred therapy for oropharyngeal candidiasis—initial episodes (7–14 day treatment): • Fluconazole 100 mg PO QD **(AI)**; or • Clotrimazole troches 10 mg PO 5 x QD **(BII)**; or • Nystatin suspension 4–6 mL QID or 1–2 flavored pastilles 4–5 times QD **(BII)**; or • Miconazole mucoadhesive tablet PO QD **(BII)** Preferred therapy for oesophageal candidiasis (14–21 days): • Fluconazole 100 mg (up to 400 mg) PO or IV QD **(AI)** • Itraconazole oral solution 200 mg PO QD **(AI)** Preferred therapy for uncomplicated vulvo-vaginal candidiasis: • Oral fluconazole 150 mg for 1 dose **(AII)** • Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days **(AII)**	Alternative therapy for oropharyngeal candidiasis—initial episodes (7–14 day treatment): • Itraconazole oral solution 200 mg PO QD **(BI)**; or • Posaconazole oral solution 400 mg PO BID x 1, then 400 mg QD **(BI)** Alternative therapy for oesophageal candidiasis (14–21 days): • Voriconazole 200 mg PO or IV BID **(BI)** • Posaconazole 400 mg PO BID **(BI)** • Caspofungin 50 mg IV QD **(BI)** • Micafungin 150 mg IV QD **(BI)** • Anidulafungin 100 mg IV x 1, then 50 mg IV QD **(BI)** • Amphotericin B deoxycholate 0.6 mg/kg IV QD **(BI)** Alternative therapy for uncomplicated vulvo-vaginal candidiasis:	• Chronic or prolonged use of azoles might promote development of resistance • Higher relapse rates of oesophageal candidiasis have been reported with echinocandins than with fluconazole • Patients with fluconazole refractory oropharyngeal or oesophageal candidiasis who responded to echinocandin should be started on voriconazole or posaconazole for secondary prophylaxis until HAART produces immune reconstitution **(CI)** • Suppressive therapy is usually not recommended **(DIII)** unless patients have frequent or severe recurrences • If using suppressive therapy: ○ Oropharyngeal candidiasis: ▪ Fluconazole 100 mg PO TIW **(BI)** ▪ Itraconazole oral solution 200 mg PO QD **(CI)** ○ Oesophageal candidiasis:

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	Preferred therapy for fluconazole-refractory oropharyngeal candidiasis or oesophageal candidiasis: • Itraconazole oral solution ≥200 mg PO QD **(AII)** • Posaconazole oral solution 400 mg PO BID **(AII)** Preferred therapy for complicated (severe or recurrent) vulvo-vaginal candidiasis: • Fluconazole 150 mg Q72H x 2–3 doses **(AII)** • Topical antifungal ≥7 days **(AII)**	• Itraconazole oral solution 200 mg PO QD for 3–7 days **(BII)** Alternative therapy for fluconazole-refractory oropharyngeal candidiasis or oesophageal candidiasis: • Amphotericin B deoxycholate 0.3 mg/kg IV QD **(BII)** • Lipid formulation of amphotericin B 3–5 mg/kg IV QD **(BII)** • Anidulafungin 100 mg IV x 1, then 50 mg IV QD **(BII)** • Caspofungin 50 mg IV QD **(CII)** • Micafungin 150 mg IV QD **(CII)** • Voriconazole 200 mg PO or IV BID **(CIII)** • Fluconazole-refractory oropharyngeal candidiasis (not oesophageal): Amphotericin B oral suspension 100 mg/mL (not available in US) – 1 mL PO QID **(CIII)**	▪ Fluconazole 100–200 mg PO QD **(BI)** ▪ Posaconazole 400 mg PO BID **(BII)** ○ Vulvo-vaginal candidiasis: ▪ Fluconazole 150 mg PO once weekly **(CII)** ▪ Topical azole QD **(CII)**
Cryptococcal meningitis	Preferred induction therapy: • Amphotericin B deoxycholate 0.7 mg/kg IV QD PLUS flucytosine 100 mg/kg PO QD in 4 divided doses for at least 2 weeks **(AI)**; or • Lipid formulation amphotericin B 4–6 mg/kg IV QD (consider for persons who have renal dysfunction on therapy or have high likelihood of renal failure); PLUS flucytosine 100 mg/kg PO QD in 4 divided doses for at least 2 weeks **(AII)** Preferred consolidation therapy after at least 2 weeks of successful induction (defined as significant clinical improvement and negative CSF culture): • Fluconazole 400 mg PO QD for 8 weeks **(AI)**	Alternative induction therapy: • Amphotericin B (deoxycholate or lipid formulation, dose as preferred therapy); PLUS fluconazole 400 mg PO or IV QD **(BII)** • Amphotericin B (deoxycholate or lipid formulation, dose as preferred therapy) alone **(BII)** • Fluconazole 400–800 mg/day (PO or IV); PLUS flucytosine 100 mg/kg PO QD in 4 divided doses for 4–6 weeks—for persons unable to tolerate or unresponsive to amphotericin B **(CII)** Alternative consolidation therapy: • Itraconazole 200 mg PO BID for 8 weeks **(BI)**, or until CD4 count >200 cells/μL for	• Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and decreased risk for subsequent relapse • Patients receiving flucytosine should have blood levels monitored; peak level 2 hours after dose should not exceed 75 μg/mL; dosage should be adjusted in patients with renal insufficiency • Opening pressure should always be measured when a lumbar puncture is performed **(AII)**; repeated lumbar punctures or CSF shunting are essential to effectively manage ICP **(BIII)**

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	Preferred maintenance therapy: • Fluconazole 200 mg PO QD **(AI)** lifelong or until CD4 count ≥200 cells/μL for >6 months as a result of HAART **(BII)**	>6 months as a result of HAART **(BII)** Alternative maintenance therapy: • Itraconazole 200 mg PO QD lifelong, unless immune reconstitution occurs as a result of potent HAART—for patients intolerant of or who failed fluconazole **(BI)**	
Histoplasma capsulatum	Preferred therapy for moderately severe to severe disseminated disease: • Induction therapy (for 2 weeks or until clinically improved): Liposomal amphotericin B at 3 mg/kg IV QD **(AI)** • Maintenance therapy: Itraconazole 200 mg PO TID for 3 days, then BID **(AII)** Preferred therapy for less severe disseminated disease: • Induction and maintenance therapy: Itraconazole 200 mg PO TID for 3 days, then 200 mg PO BID **(AII)** Duration of therapy: At least 12 months Preferred therapy for meningitis: • Induction therapy (4–6 weeks): Liposomal amphotericin B 5 mg/kg/day **(AII)** • Maintenance therapy: Itraconazole 200 mg PO BID-TID for ≥1 year and until resolution of abnormal CSF findings **(AII)** Preferred therapy for long term suppression therapy: • In patients with severe disseminated or CNS infection **(AII)** and in patients who relapse despite appropriate therapy **(CIII)**: Itraconazole 200 mg PO QD	Alternative therapy for moderately severe to severe disseminated disease: • Induction therapy (for 2 weeks or until clinically improved): ○ Amphotericin B deoxycholate 0.7 mg/kg IV QD **(BI)** ○ Amphotericin B lipid complex 5 mg/kg IV QD **(CIII)** • Maintenance therapy: Itraconazole 200 mg PO TID for 3 days, then BID **(AII)**	• Itraconazole levels should be obtained in all patients to ensure adequate absorption **(AIII)**; serum concentrations of itraconazole PLUS hydroxyitraconazole should be >1 μg/mL • Itraconazole oral solution is preferred over capsule by certain specialists because of improved absorption • Acute pulmonary histoplasmosis in HIV-infected patients with CD4 count >300 cells/μL should be managed as non-immunocompromised host **(AIII)**

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
Coccidioido-mycosis	Preferred therapy for mild infections (focal pneumonia or positive coccidiodal serologic test alone): • Fluconazole 400 mg PO QD **(BII)**; or • Itraconazole 200 mg PO TID x 3 days, then 200 mg BID **(BII)** Preferred therapy for severe, nonmeningeal infection (diffuse pulmonary or severely ill patients with extrathoracic disseminated disease) in the acute phase: • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV QD **(AII)** • Lipid formulation amphotericin B 4–6 mg/kg IV QD **(AIII)** Duration of therapy: Until clinical improvement, then switch to azole Preferred therapy for meningeal infections: • Fluconazole 400–800 mg PO or IV QD **(AII)** Maintenance therapy (for all cases): • Fluconazole 400 mg PO QD **(AII)**; or • Itraconazole 200 mg PO BID **(AII)**	Alternative therapy for severe nonmeningeal infection (diffuse pulmonary or disseminated disease) in the acute phase • Certain specialists add triazole to amphotericin B therapy and continue triazole once amphotericin B is stopped **(BIII)** Alternative therapy for meningeal infections: • Itraconazole 200 mg PO TID x 3 days, then 200 mg PO BID **(BII)** • Intrathecal amphotericin B when triazole antifungals are not effective **(AIII)**	• Certain patients with meningitis may develop hydrocephalus and require CSF shunting • Therapy should be continued indefinitely for patients with diffuse pulmonary or disseminated diseases, as relapse can occur in 25–33% in HIV-negative patients **(AIII)** • Therapy should be lifelong in patients with meningeal infections, as relapse occurred in 80% of HIV-infected patients after discontinuation of triazole therapy **(AII)** • Case reports of successful therapy with voriconazole and posaconazole are available
Invasive aspergillosis	Preferred therapy: • Voriconazole 6 mg/kg Q12H x 1 day, then 4 mg/kg Q12H IV **(BIII)**, followed by voriconazole PO 200 mg Q12H after clinical improvement Duration of therapy: Until CD4 count is >200 cells/μL and there is evidence of clinical response	Alternative therapy: • Amphotericin B deoxycholate 0.1 mg/kg/day IV **(AIII)**; or • Lipid formulation of amphotericin B 5 mg/kg/day IV **(AIII)**; or • Caspofungin 70 mg IV x 1, then 50 mg IV QD **(BII)**; or • Posaconazole 400 mg BID PO **(BII)**	Voriconazole can potentially cause significant pharmacokinetic interactions between PIs or NNRTIs and should be used cautiously in these situations; consider therapeutic drug monitoring and dosage adjustment if necessary
CMV	Preferred therapy for CMV retinitis: • For immediate sight-threatening lesions: ○ Ganciclovir intraocular implant + valganciclovir	Alternative therapy for CMV retinitis: • Ganciclovir 5 mg/kg IV Q12H for 14 to 21 days, then 5 mg/kg IV QD **(AI)**; or • Ganciclovir 5 mg/kg IV	• The choice of initial therapy for CMV retinitis should be individualized, based on: location and severity of lesion(s), level of immunosuppression,

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	900 mg PO (BID for 14–21 days, then once QD) **(AI)**; or ○ One dose of intravitreal ganciclovir may be administered immediately after diagnosis until ganciclovir implant can be placed **(CIII)** • For small peripheral lesions: ○ Valganciclovir 900 mg PO BID for 14–21 days, then 900 mg PO daily **(BII)** Preferred chronic maintenance therapy (secondary prophylaxis) for CMV retinitis: • Valganciclovir 900 mg PO QD **(AI)**; or • Ganciclovir implant (may be replaced every 6–8 months if CD4 count remains <100 cells/μL); PLUS valganciclovir 900 mg PO QD until immune recovery **(BIII)** Preferred therapy for CMV oesophagitis or colitis: • Ganciclovir IV or foscarnet IV for 21–28 days or until resolution of signs and symptoms **(BII)** • Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption **(BII)** • Maintenance therapy is usually not necessary, but should be considered after relapses **(BII)** Preferred therapy CMV pneumonitis: • Treatment should be considered in patients with histologic evidence of CMV pneumonitis who do not respond to treatment of other pathogens **(AIII)**	Q12H for 14–21 days, then valganciclovir 900 mg PO QD **(AI)**; or • Foscarnet 60 mg/kg IV Q8H or 90 mg/kg IV Q12H for 14–21 days, then 90–120 mg/kg IV Q24H **(AI)**; or • Cidofovir 5 mg/kg/week IV for 2 weeks, then 5 mg/kg every other week with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) **(AI)** *Note: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid* Alternative chronic maintenance (secondary prophylaxis) for CMV retinitis: • Ganciclovir 5 mg/kg IV 5–7 times weekly **(AI)**; or • Foscarnet 90–120 mg/kg body weight IV once QD **(AI)**; or • Cidofovir 5 mg/kg body weight IV every other week with saline hydration and probenecid as above **(AI)**	concomitant medications, and ability to adhere to treatment **(AIII)** • Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include initiation or optimization of HAART **(BIII)** • In patients with CMV neurological disease, localized morbidity might occur because of IRIS; it might be prudent to briefly delay HAART initiation until clinical improvement is seen **(CIII)** • Maintenance therapy for CMV retinitis can be safely discontinued in patients with inactive disease and sustained CD4 count (>100 cells/mm^3 for ≥3–6 months); consultation with an ophthalmologist is advised **(BII)** • Patients with CMV retinitis who discontinued maintenance therapy should undergo regular eye examination (optimally every 3 months) for early detection of relapse or immune recovery uveitis (IRU) **(AIII)** • **Foscarnet is administered slowly, over 1–2 hours** • **Intraocular ganciclovir should only be performed by an ophthalmologist trained in this technique** • IRU might develop in the setting of immune reconstitution; treat IRU with a periocular corticosteroid or short courses of systemic steroid

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	• The role of maintenance therapy has not been established **(CIII)** Preferred therapy CMV neurological disease: • Treatment should be initiated promptly with a combination of ganciclovir IV PLUS foscarnet IV to stabilize disease and maximize response; continue until symptomatic improvement **(BII)** • Maintenance therapy (with valganciclovir PO PLUS IV foscarnet) should be continued for life unless evidence of immune recovery is evident **(BII)**		
HSV	Preferred therapy for orolabial lesions and initial or recurrent genital HSV: • Valacyclovir 1 g PO BID; famciclovir 500 mg PO BID; or acyclovir 400 mg PO TID **(AI)** Duration of therapy: • Orolabial HSV: 5–10 days **(AII)** • Genital HSV: 5–14 days **(AI)** Preferred therapy for severe mucocutaneous HSV infections: • Initial therapy acyclovir 5 mg/kg IV Q8H **(AII)** • After lesions began to regress, change to PO therapy as above **(AI)**; continue therapy until lesions have completely healed Preferred therapy for acyclovir-resistant mucocutaneous HSV infections: • Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response **(AI)** Preferred therapy for HSV encephalitis:	Alternative therapy for acyclovir-resistant mucocutaneous HSV infections **(CIII)**: • Topical trifluridine • Topical cidofovir • Topical imiquimod Duration of therapy: 21–28 days or longer	Topical formulations of trifluridine and cidofovir are not commercially available in the US; extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	• Acyclovir 10 mg/kg IV Q8H for 21 days **(AII)** Suppressive therapy (for patients with frequent or severe recurrences of genital herpes) **(AI)**: • Valacyclovir 500 mg PO BID **(AI)** • Famciclovir 500 mg PO BID **(AI)** • Acyclovir 400 mg PO BID **(AI)**		
VZV	Varicella (chickenpox): • Uncomplicated cases: Acyclovir (20 mg/kg body weight up to a maximum of 800 mg PO 5 x QD); valacyclovir 1,000 mg PO TID; or famciclovir 500 mg PO TID x 5–7 days **(AII)** • Severe or complicated cases: Acyclovir 10–15 mg/kg IV Q8H x 7–10 days **(AIII)** • May switch to oral acyclovir, famciclovir, or valacyclovir after defervescence if there is no evidence of visceral involvement **(AIII)** Zoster (shingles): • Acute localized dermatomal: Valacyclovir 1g TID or famciclovir 500 mg TID, or acyclovir 800 mg PO 5 x QD x 7–10 days **(AII)**; longer duration should be considered if lesions are slow to resolve • Extensive cutaneous lesion or visceral involvement: Acyclovir 10–15 mg/kg IV Q8H until clinical improvement is evident **(AII)** • Switch to oral therapy (valacyclovir 1,000 mg TID or famciclovir 500 mg TID, OR acyclovir 800 mg PO 5 x QD) after clinical improvement is evident, to complete a 10 to 14 day course **(AIII)**	Infection caused by acyclovir-resistant VZV: • Foscarnet 90 mg/kg IV q12h **(AII)**	• Consult an ophthalmologist experienced in managing VZV retinitis **(AIII)** • Corticosteroid therapy for HZV is not recommended **(DIII)**

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	Progressive outer retinal necrosis: • Ganciclovir 5 mg/kg IV Q12H; PLUS foscarnet 90 mg/kg IV Q12H; PLUS ganciclovir 2 mg/0.05mL intravitreal twice weekly, and/or foscarnet 1.2 mg/0.05mL intravitreal twice weekly **(AIII)** • Optimization of HAART **(AIII)** Acute retinal necrosis: • Acyclovir 10 mg/kg IV Q8H x 10 to 14 days, followed by valacyclovir 1,000 mg PO TID x 6 weeks **(AIII)**		
Human herpes virus-8 (HHV-8) diseases (*Kaposi's sarcoma, primary effusion lymphoma [PEL], multicentric Castleman's disease [MCD])*	Initiation or optimization of HAART should be done for all patients with KS, PEL, or MCD **(BII)** Preferred therapy for visceral Kaposi's sarcoma **(BII)**, disseminated cutaneous Kaposi's sarcoma **(CIII)**, and PEL **(BIII)**: • Chemotherapy PLUS HAART **(BII)** • Oral valganciclovir or IV ganciclovir might be useful as adjunctive therapy in PEL **(BII)** Preferred therapy for MCD: • Valganciclovir 900 mg PO BID **(BII)**; or • Ganciclovir 5 mg/kg IV Q12H **(BII)**	Alternative therapy for MCD: • Rituximab, 375 mg/m2 given weekly x 4–8 weeks, may be an alternative to antiviral therapy **(BII)**	
HPV	Treatment of condyloma acuminata (genital warts)		
	Patient-applied therapy: • Podofilox 0.5% solution or 0.5% gel: Apply to all lesions BID x 3 consecutive days, followed by 4 days of no therapy; repeat weekly for up to 4 cycles **(BIII)**; or • Imiquimod 5% cream: Apply to lesion at bedtime and remove in the morning on 3	Provider-applied therapy: • Cryotherapy (liquid nitrogen or cryoprobe): Apply until each lesion is thoroughly frozen; repeat every 1–2 weeks o Some providers allow the lesion to thaw, then freeze a second time in each session **(BIII)**	• Intralesional interferon-alpha is usually not recommended because of high cost, difficult administration, and potential for systemic side effects **(DIII)** • The rate of recurrence of genital warts is high, despite treatment

OI	Preferred acute and chronic maintenance (secondary prophylaxis) therapy options	Alternative acute and chronic maintenance therapy options	Notes/comments
	nonconsecutive nights weekly for up to 16 weeks; each treatment should be washed with soap and water 6–10 hours after application **(BII)**	• Trichloroacetic acid or bicloroacetic acid cauterization: Apply 80–90% aqueous solution to each lesion; repeat weekly for 3–6 weeks **(BIII)** • Surgical excision **(BIII)** or laser surgery **(CIII)** • Podophyllin resin 10–25% suspension in tincture of benzoin: Apply to all lesions, then wash off a few hours later; repeat weekly for 3–6 weeks **(CIII)**	
Progressive multi-focal leuko-encephalopathy (PML)	• Initiate HAART in naïve patients **(AII)** • Optimize HAART in patients who develop PML in phase of HIV viremia **(AIII)**		• Some patients might experience a remission after initiating HAART; although their neurological deficits frequently persist, disease progression remits • Corticosteroids may be used in patients with progressive clinical deficits and neuroimaging features suggesting inflammatory disease (e.g., oedema, swelling, contrast enhancement) as a result of initiating HAART **(BIII)**
Isospora belli	Preferred therapy for acute infection: • Co-trimoxazole **(AI)** (160 mg/800 mg) PO (or IV) QID for 10 days **(AII)**; or • Co-trimoxazole (160 mg/800 mg) PO (or IV) BID for 7–10 days **(BI)** • May increase QD dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist **(BIII)** Preferred chronic maintenance therapy (secondary prophylaxis): • In patients with CD4 count <200/μL, co-trimoxazole (160 mg/800 mg) PO tiw **(AI)**	Alternative therapy for acute infection: • Pyrimethamine 50–75 mg PO QD PLUS leucovorin 10–25 mg PO QD **(BIII)**; or • Ciprofloxacin 500 mg PO BID x 7 days **(CI)** (as a second line alternative) Alternative chronic maintenance therapy (secondary prophylaxis): • Co-trimoxazole (160 mg/800 mg) PO QD or (320 mg/ 1,600 mg) tiw **(BIII)** • Pyrimethamine 25 mg PO QD + leucovorin 5–10 mg PO QD **(BIII)** • Ciprofloxacin 500 mg tiw **(CI)** (as a second line alternative)	• Fluid and electrolytes must be managed in patients with dehydration **(AIII)** • Malnourished patients need nutritional supplementation **(AIII)** • Immune reconstitution with HAART may result in fewer relapses **(AIII)**

* Pyrimethamine and leucovorin doses are the same as the preferred therapy for toxoplasmosis.

† All patients receiving isoniazid should receive pyridoxine 25–50 mg PO QD **(BIII).**

2.7 PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV

2.7.1 Antenatal HIV Testing

2.7.1.1 General Considerations

All pregnant women should be offered HIV and syphilis testing at the time of antenatal care enrolment, and, if negative, again in the third trimester.

HIV testing should be one of the routine panels of blood tests taken during antenatal care, unless the patient specifically declines an HIV test, post-counselling. More frequent HIV screening may also be considered based on local programme considerations. Records should be kept on who received counselling, testing, and results.

As for syphilis, all pregnant women should be screened at their initial antenatal care visit and again at 32 weeks gestation, per the regional syphilis elimination program[20].

2.7.1.2 Managing HIV in a Newly-diagnosed Pregnant Woman

- Arrange post-test counselling for the patient (and her partner, if possible).
- Arrange for CD4 count and viral load testing, as per local protocol.
- Refer the patient to an appropriate clinic/provider experienced in PMTCT.
- Inform:
  - The responsible obstetrician/high-risk clinic.
  - The national HIV/AIDS clinical care coordinator.
  - The child's paediatrician.
- Ensure that the patient enrols in care; if defaulting occurs, inform the personnel listed above.

2.7.1.3 HIV Testing for Women Who Present in Labour

Women who present for care during labour with an unknown HIV status should be tested for HIV as soon as possible using a rapid HIV test. The risk of transmitting HIV to the infant can be reduced significantly by taking appropriate actions, even if the woman has not received any prior PMTCT interventions. In case of a positive result from a rapid HIV test, it should be assumed that the woman is truly HIV-infected and therefore PMTCT strategies should be immediately undertaken. Time does not allow for repeat confirmatory testing at that point, though it should still be performed post-delievery.

Management of the (presumed) HIV-infected woman in labour who has not received prior PMTCT interventions is reviewed below.

2.7.2 PMTCT Options for HIV-infected Women in Antenatal Care

See also table 22 for a summary.

[20] Pan American Health Organization. Mother-to-child transmission of HIV and syphilis [last updated 14 May 2013]. Available from: www.paho.org/eliminationinitiative/.

2.7.2.1 HIV-infected Pregnant Women Already on HAART

HIV-infected pregnant women already on HAART should continue their current regimen, including during labour and following delivery.

The infant should be given AZT or NVP for the first 6 weeks of life (see table 23 for dosing).

2.7.2.2 HIV-infected Pregnant Women Not Yet on HAART But Who Qualify for HAART

Women who qualify for HAART based on their CD4 count (absolute CD4 count <350/mm^3) or clinical stage (WHO stage 3 or 4) should initiate HAART as soon as possible, following adherence counselling and confirmation of readiness. The recommended regimen is TDF + (3TC or FTC) + EFV, primarily for its relative lack of toxicity, its simplicity (it's available in a once-daily fixed-dose combination tablet), and reassuring data regarding the safety of both EFV and TDF in pregnancy.

Equally acceptable alternative regimens include:

- NVP or an r/PI can be substituted for EFV in patients with uncontrolled psychiatric disease, or if post-partum depression or anxiety is a concern. However, women with baseline CD4 counts >250 cells/mm^3 should avoid NVP.
- If possible, AZT should be substituted for TDF in patients with pre-existing renal disease.

The infant should be given AZT or NVP for the first 6 weeks of life (see table 23 for dosing).

2.7.2.3 HIV-infected Pregnant Women Who Do Not Qualify for HAART Based on Immunological or Clinical Criteria

HIV-infected pregnant women who would not otherwise qualify for HAART based on immunological or clinical criteria should also be started on HAART, as maternal HAART is associated with a very low risk of MTCT. HAART should be initiated at the beginning of the second trimester (approximately 14 weeks gestation) or as soon as possible thereafter. HAART should be continued without interruption during labour and following delivery, as discussed in section 2.7.2.4 below.

The recommended HAART regimen is TDF + (3TC or FTC) + EFV, primarily for its relative lack of toxicity, its simplicity (it's available in a once-daily fixed-dose combination tablet), and reassuring data regarding the safety of both EFV and TDF in pregnancy.

Equally acceptable alternative regimens include:

- NVP or an r/PI can be substituted for EFV in patients with uncontrolled psychiatric disease, or if post-partum depression or anxiety is a concern. However, women with baseline CD4 counts >250 cells/mm^3 should avoid NVP.
- If possible, AZT should be substituted for TDF if patients with pre-existing renal disease.

These recommendations apply equally for HIV-infected women who are late to engage in antenatal care. Women who present in their second or third trimester should begin HAART as soon as possible, as the risk of MTCT is lowest when the mother's serum HIV viral load is undetectable. The only exception is women who present when they are already in labour—they should be given single-dose NVP. (See section 2.7.4. for further details.)

HIV-infected pregnant women who initiate HAART for the purposes of PMTCT should ideally continue taking it after delivery, even if their baseline CD4 count and clinical stage did not suggest a need for HAART. This approach aligns with the WHO's 'Option B+', which preserves maternal health, reduces the risk of HIV transmission to the mother's sexual partner(s), and reduces the risk of HIV transmission in the setting of future pregnancies.

The infant should be given AZT or NVP for the first 6 weeks of life (see table 23 for dosing)

2.7.2.4 Pregnant Women Who Decline or Cannot Take HAART

If the pregnant woman cannot or will not take HAART for whatever reason, a highly effective alternative approach for reducing the risk of MTCT involves AZT monotherapy for the mother:

- The mother initiates AZT monotherapy (standard dosing of 300 mg twice daily) at 14 weeks gestation (or as soon as possible thereafter).
- If the mother receives at least 4 weeks of AZT prior to delivery, no further ARV medication is indicated for the mother during labour and delivery.
- If the mother receives less than 4 weeks of AZT prior to delivery, then she should receive single-dose NVP at the onset of labour, and then AZT + 3TC throughout labour and delivery. Maternal AZT + 3TC should be continued for 7 days post-partum.

Post-partum, the mother should be promptly referred to a clinician for further monitoring of her HIV disease.

The infant should be given AZT or NVP for the first 6 weeks of life (see table 23 for dosing)

2.7.3 Monitoring Antiretroviral Therapy during Antenatal Care

Women on antiretroviral therapy should return for weekly visits for at least the first 2 weeks, then move to one visit every 4 weeks until 38 weeks gestation when weekly visits should resume. Patients who are experiencing side effects, problems with adherence or other issues, such as hyper-emesis, should be in more frequent contact with their clinics. At each follow-up visit, providers should assess adherence to ARVs as well as adverse reactions to them and provide interventions or support as indicated. Blood investigations (such as liver function- and haemoglobin tests) for adverse effects should be performed 2 weeks after starting antiretroviral therapy; haemoglobin should be monitored monthly thereafter. Patients should be given CD4 count- and viral load monitoring tests as recommended for non-pregnant HIV-infected adults (see appendix 4.1). At each follow-up visit, providers should determine patient adherence to safer sex practices and provide interventions or support as indicated.

Infant feeding plans should be made prior to delivery. Formula feeding ('replacement feeding') is preferred, as breastfeeding is associated with a risk of HIV transmission to the infant. However, if formula feeding is not an option, interventions to reduce the risk of HIV transmission via breastfeeding should be discussed and planned. These interventions are described below in section 2.7.11.

2.7.4 PMTCT for the HIV-infected Woman Not on Antiretroviral Therapy Who Presents in Labour

This scenario could apply to a woman whose HIV status has just become known through rapid testing at the time of labour, or a woman infected with HIV but not on ART. Women in labour for whom delivery is not immediately imminent should receive the following interventions:

- Single dose NVP at the onset of labour (or as soon as possible thereafter); AND
- AZT + 3TC starting at the onset of labour (or as soon as possible thereafter) and continuing throughout labour and delivery; AND
- AZT + 3TC for seven days post-partum.

Post-partum, the mother should be promptly referred to a clinician for further monitoring of her HIV disease. Prompt initiation of HAART should be an option for the mother, regardless of her CD4 count and clinical stage.

The infant should receive AZT for the first 6 weeks of life, plus three doses of NVP during the first 8 days of life[21,22].

2.7.5 PMTCT for Infants of HIV-infected Mothers Who Received No Antiretroviral Therapy Pre- or Intra-partum

The infant should receive AZT for 6 weeks, plus three doses of NVP during the first 8 days of life[21,22]. AZT and NVP are unlikely to be useful for infants if not given within 3 days of birth.

Post-partum, the mother should be promptly referred to a clinician for further monitoring of her HIV disease.

2.7.6 Summary of PMTCT Recommendations

Table 22. Summary of PMTCT recommendations by scenario

Scenario	Mother	Infant*	Comments
A: Woman already on HAART pre-pregnancy	**Do not discontinue or change HAART regimen**; continue during pregnancy, labour and delivery, and post-partum	Daily AZT or NVP until 6 weeks of age (see table 23 for dosing)	
B: Pregnant woman not on HAART who now requires HAART based on clinical and/or immunological staging	**Initiate HAART immediately:** • Preferred regimen: TDF + (3TC or FTC) + EFV • Alternative regimens: AZT + 3TC + (NVP or EFV or r/PI) Continue HAART during labour and delivery, and post-partum	Daily AZT or NVP until 6 weeks of age (see table 23 for dosing)	• Can substitute AZT for TDF in the mother's HAART regimen if TDF is contra-indicated (e.g., pre-existing renal disease) • Use EFV or an r/PI instead of NVP where CD4 counts are >250/mm^3 due to a significantly higher risk of liver toxicity
C: Pregnant	Initiate HAART at 14 weeks	Daily AZT or	NVP is not recommended for the mother

[21] The first dose of NVP should be given within 48 hours after birth, the second dose 48 hours after the first dose, and the third dose 96 hours after the second dose. Each dose should be either 12 mg (if the birth weight is >2.0 kg) or 8 mg (if the birth weight is ≤2.0 kg).

[22] If the mother breastfeeds, she should take HAART throughout the breastfeeding period for PMTCT. If she cannot or will not take HAART, the infant should continue to receive daily NVP throughout the entire period of breastfeeding.

woman who does not require HAART for her own health	gestation (or as soon as possible thereafter): • Preferred regimen: TDF + (3TC or FTC) + EFV • Alternative regimens: AZT + 3TC + (EFV or rPI) Continue HAART during labour and delivery as well as post-partum (see comments)	NVP until 6 weeks of age (see table 23 for dosing)	in this scenario due to a significantly higher risk of liver toxicity in women with CD4 counts >250/mm^3 who initiate NVP While life-long HAART is generally recommended in this scenario, consideration can be given to stopping HAART after delivery if mother is not motivated to continue HAART post-partum.
D: HIV-infected woman without any prenatal ART who presents in labour	Single-dose NVP immediately; PLUS AZT/3TC immediately and continued for 7 days post-partum	AZT for 6 weeks PLUS three doses of NVP during the first 8 days of life[23,24]	Have mother promptly assessed post-partum for possible HAART initiation and enrolment into HIV care.
E: Woman of unknown HIV status who presents in labour	Test for HIV (ideally using rapid test): • If positive, manage as scenario D • If positive but woman does not receive single-dose NVP during labour, manage as per scenario F below	Manage per scenario D or F, whichever is applicable	• Do not wait for confirmatory testing before proceeding with PMTCT interventions; assume she is HIV-infected based upon one positive test result from rapid testing (but confirm after delivery) • If mother tests positive for HIV, have her assessed post-partum for HAART need and enrolment into HIV care
F: HIV-infected woman who has received no ART for PMTCT, either pre-partum or during labour	N/A	AZT for 6 weeks PLUS three doses of NVP during the first 8 days of life[16,17]	• Give AZT and NVP within 3 days of birth, otherwise it is not effective • Have mother assessed post-partum for HAART need and enrolment into HIV care

** Infant PMTCT prophylaxis recommendations in this table assume formula feeding. If mother is breastfeeding, see section 2.8.4 for details regarding infant prophylaxis.*

2.7.7 Maternal and Infant Antiretroviral Therapy Dosing for PMTCT

2.7.7.1 Maternal Antiretroviral Therapy Dosing for PMTCT

ARV doses for pregnant women are generally the same as for non-pregnant adults (see table 5 in section 2.4.2.2 for details). However, there are the following exceptions:

- Pregnant women receiving ATV should also receive 100 mg of RTV; unboosted ATV should not be used in pregnancy. Pregnant women who are also taking TDF or an H2-receptor antagonist should receive an increased dose of ATV (400 mg once daily) during the second and third trimesters of pregnancy—again, boosted by 100 mg of RTV.

[23] The first dose of NVP should be given within 48 hours after birth, the second dose 48 hours after the first dose, and the third dose 96 hours after the second dose. Each dose should be either 12 mg (if the birth weight is >2.0 kg) or 8 mg (if the birth weight is ≤2.0 kg).

[24] If the mother breastfeeds, she should take HAART throughout the breastfeeding period for PMTCT. If she cannot or will not take HAART, the infant should continue to receive daily NVP throughout the entire period of breastfeeding.

- The dose of LPV/RTV should be increased from three capsules twice daily to four capsules twice daily during the third trimester of pregnancy (thereby increasing the dose of LPV/RTV from 300 mg/100 mg twice daily to 400 mg/133 mg twice daily).
- The dosage of a single-dose NVP is 200 mg administered once at the onset of labour.
- Women taking triple-drug ART regimens should be prescribed fixed-dose combination pills wherever possible.

2.7.7.2 Infant Antiretroviral Therapy Dosing for PMTCT

Infants should receive either twice-daily AZT or daily NVP from birth (within 6–12 hours) or as soon as feasible thereafter until 4–6 weeks of age; dosing of NVP and AZT during this period is provided in Tables 23a and 23b.

Either AZT or NVP can be used for extended PMTCT prophylaxis (indicated only for breastfeeding infants of mothers who are not receiving HAART). Considerations regarding the use of AZT versus NVP for extended infant PMTCT prophylaxis are provided in table 24. Infant dosing information of these drugs for infants greater than six weeks of age is provided in tables 30, 31, and 32.

Table 23a. NVP dosing for infants, birth to six weeks of age*

Infant birth weight	NVP daily dosing
• Birth weight <2,000 g** • Birth weight 2,000–2,499 g • Birth weight ≥ 2,500 g	2 mg/kg per day, once daily** 10 mg once daily 15 mg once daily
*Based on the dosing required to sustain exposure in the infant of >100 ng/ml with the least dose changes.	
** Low birth weight infants should receive mg/kg dosing; suggested starting dose is 2 mg/kg once daily. Theraputic drug monitoring is recommended.	

Table 23b. AZT dosing for infants, birth to six weeks of age

Infant gestational age at birth	AZT dosing
< 30 weeks' gestation at birth	2 mg/kg/dose PO (or 1.5 mg/kg/dose IV) started as soon after birth as possible, preferably within 6–12 hours of delivery, then every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours after age 4 weeks
30 – 35 weeks' gestation at birth	2 mg/kg/dose PO (or 1.5 mg/kg/dose IV), started as soon after birth as possible, preferably within 6–12 hours of delivery, then every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours at age 15 days
> 35 weeks' gestation at birth	4 mg/kg/dose PO twice daily, started as soon after birth as possible and preferably within 6–12 hours of delivery (or, if unable to tolerate oral agents, 3 mg/kg/dose IV, beginning within 6–12 hours of delivery, then every 12 hours)

Table 24. Considerations for using AZT versus NVP for extended infant PMTCT prophylaxis

Infant prophylaxis	Feasibility and operational considerations	Safety considerations
AZT	• Twice daily regimen • Substantial experience among infants receiving replacement feeding	• Potential risk of anaemia (reversible)
NVP	• Once-daily regimen • Limited safety monitoring required	• Risk of acquired drug resistance for infants becoming infected despite interventions

	• Substantial experience among breastfeeding infants • No evidence assessing the efficacy among infants receiving replacement feeding for any duration beyond a singe dose at birth • NVP is not recommended for infants born to mothers infected solely with HIV-2	• Potential risk for NVP toxicity if mother receives NVP-based ART regimen during breastfeeding (there is some passage of NVP to the infant through breast milk)

2.7.8 Considerations on the Mode of Infant Delivery

Elective caesarean section, when performed before the onset of labour or membrane rupture, has been associated with reduced MTCT among women not receiving HAART. If the pregnant woman is not on HAART prior to delivery, or is on HAART but is known to have a viral load >1,000 copies/mL at the time of delivery, elective caesarean section can be considered to reduce the risk of MTCT. However, clinicians must take into account the potential risks of elective caesarean section, as this procedure is generally associated with higher levels of morbidity and mortality, as compared with vaginal deliveries. Access to a caesarean section for women for whom C-section is indicated based on standard indications other than HIV infection must be ensured.

2.7.9 Management of the HIV-infected Woman in Labour

Labor for pregnant women with HIV infection should be managed in the same way as uninfected women's labor, with the following additional reminders:

- Universal precautions are especially important—use protective gear (e.g., gowns, gloves, boots, protective eyewear), safely use and dispose of sharps, sterilise equipment, and safely dispose of contaminated materials.
- Perform cervical examinations only when absolutely necessary and with appropriate clean techniques.
- Avoid unnecessary invasive procedures.
- Avoid episiotomy unless otherwise indicated.
- Avoid artificially rupturing the membranes unless obstetrically indicated.
- Minimise the use of forceps or vacuum extractors.
- Avoid 'milking' the umbilical cord.
- Avoid prolonged rupture of membranes, as rupture of the membranes for more than 6 hours is associated with an increased risk of MTCT. Consider using oxytocin to expedite delivery in this situation. Caesarean section is not recommended as a means to expedite delivery unless it is otherwise obstetrically indicated.
- Avoid using straight suture needles if possible to reduce the risk of needlestick.
- Clamp and cut the umbilical cord immediately after delivery and, if possible, avoid using a scalpel to cut the umbilical cord.
- Use special care in handling the placenta.

2.7.10 Follow-up Care of the HIV-infected Woman Post-partum

- Mother and infant should return for follow-up care at 4–6 weeks post-partum. The community nursing service post-natal clinics will also follow women as per their MCH schedule.

- Linkages should be made for the mother's and infant's HIV care with referral to the HIV clinic and the paediatric outpatient department.
- The surveillance officer or designate will ensure that the mother attends her specialist clinic appointments; a protocol will be put in place to track appointments and missed visits.
- The mother should be educated on breastfeeding, breast care, and engorgement prevention. She should also be monitored to ensure she is coping with and adhering to her chosen feeding strategy (replacement feeding or exclusive breastfeeding) as well as has an adequate supply of replacement feed, if needed.
- The mother should have adequate ARVs and other supplies and be given ongoing support to maximize adherence for her and her infant (if appropriate).
- The mother should be monitored for complications related to delivery, HIV, ART, etc. and refered to relevant services, as indicated.
- Family planning counselling should be initiated and referrals for follow-up services should be made, if indicated.
- Disclosure and testing for partner(s) and older children should be encouraged (if not already done) as appropriate, including referrals, as indicated.
- Referrals should be made for PLHIV support groups and other care services.
- Patient education, including nutrition and management of HIV, should be offered to the mother and her family; where applicable, referals to a nutrition specialist and a social worker should be made.

2.7.11 Management of the HIV-exposed Infant Immediately after Delivery

Infants of HIV-infected mothers are termed 'HIV-exposed infants' (HEI) until their HIV status is definitively established. HEIs require special treatment and testing, which is covered comprehensively in section 2.8. Initial management of the HEI should be guided by the following principles:

- Using gloves, bathe the infant as soon as possible with soap and water.
- Perform routine post-delivery care, including weighing and measuring the infant, vitamin K prophylaxis, and eye care. Cord blood samples for blood group and Hb electrophoresis screen should be collected as usual. (Note: Cord blood is not used for testing for syphilis.)
- Have a paediatrician examine the HEI as soon as possible.
- Confirm maternal history, including status of ARV prophylaxis and HBV status, as well as any maternal OIs.
- Avoid unnecessary invasive procedures.
- Ensure that the infant and mother receive ARV prophylaxis as outlined by protocol.
- Administer HBV vaccine and immunglobulin (within 12–24 hours of age) if the mother's HBsAg is positive.
- Confirm individual feeding plan, including formula choice, feed schedule, and volumes.
- Counsel HIV-infected mothers on the risk of MTCT via breastfeeding. Breastfeeding by HIV-infected mothers is generally discouraged in the OECS given the relative availability of safe drinking water, infant formula, and the social acceptability of formula feeding. However, some mothers may want to, or feel compelled to, breastfeed for a variety of reasons. The following interventions reduce the risk of MTCT via breastfeeding:
    - Continue exclusive breastfeeding for the first 6 months of life, meaning that the infant receives only breastmilk without any supplemental or mixed feedings (i.e., no water, tea,

porridge). Gradually introduce mixed feedings thereafter, concomitant with breastfeeding for the first 12 months of life or until a nutritionally adequate and safe diet without breastmilk can be provided. Because rapid weaning has also been associated with HIV transmission to the infant and maternal mastitis, encourage gradual weaning over 1 month. For infants and mothers on antiretroviral prophylaxis for PMTCT, continue their ARVs for 1 week following complete weaning.

- Unless the mother is on HAART, give the infant NVP daily throughout the entire period of breastfeeding, stopping 1 week after complete weaning.

2.8 CARE OF INFANTS BORN TO HIV-INFECTED MOTHERS

2.8.1 HIV Testing

All HEI should be tested for HIV using specialized HIV DNA or RNA tests. Traditional HIV antibody testing is not accurate in this age group, as any HIV antibodies found in infants could be maternal HIV antibodies that crossed the placenta; instead, virologic testing using dried blood spot (DBS) technology is indicated. At 4–6 weeks of life, a small sample (spot) of blood is collected on special filter paper, typically from a heel prick (phlebotomy is not required); after the blood dries, it is sent to the Ladymeade Reference Unit in Barbados for HIV DNA testing. Results are typically available within 3–4 weeks. HEI who have a positive virologic test at 4-6 weeks of age should be presumed to be HIV-infected and started on HAART immediately (see section 2.10); another confirmatory DBS virologic test should be promptly sent. HEI who have a negative virologic test at 4–6 weeks of age but continue to breastfeed should undergo serologic testing at 9 months of age. A positive serologic test should be followed by a confirmatory virologic test (again using dried blood spot technology) to confirm suspected infant infection. Serologic tests should be repeated at least 6 weeks after complete weaning and/or at 18 months of age.

2.8.2 Co-trimoxazole Prophylaxis

All HEIs should receive daily co-trimoxazole starting at 4–6 weeks of age, continuing until HIV infection is ruled out. Co-trimoxazole dosing options include:

- Co-trimoxazole 5 mg/kg/day of the TMP component BID for 7 days; OR
- Co-trimoxazole 5 mg/kg/day of the TMP component BID 3 times a week on alternate days (e.g., Monday/Wednesday/Friday)

Co-trimoxazole is also recommended for HIV-exposed breastfeeding children of any age. Co-trimoxazole prophylaxis should be continued for breastfeeding children until HIV infection can be excluded by HIV antibody testing (beyond 18 months of age) or virological testing (before 18 months of age) at least 6 weeks after complete weaning.

2.8.3 PMTCT for HIV-exposed Infants

Infant PMTCT prophylaxis depends upon what the mother received for PMTCT and whether or not the mother is breastfeeding. See tables 23a and 23b for infant PMTCT prophylaxis dosing.

- HEIs with mothers who are on HAART:
  - If the mother is not breastfeeding, the infant should receive daily AZT or NVP for 6 weeks after delivery.
  - If the mother is breastfeeding, the infant should receive daily NVP for 6 weeks following delivery.
- HEIs with mothers who received single-dose AZT during pregnancy with or without single-dose NVP at birth:
  - If the mother is not breastfeeding, the infant should receive daily AZT or NVP for 6 weeks after delivery.
  - If the mother is breastfeeding, the infant should receive daily NVP from birth until 1 week after complete weaning.
- HEIs with mothers who received no ARV prophylaxis during pregnancy or delivery:

- If the mother is replacement feeding, the infant should receive AZT for 6 weeks plus three doses of NVP during the first 8 days of life[25].
- If the mother is breastfeeding, there are two options:
  - The infant should receive daily NVP from birth until 1 week after all breastfeeding has stopped; OR
  - The mother should start HAART immediately and the infant should receive AZT for 6 weeks plus three doses of NVP during the first 8 days of life.[15]
- Notes:
  - AZT and NVP are not likely to have any impact if not given to the infant within 3 days of birth.
  - The mother should be carefully assessed for starting HAART, regardless of her infant feeding choice.

2.8.4 Feeding HIV-exposed Infants

Breastfeeding HEIs is not recommended given the risk of HIV transmission through breastmilk. However, if formula feeding is not a reliable, feasible option for whatever reason, the mother should be allowed to breastfeed with the following interventions, which significantly reduce the risk of MTCT:

- ART for the mother and/or infant, as detailed above in section 2.8.3.
- Exclusive breastfeeding should continue for the first 6 months of life, meaning that the infant receives only breastmilk without any supplemental or mixed feedings (i.e., no water, tea, porridge). Mixed feedings should be gradually introduced thereafter, concomitant with breastfeeding for the first 12 months of life or until a nutritionally adequate and safe diet without breastmilk can be provided. Because rapid weaning has also been associated with HIV transmission to the infant and maternal mastitis, weaning should take place gradually over 1 month. For infants and mothers on ARV prophylaxis to prevent HIV transmission, the ARVs should be continued for 1 week following complete weaning.

2.8.5 Immunizations for HIV-exposed Infants (HEIs)

HEIs should not be given BCG until the infant's HIV status is known. If HIV infection is ruled out, then infants can receive BCG, and follow the ordinary OECS vaccination schedule for non-HIV infected children. If the HEI is ultimately diagnosed with HIV infection, immunizations should be given per section 2.11.1.

2.8.6 Growth and Nutrition

Growth failure is a prominent feature of HIV infection. Nutritional assessment is important both as a diagnostic marker (when HIV status is unknown) and to maximise growth in infected children.

[25] The first dose of NVP should be given within 48 hours after birth, the second dose 48 hours after the first dose, and the third dose 96 hours after the second dose. Each dose should be either 12 mg (if the birth weight is >2.0 kg) or 8 mg (if the birth weight is ≤2.0 kg).

2.8.7 Follow-up Care

It is critical to monitor HEIs and HIV-infected infants closely. Key interventions prior to discharge and at scheduled follow-up visits are detailed in the sub-sections below.

2.8.7.1 Prior to Discharge from Hospital

- Have a paediatrician or the most senior clinician available review the infant prior to discharge.
- Docket the infant in the HIV clinical care system to ensure follow-up visits.
- Teach the mother how to administer ARV prophylaxis to her infant.
- Investigate and address any issues preventing adherence to the infant's ARVs or prophylactic medications.
- Provide a supply of replacement feeds to the mother and set an appointment with the nutritionist for the infant.

2.8.7.2 Follow-up—1–2 Weeks

- Perform a routine physical examination of the infant, including growth parameters.
- Assess and address adherence to the infant's ARVs or other prophylactic medications.
- Note any evidence of side effects in the infant to the ARVs or other prophylactic medications.
- If appropriate, advise the mother to continue formula feeds and ensure they are being prepared hygienically.
- Assess and address any of the parents' concerns.

2.8.7.3 Follow-up—6 Weeks to 2 Months

- Perform a routine physical examination of the infant, including growth and development parameters.
- Discontinue ARV prophylaxis if the infant is not being breastfed.
- Initiate co-trimoxazole prophylaxis using one of the dosing options outlined in section 2.8.2.; continue prophylaxis until the infant is confirmed HIV-negative.
- Initiate iron and vitamin supplementation.
- Draw blood samples for DBS testing and others (e.g., CBC and differential; toxoplasmosis, rubella, CMV, HSV, and HIV (TORCH) screen; venereal disease research laboratory (VDRL) test; Hepatitis BsAg; and HTLV-1 serology, as appropriate).
- If the DBS virologic test is positive, assume the infant is HIV-infected and start HAART immediately for the infant (see section 2.10) while sending a repeat DBS specimen for confirmatory virologic testing.
- Administer first pentavalent (DTaP Hib, and HBV) and polio vaccinations (Note: inactivated [IPV] is preferred, but if not available, OPV may be administered to asymptomatic infants).
- If appropriate, advise the mother to continue formula feeds and ensure they are being prepared hygienically.
- Treat any medical problems.
- Assess and address any of the parents' concerns.

2.8.7.4 Follow-up—4 Months

- Perform a routine physical examination of the infant, including growth and development parameters.
- Administer second dose of vaccinations
- If the first DBS virologic test was negative, draw a blood sample for the second HIV DNA PCR (by DBS) test.
- Continue co-trimoxazole prophylaxis.
- Continue iron and vitamin supplementation.
- If appropriate, advise the mother to continue formula feeds and ensure they are being prepared hygienically.
- Treat any medical problems.
- Assess and address any of the parents' concerns.

2.8.7.5 Follow-up—beyond 4 Months

Ideally, HEIs should be followed up by a comprehensive team of paediatricians, nurses, and nutritionists. The routine follow-up schedule is similar to that of infants who are not exposed to HIV. Subsequent to the 4-month visit, HEIs should be seen again at 6 months, then at 3-month intervals, or more frequently if indicated.

At each visit:

- Perform a routine physical examination of the infant, including growth and development parameters. Baseline follow-up physical examinations include: taking temperature; measuring weight, height, and head circumference (and monitoring them on growth charts); and examining for thrush, adenopathy, skin eruptions, ear-, nose-, and throat infections, chest infections, abdominal organ enlargement, and neurological- and developmental abnormalities.
- Assess and address the infant's diet.
- Ensure adequate vaccination coverage.
- Continue co-trimoxazole prophylaxis.
- Continue iron and vitamin supplementation.
- Look for evidence of HIV or OIs.
- Treat any medical problems.
- Assess and address any of the parents' concerns.

2.9 INITIAL MANAGEMENT OF INFANTS AND CHILDREN NEWLY DIAGNOSED WITH HIV

2.9.1 Initial Steps

The first steps in managing an infant or child newly diagnosed with HIV include the following.

1. Perform a thorough history and physical examination, in order to:
a. Identify any current or past complications of HIV disease (such as OIs) to establish the child's WHO clinical stage (table 26). Children diagnosed with an OI should be treated for it immediately; in the case of most OIs, antiretroviral therapy should be started shortly thereafter.
b. Identify co-morbid acute and chronic diseases/conditions that need to be managed along with HIV.
c. Assess the child's development according to height, weight, and Tanner staging charts, as well as developmental milestones.
d. Identify partners who should be notified and tested for HIV.

2. Arrange appropriate laboratory investigations (table 3), in order to:
a. Establish the child's degree of immunodeficiency.
b. Screen for renal, hepatic, or haematologic disorders.
c. Screen for other STIs, where indicated.
d. Screen for TB infection and/or disease.

3. Assess the psychological states of the child and caregiver(s), as many individuals experience severe emotional distress upon learning that they are infected with HIV. Intensive counselling and/or referral for psychiatric care may be warranted.

4. Initiate appropriate chemoprophylaxis against OIs where indicated. Refer to sections 2.11 and 2.12 for more details on indications, dosing, and precautions.

5. Assess the child's eligibility for HAART, as described in section 2.10. Any infant or child less than five years of age should be started on HAART, regardless of clinical and immunological status. For older children, HAART eligibility depends upon the clinical stage of the disease and CD4 count. Children and their caregivers who are eligible for HAART should be scheduled for intensive adherence counselling.

6. Arrange for close follow-up with a clinician experienced in the care and treatment of paediatric HIV; take measures to ensure that the child is not lost to follow-up.

HIV-infected infants and children in the OECS should be staged using the WHO's paediatric HIV disease classification system, shown in table 26 below.

Table 26. WHO Classification of paediatric HIV/AIDS

Clinical stage 1
• Asymptomatic • Persistent generalised lymphadenopathy
Clinical stage 2
• Unexplained persistent hepatosplenomegaly • Papular pruritic eruptions • Extensive wart virus infection • Extensive molluscum contagiosum • Recurrent oral ulcerations • Unexplained persistent parotid enlargement • Lineal gingival erythema • HZV • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis) • Fungal nail infection
Clinical stage 3
• Unexplained moderate malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one month) • Persistent oral candidiasis (after first 6 weeks of life) • Oral hairy leukoplakia • Acute necrotising ulcerative gingivitis or periodontitis • Lymph node TB • Pulmonary TB • Severe recurrent bacterial pneumonia • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease including brochiectasis • Unexplained anaemia (<8.0 g/dl), neutropaenia (<0.5×10^9/mL) and/or chronic thrombocytopaenia (<50×10^9 per mL)
Clinical stage 4
• Unexplained severe wasting,* stunting or severe malnutrition not responding to standard therapy • Pneumocystis pneumonia (PCP) • Recurrent severe bacterial infections (e.g., empyema, pyomyositis, bone or joint infection, or meningitis but excluding pneumonia) • Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site) • Extrapulmonary TB • Kaposi's sarcoma • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • CNS toxoplasmosis (after one month of life) • HIV encephalopathy • CMV infection: retinitis or CMV infection affecting another organ, with onset at age more than one month • Extrapulmonary cryptococcosis (including meningitis) • Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis) • Chronic cryptosporidiosis (with diarrhoea) • Chronic isosporiasis • Disseminated non-tuberculous mycobacterial infection • Cerebral or B-cell non-Hodgkin's lymphoma • Progressive multifocal leukoencephalopathy (PML) • HIV-associated cardiomyopathy or nephropathy
**Persistent weight loss of >10% of baseline or <5th percentile on weight-for-height chart on 2 consecutive measurements >1 month apart in the absence of another aetiology or concurrent illness.*

2.9.2 Recommended Laboratory Tests—Initial Care

Table 27. Recommended laboratory studies for infants and children initially presenting for HIV care

Test	Strength of recommendation
HIV-disease tests	
Confirm positive HIV antibody status (records review or serology or DNA/RNA testing)	Mandatory
CD4 count and percentage	Mandatory
Plasma HIV RNA level (viral load)	Recommended
Safety laboratory tests	
CBC count with differential	Mandatory
Serum chemistry	
Liver function tests	Mandatory
Electrolytes, blood urea nitrogen, creatinine levels	Mandatory
Urinalysis	Recommended
Coinfection and comorbidity laboratory tests	
Screening for other STIs (syphilis, chlamydia, gonorrhoea, trichomoniasis)	Only for children who are sexually active or may be victims of sexual abuse. Mandatory for syphilis; recommended for chlamydia, gonorrhoea, trichomoniasis.
Serologic testing for *Toxoplasma gondii*	Optional
TB screening[b]	Mandatory
Viral hepatitis screening (HBV, HCV)[c]	Mandatory for HBV; recommended for HCV
HTLV-1, -2	Recommended

[b] *TST.*
[c] *HBV surface antigen, antibody to HBV surface antigen or to HBV core antigen, antibody to HCV.*

2.10 PAEDIATRIC HAART

2.10.1 General Considerations for Initiating HAART in Paediatric Patients

These recommendations provide general guidance rather than absolute recommendations for an individual patient. As is true for adult HAART, many factors must be considered in deciding whether to initiate, including:

- The potential benefits and risks of therapy.
- The abilities of the caregiver and child to adhere to the proper administration of the therapeutic regimen (discussed in more detail below).
- The age of the child.
- The risk of disease progression as suggested by the CD4 count and HIV viral load (if testing is available).

HIV infection generally progresses more rapidly in children than in adults. Infants are at particular risk for rapid disease progression and are especially vulnerable to CNS complications. All infants and children less than five years of age should be started on HAART regardless of clinical or immunological stage.

For most ARVs, the level of penetration into human breastmilk has not been quantified. Therefore, it is unknown whether the quantity and concentration of any ARV secreted into breastmilk are sufficient to achieve therapeutic levels in the infant. For this reason, ARVs should be given in standard doses to infants who require them regardless of whether the mother is on ARVs as well.

2.10.2 When to Initiate HAART in Infants and Children

Table 28. When to start HAART in infants and children

Age	Infants and children less than 5 years of age	5 years of age or older
Absolute CD4	All	$\leq$500 cells/mm^3 (as in adults)

Infants:

- Initiate HAART for all HIV-infected infants diagnosed in the first year of life, irrespective of CD4 count or WHO clinical stage.

Children:

- Initiate HAART for all HIV-infected children less than five years of age irrespective of CD4 count or WHO clinical stage.
- Initiate HAART for all HIV-infected children more than 5 years of age with a CD4 count $\leq$500 cells/mm^3 (as in adults), irrespective of WHO clinical stage.
- Initiate HAART for all HIV-infected children with WHO clinical stages 3 and 4, irrespective of CD4 count.
- Initiate HAART for any child less than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection.

2.10.3 Recommended First-line HAART Regimens for Infants and Children

Table 29. Recommended first-line HAART regimens for infants and children*

Patient group	Preferred first-line regimen	Alternate first-line regimen
Infant or child < 3 years (36 months) of age	(ABC or AZT) + 3TC + r/LPV	(ABC or AZT) + 3TC + NVP
Children 3 years to less than10 years of age	ABC + 3TC + EFV	(AZT or TDF) + (3TC or FTC) + EFV ABC + 3TC + NVP (AZT or TDF) + (3TC or FTC) + NVP (ABC or AZT) + 3TC + r/LPV
Children 10-19 years of age	TDF + (3TC or FTC) + EFV	(AZT or ABC) + (3TC or FTC) + EFV (AZT or ABC or TDF) + (3TC or FTC) + NVP

*ARV dosing can be found in Tables 31, 32, and 33.

Infants and children with specific conditions:

- For children more than 3 years of age with TB, the preferred regimen is EFV + 2 NRTIs.
- For infants and children less than 3 years of age with TB, the preferred regimens are NVP + 2 NRTIs, or a triple nucleoside regimen such as AZT + 3TC + ABC.
- For a child or adolescent with severe anaemia (<7.5 g/dl) or severe neutropenia (<0.5/mm3), AZT should not be included in the NRTI backbone; ABC or TDF should be used (depending on the age of the child)
- For adolescents more than 12 years of age with HBV, the preferred regimen is TDF + (3TC or FTC) + NNRTI

2.10.4 Recommended Laboratory Tests—Ongoing Care

2.10.4.1 Routine Clinical and Laboratory Monitoring

- Baseline haemoglobin level (and white cell count, if available) should have been determined at HAART initiation.
  - Measure haemoglobin 8 weeks after initiating AZT-containing regimens, or more frequently if clinical signs & symptoms indicate.
  - Monitor child's growth, development, and nutrition on a monthly basis.
  - Monitor symptoms that might indicate ARV toxicity and do laboratory testing as appropriate.

2.10.4.2 CD4 Count Monitoring

- CD4 count should have been measured at the time of HIV diagnosis; measure it every 3–4 months thereafter.
- Measure CD4 count if new clinical staging events develop, including growth faltering and neuro-developmental delay.
- Where CD4 count measurement availability is limited, use CD4 count monitoring to assess the significance of clinical events.

2.10.4.3 Viral Load Monitoring

- Viral load determination is desirable, but not essential, prior to initiating ART.
- Measure viral load every 6 months after initiating HAART, as well as whenever treatment failure is suspected based on clinical or immunological deterioration.

2.10.5 First-line Regimen Treatment Failure—When to Switch Regimens

Clinical failure is defined as the appearance or reappearance of WHO clinical stage 3 or stage 4 events after at least 24 weeks on HAART in a treatment-adherent child. Clinical failure should prompt HIV viral load testing to determine whether or not virologic failure has in fact occurred.

Immunological failure is defined as developing or returning to the following age-related immunological thresholds after at least 24 weeks on HAART in a treatment-adherent child:

- Persistent CD4 count <200 cells/mm^3 or CD4 percentage <10% for a child less than 5 years of age.
- Persistent CD4 count <100 cells/mm^3 for a child 5 years of age or older.

Immunologic failure should prompt HIV viral load testing to determine whether or not virologic failure has in fact occurred.

Virological failure is defined as a *persistent* viral load above 1,000 RNA copies/ml, after at least 24 weeks on HAART in a treatment-adherent child. A single viral load measurement of greater than 1,000 copies/mL should prompt adherence counseling for the child and/or caregiver, followed by repeat virologic testing three months later (see Figure 4). If the viral load remains elevated, a genotypic resistance assay should be ordered from the Ladymeade Reference Unit in Barbados to guide the selection of second-line therapy; consultation with an HIV expert is recommended.

2.10.5.1 Second-line Regimens in the Event of Treatment Failure

- The design of the second line regimen for children should be guided by antiretroviral resistance testing, available through the Ladymeade Reference Unit in Barbados, and consultation with an HIV expert wherever possible.
- If a second line regimen cannot be designed with guidance from antiretroviral resistance testing, the following principles should be followed:
    - After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI.
    - After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken.
    - After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI.
    - After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC.
    - After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC)

2.10.5.2 Salvage Therapy

If second line-therapy fails, refer to experienced HIV clinician for individualized salvage regimen.

2.10.6 Considerations for Infants and Children with TB and HIV

2.10.6.1 Isoniazid preventive therapy

- All HIV-infected infants and children exposed to TB through household contacts, but with no evidence of active disease, should begin isoniazid preventive therapy (IPT)—10 mg/kg/daily (maximum dose 300 mg daily) for 6 months.
- HIV-infected children (older than 12 months of age and including those previously treated for TB) who are not likely to have active TB and are not known to be exposed to TB should receive 6 months of IPT as part of a comprehensive package of HIV care.
- HIV-infected infants who are unlikely to have active TB and are not known to have been exposed to TB should not receive IPT as part of a comprehensive package of HIV care.

2.10.6.2 Infants and Children Diagnosed with TB and HIV

- Any child with active TB disease should begin treatment immediately; HAART should be initiated in the first 8 weeks of TB therapy as soon as tolerated, irrespective of CD4 count and clinical stage.
- The preferred first-line ARV regimen for infants and children less than 3 years of age who are taking a rifampicin-containing regimen for TB is: 2 NRTIs + NVP or a triple NRTI regimen.
- The preferred first-line ARV regimen for children more than 3 years of age who are taking a rifampicin-containing regimen for TB is: 2 NRTIs + EFV.
- The preferred first-line ARV regimen for infants and children less than 2 years of age who have been exposed to NVP and are taking a rifampicin-containing regimen for TB is: a triple NRTI regimen.

Consult a paediatric HIV/TB expert. More information can be found in the *Caribbean Guidelines for the Prevention, Treatment, Care, and Control of Tuberculosis and TB/HIV*[26].

[26] Caribbean HIV/AIDS Regional Training Network. Caribbean guidelines for the prevention, treatment, care and control of tuberculosis and TB/HIV. Washington, DC: Pan American Health Organization. Available from: http://www.chartcaribbean.org/images/stories/ctbg_guidelines_2010_web2.pdf.

Harmonized dosing schedule

Table 31. Simplified table giving number of tablets of child-friendly solid formulations for morning and evening dosing

Drug	Strength of paediatric tab (mg)	Children 6 weeks of age and above										Strength of adult tab (mg)	Number of tablets by weight-band	
		Number of tablets by weight-band morning and evening												
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 kg	
		am	pm	am	pm	am	pm	am	pm	am	pm		am	pm
Single drugs														
AZT	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
ABC	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
NVP	50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200	1	1
ddI	25	2[a]	2[a]	3	2	3	3	4	3	4	4	25	5	5
Combinations														
AZT/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150	1	1
AZT/3TC/NVP	60/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150/200	1	1
ABC/AZT/3TC	60/60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/300/150	1	1
ABC/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	variable[b]		
d4T/3TC	6/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150	1	1
d4T3TC/NVP	6/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	30/150/200	1	1
LPV/r[c]	100/25	NR	NR	NR	NR	2	1	2	2	2	2	100/25	3	3

[a] *This dose of ddI is only appropriate for children 3 months of age or older and weighing between 5 kg and 5.9 kg.*

[b] *consult HIV expert, dosing depends upon strength of adult tab.*

[c] *Higher doses of LPV/r maybe required when co-administered with enzyme-inducing drugs, such as NVP, EFV, fos-amprenavir (FPV), rifampicin.*

Table 32. Simplified table giving ml of liquid formulation and number of tablets or capsules of adult solid formulation for morning and evening dosing

Drug	Strength of paediatric liquid (mg/ml) and adult tab/cap (mg)	Children 6 weeks of age and above									
		Number of tablets/capsules or ml by weight-band morning and evening									
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg	
		am	pm	am	pm	am	pm	am	pm	am	pm
AZT	10 mg/ml; 300 mg	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	0.5	0.5	1	0.5
ABC	20 mg/ml; 300 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5
3TC	10 mg/ml; 150 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5
d4T	1 mg/ml; 15 mg or 20 mg	6 ml	6 ml	9 ml	9 ml	1 (15 mg)	1 (15 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)
NVP	10 mg/ml; 200 mg	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	1	0.5	1	0.5
ddl	10 mg/ml; 25 mg	3 ml[a]	3 ml[a]	5 ml	5 ml	6 ml	6 ml	4	3	4	4
LPV/r	80/20 mg/ml	1 or 1.5 ml[b]	1 or 1.5 ml[b]	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml

[a] *This dose of ddl is only appropriate for children 3 months of age or older and weighing between 5 kg and 5.9 kg.*
[b] *LPV/r liquid for 3–3.9 kg, use 1 ml in the am and 1 ml in the pm; for 4–5.9 kg, use 1.5 ml in the am and 1.5 ml in the pm. In addition, higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, FPV, or rifampicin.*

Table 33. Simplified table giving number of tablets of child-friendly solid formulations for once-daily dosing

Drug	Strength of tab/cap (mg)	Number of tablets or capsules by weight-band once daily					Strength of adult tab (mg)	Number of tablets or capsules by weight-band once daily
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		25–34.9 kg
		Once daily	Once daily	Once daily	Once daily	Once daily		Once daily
Single drugs								
EFV[a]	200 mg	NR	NR	1	1.5	1.5	200	2
ddl	125 mg or 200 mg EC	NR	NR	1 (125 mg)	1 (200 mg)	2 (125 mg)	125 mg EC	2

[a] *EFV is not recommended for children below 3 years and weighing less than 10 kg.*
[b] *ddl EC is not recommended for children weighing less that 10 kg; this dose is recommended only for those 10 kg and above.*
NR = not recommended EC = enteric coated

2.11 PAEDIATRIC OPPORTUNISTIC INFECTION PROPHYLAXIS GUIDELINES

This section provides detailed guidance on the management of selected OIs commonly seen in HIV-infected children in the Caribbean region. These recommendations have been adapted for the Eastern Caribbean region from paediatric OI guidelines written by the CDC et al[27]. Not all treatments listed may be available in the OECS but are included in case referral outside the region is an option. For management of OIs not listed below, please consult the CDC OI Guidelines.[26]

Preferred and alternative treatment options are presented; each recommendation includes a rating of its strength as well as the quality of the evidence supporting it, coded as follows.

Strength of recommendation:

A. Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B. Moderate evidence for efficacy, or strong evidence for efficacy but only limited clinical benefit, supports recommendation for use. Should generally be offered.
C. Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of treatment or alternative approaches. Optional.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

Quality of the evidence supporting the recommendation

I. Evidence from at least one properly-designed randomized, controlled trial.
II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one centre), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

[27]Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR. 2009 Sep 4; 58(11). Available from: http://www.cdc.gov/mmwr/pdf/rr/rr5811.pdf.

TABLE 34. Prophylaxis to prevent first episode of OI in HIV-exposed- and HIV-infected infants and children

Preventive regimen			
Pathogen	**Indication**	**First choice**	**Alternative**
Strongly recommended as standard of care			
PCP[a]	HIV-infected or HIV-indeterminate infants aged 1–12 months; HIV-infected children aged 1–5 years with CD4 count <500 cells/mm^3 or CD4 percentage <15%; HIV-infected children aged 6–12 years with CD4 count <200 cells/mm^3 or CD4 percentage <15%	• Co-trimoxazole: 150/750 mg/m^2 body surface area per day (max. 320/1,600 mg) orally divided into 2 doses QD and administered 3 times weekly on consecutive days (**AI**) • Acceptable alternative dosage schedules for same dose (**Al**): Single dose orally 3 x QW on consecutive days; 2 divided doses PO QD; or 2 divided doses PO 3 x QW on alternate days	• Dapsone: o Children aged >1 month: 2 mg/kg body weight (max. 100 mg) PO QD; OR o 4 mg/kg body weight (max. 200 mg) PO QW (**BI**) • Atovaquone: o Children aged 1–3 months and >24 months: 30 mg/kg body weight PO QD o Children aged 4–24 months: 45 mg/kg body weight PO QD (**BI**) • Aerosolized pentamidine: o Children aged >5 years: 300 mg every mo by nebulizer (**BI**)
MTB			
Isoniazid-sensitive	• TST reaction >5 mm or prior positive TST result without treatment; or regardless of current TST result and previous treatment, close contact with any person who has contagious TB • TB disease must be excluded before start of treatment	• Isoniazid: 10–15 mg/kg body weight (max. 300 mg) PO QD for 9 months (**AII**); or • 20–30 mg/kg body weight (max. 900 mg) PO 2 x QW for 9 months (**BII**)	Rifampicin: 10–20 mg/kg body weight (max. 600 mg) PO QD for 4–6 months (**BIII**)
Isoniazid-resistant	Same as previous pathogen; increased probability of exposure to isoniazid-resistant TB	Rifampicin: 10–20 mg/kg body weight (max. 600 mg) PO QD for 4–6 months (**BIII**)	Uncertain
MDR (isoniazid and rifampicin)	Same as previous pathogen; increased probability of exposure to	Choice of drugs requires consultation with	

Preventive regimen			
Pathogen	**Indication**	**First choice**	**Alternative**
	MDR-TB	public health authorities and depends on susceptibility of isolate from source patient	
MAC[b]	For children aged >6 years with CD4 count <50 cells/mm^3; aged 2–5 years with CD4 count <75 cells/mm^3; aged 1–2 years with CD4 count <500 cells/mm^3; aged <1 year with CD4 count <750 cells/mm^3	• Clarithro-mycin: 7.5 mg/kg body weight (max. 500 mg) orally 2 x QD (**AII**); OR • Azithromycin: 20 mg/kg body weight (max. 1,200 mg) PO QW (**AII**)	• Azithromycin: 5 mg/kg body weight (max. 250 mg) PO QD (**AII**); • Children aged >6 years: Rifabutin (300 mg PO QD) (**BI**)
VZV[c]	Substantial exposure to varicella or shingles with no history of varicella or zoster or seronegative status for VZV by a sensitive, specific antibody assay or lack of evidence for age-appropriate vaccination	Varicella-zoster immune globulin (VariZIG): 125 IU per 10 kg (max. 625 IU) IM, administered within 96 hrs after exposure[d] (**AIII**)	• If VariZIG is not available or >96 hrs have passed since exposure, some experts recommend prophylaxis with acyclovir—20 mg/kg body weight (max. 800 mg) per dose orally 4 times a day for 5–7 days • Another alternative to VariZIG is IV immunoglobulin (IVIG)—400 mg/kg, administered once within 96 hrs after exposure (**CIII**)
Vaccine-preventable pathogens	Standard recommendations for HIV-exposed and HIV-infected children	Routine vaccinations (see figures 5 or 9 and/or tables 36 and 42)	
Usually recommended			
Toxoplasma gondii[e]	Immunoglobulin G (IgG) antibody to *Toxoplasma* and severe immunosuppression: HIV-infected children aged <6 years with CD4 percentage <15%; HIV-infected children aged >6 years with CD4 count <100 cells/mm^3 (**BIII**)	• Co-trimoxazole: 150/750 mg/m^2 body surface area PO QD in 2 divided doses (**BIII**) • Acceptable alternative dosage schedules for same dosage (**AI**): Single dose PO 3 x QW on consecutive days; 2 divided doses PO QD; or 2 divided	• Children aged >1 month: o Dapsone: 2 mg/kg body weight or 15 mg/m^2 body surface area (max. 25 mg) PO QD; PLUS o Pyrimethamine: 1 mg/kg body weight (max. 25 mg) PO QD; PLUS o Leucovorin: 5 mg PO every 3 days (**BI**) • Atovaquone: o Children aged 1–3 months and >24 months: 30 mg/kg body weight PO QD; o Children aged 4–24 months, 45 mg/kg body weight PO QD) o For both ages: With or without pyrimethamine: 1 mg/kg body weight or 15 mg/m^2 body surface area (max. 25 mg) PO QD; PLUS

Preventive regimen			
Pathogen	**Indication**	**First choice**	**Alternative**
		doses PO 3 x QW on alternate days	Leucovorin (5 mg PO every 3 days) (**CIII**)
Not recommended for most children; indicated for use only in unusual circumstances			
Invasive bacterial infections	Hypogammaglobulinemia (i.e., IgG <400 mg/dL)	• IVIG (400 mg/kg body weight every 2–4 wks) (**AI**)	
CMV	CMV antibody positivity and severe immunosuppression (CD4 count <50 cells/mm^3)	• Valganciclovir, 900 mg orally 1 x QD with food for older children who can receive adult dosing (**CIII**)	

[a] *Daily co-trimoxazole reduces the frequency of certain bacterial infections. Co-trimoxazole, dapsone-pyrimethamine, and possibly atovaquone (with or without pyrimethamine) protect against toxoplasmosis; however, data have not been prospectively collected. Compared with weekly dapsone, daily dapsone is associated with lower incidence of PCP but higher hematologic toxicity and mortality. Patients receiving therapy for toxoplasmosis with sulfadiazine-pyrimethamine are protected against PCP and do not need co-trimoxazole.*

[b] *Substantial drug interactions can occur between rifamycins (i.e., rifampicin and rifabutin) and PIs and NNRTIs; a specialist should be consulted.*

[c] *Children routinely being administered IVIG should receive VariZIG if the last dose of IVIG was administered >21 days before exposure.*

[d] *As of 2007, VariZIG can be obtained only under a treatment Investigational New Drug protocol (1-800-843-7477, FFF Enterprises, Temecula, CA, US.)*

[e] *Protection against toxoplasmosis is provided by the preferred anti-Pneumocystis regimens and possibly by atovaquone.*

The following table outlines OECS's prevention guidelines for OI recurrence (post-treatment) in HIV-infected infants and children (also called 'maintenance therapy').

TABLE 35. Prophylaxis to prevent OI recurrence in HIV-exposed and HIV-infected infants and children

Preventive regimen—recurrence			
Pathogen	**Indication**	**First choice**	**Alternative**
Recommended as standard of care after completion of initial therapy			
PCP[a]	Prior PCP	• Co-trimoxazole: 150/750 mg/m^2 body surface area QD (max. 320/1,600 mg) PO divided into 2 doses and administered 3 x QW on consecutive days (**AI**) • Acceptable alternative dosage schedules for same dosage: Single dose PO 3 x QW on consecutive days; 2 divided doses PO QD; or 2 divided doses PO 3 x QW on alternate days (**Al**)	• Dapsone: o Children aged >1 month: 2 mg/kg body weight (max. 100 mg) PO QD or 4 mg/kg body weight (max. 200 mg) orally weekly (**BI**) • Atovaquone: o Children aged 1–3 months and >24 months: 30 mg/kg body weight PO QD o Children aged 4–24 months: 45 mg/kg body weight PO QD (**BI**) • Aerosolized pentamidine: Children aged >5 years: 300 mg every morning by nebulizer (**BI**)
Toxoplasma gondii[a]	Before *Toxoplasma* encephalitis	• Sulfadiazine: 85–120 mg/kg body weight (max. 2–4 g) PO QD divided into in 2–4 doses; PLUS • Pyrimethamine: 1 mg/kg body weight or 15 mg/m^2 body surface area (max. 25 mg) PO QD; PLUS • Leucovorin: 5 mg orally every 3 days (**AI**)	• Clindamycin: 20–30 mg/kg body weight PO QD divided into 3–4 doses; PLUS • Pyrimethamine: 1 mg/kg body weight or 15 mg/m^2 body surface area (max. 25 mg) PO QD; PLUS • Leucovorin: 5 mg orally every 3 days (**BI**) • Atovaquone: o Children aged 1–3 months and >24 months: 30 mg/kg body weight PO QD; o Children aged 4–24 months: 45 mg/kg body weight PO QD) o For both ages: With or without pyrimethamine: 1 mg/kg body weight or 15 mg/m^2 body surface area (max. 25 mg) PO QD; PLUS Leucovorin: 5 mg orally every 3 days (**CIII**)
MAC[b]	Prior disease	• Clarithromycin: 7.5 mg/kg body weight (max. 500 mg) orally 2 x QD (**AII**); PLUS • Ethambutol: 15–25 mg/kg body weight (max. 2.5 g)	• Azithromycin: 5 mg/kg body weight (max. 250 mg) PO QD (**AII**); PLUS • Ethambutol: 15–25 mg/kg body weight (max. 2.5 g) PO QD

Preventive regimen—recurrence			
Pathogen	**Indication**	**First choice**	**Alternative**
		PO QD (**AII**); • With or without rifabutin: 5 mg/kg body weight (max. 300 mg) PO QD (**CII**)	(**AII**); • With or without rifabutin: 5 mg/kg body weight (max. 300 mg) PO QD (**CII**)
Coccidioides spp.	Documented disease	Fluconazole: 6 mg/kg body weight (max. 400 mg) PO QD (**AII**)	Itraconazole: 2–5 mg/kg body weight (max. 200 mg) orally per dose 2 x QD (**AII**)
Cryptococcus neoformans	Documented disease	Fluconazole: 6 mg/kg body weight (max. 200 mg) PO QD (**AI**)	Itraconazole oral solution: 5 mg/kg body weight (max. 200 mg) PO QD (**BI**)
Histoplasma capsulatum	Documented disease	Itraconazole oral solution: 5 mg/kg body weight (max. 200 mg) PO per dose 2 x QD (**AII**)	Fluconazole: 3–6 mg/kg body weight (max. 200 mg) PO QD (**CII**)
Microsporidiosis	Disseminated, nonocular infection caused by microsporidia other than *Enterocytozoonbieneusi*	Albendazole: 7.5 mg/kg body weight (max. 400 mg/dose) per dose orally 2 x QD (**AII**) until immune reconstitution after initiation of HAART	
	Ocular infection	• Topical fumagillin bicylohexylammonium(Fumidil B): 3 mg/mL in saline (fumagillin 70 μg/mL) eye drops—2 drops every 2 hrs for 4 days, then 2 drops 4 x QD (investigational use only in the US) (**BII**); PLUS • Albendazole: 7.5 mg/kg body weight (max. 400 mg/dose) PO 2 x QD to manage systemic infection (**BIII**)	
CMV	Prior retinitis, neurologic disease, or gastrointestinal disease with relapse	• Ganciclovir: 5 mg/kg body weight IV QD (**AI**); or • Foscarnet: 90–120 mg/kg body weight IV QD (**AI**); or • Valganciclovir: 900 mg PO 1 time QD with food for older children who can receive adult dosing (**AI**)	• For retinitis: ○ Ganciclovir sustained-release implant: Every 6–9 months; PLUS ○ Ganciclovir: 30 mg/kg body weight orally 3 x QD (**BIII)**
Recommended only if subsequent episodes are frequent or severe			
Invasive bacterial Infections[c]	>2 infections in a 1-year period	• Co-trimoxazole: 150/750 mg/m^2 body surface area PO QD divided into in 2 doses (**BI**) • IVIG: 400 mg/kg body weight every 2–4 weeks (**BI**)	Antibiotic chemoprophylaxis with another active agent (**BIII**)
Bartonellosis	Frequent or severe recurrences	• Doxycycline: 2–4 mg/kg body weight (max. 100–200 mg/day) per day PO 1 x QD or divided into 2 doses	• One of the macrolide antibiotics (**AIII**)—e.g., azithromycin, 5–12 mg/kg body weight (max. 600

Preventive regimen—recurrence			
Pathogen	**Indication**	**First choice**	**Alternative**
		(**AIII**) • Note: Tetracyclines contra-indicated in children <8 years of age	mg/day) PO 1 x QD; OR • Clarithromycin: 15 mg/kg body weight (max. 1 g/day) PO QD divided into 2 doses; OR • Erythromycin: 30–50 mg/kg body weight (max. 2 g/day) PO QD divided into 2 doses (**AIII**)
Candida (oesophageal)	Frequent or severe recurrences	Fluconazole: 3–6 mg/kg body weight (max. 200 mg) PO QD (**BI**)	—
HSV	Frequent or severe recurrences	Acyclovir: 20 mg/kg body weight (max. 400 mg/dose) per dose PO 2 x QD (**AI**)	• Valacyclovir: 500 mg PO 2 x QD; OR • Famicilovir: 500 mg PO 2 x QD for children old enough to receive adult dosing (**AI**)

[a] *Pyrimethamine plus sulfadiazine, and possibly atovaquone, confers protection against PCP as well as against toxoplasmosis. Although the clindamycin-plus-pyrimethamine or atovaquone-with/without-pyrimethamine regimens are recommended for adults, they have not been tested in children. However, these drugs are safe and are used for other infections in children.*

[b] *Substantial drug interactions might occur between rifabutin and PIs and NNRTIs; a specialist should be consulted.*

[c] *Antimicrobial prophylaxis should be chosen on the basis of microorganism identification and antibiotic susceptibility testing. Co-trimoxazole, if used, should be administered daily. Health-care providers should be cautious about using antibiotics solely for this purpose because of the potential for development of drug-resistant microorganisms. IVIG might not provide additional benefit to children receiving daily co-trimoxazole but might be considered for children who have recurrent bacterial infections despite co-trimoxazole prophylaxis. Choice of antibiotic prophylaxis versus IVIG also should involve consideration of adherence, ease of IV access, and cost. If IVIG is used, respiratory syncytial virus (RSV) IVIG (750 mg/kg body weight), not monoclonal RSV antibody, can be substituted for IVIG during the RSV season to provide broad anti-infective protection, if this product is available.*

2.11.1 Immunizations for HIV-infected Infants and Children

Immunization recommendations for HIV-infected children in the OECS are the same as immunization recommendations for non-HIV infected children, with the following exceptions:

- BCG is contra-indicated;
- MMR and Varicella vaccines should not be administered to children who are severely immuno-compromised (CD4% less than 15%)
- Inactivated Polio Vaccine (IPV) is preferred over Oral Polio Vaccine (OPV)
- Pneumococcal vaccination (polysaccharide PPSV 23-valent, and/or conjugate PCV 7-valent) is recommended for HIV-infected infants and children given their vulnerability to pneumococcal pneumonia. See http://www.cdc.gov/mmwr/pdf/rr/rr5811.pdf for details regarding paediatric pneumococcal vaccination options.

These recommendations also correspond to perinatally HIV-exposed infants (HEIs) who are awaiting laboratory confirmation that they are HIV-uninfected. Once HIV infection has been ruled out in an HEI, the normal vaccination schedule can be followed.

2.12 PAEDIATRIC THERAPIES FOR OPPORTUNISTIC INFECTIONS

This section provides detailed guidance on the management of selected OIs commonly seen in HIV-infected children in the Caribbean region. These recommendations have been adapted for the Eastern Caribbean region from paediatric OI guidelines written by the CDC et al[28]. Not all treatments listed may be available in the OECS but are included in case referral outside the region is an option. For management of OIs not listed below, please consult the original CDC OI Guidelines.[29]

Preferred and alternative treatment options are presented; each recommendation includes a rating of its strength as well as the quality of the evidence supporting it, coded as follows.

Strength of recommendation:

A. Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B. Moderate evidence for efficacy, or strong evidence for efficacy but only limited clinical benefit, supports recommendation for use. Should generally be offered.
C. Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of treatment or alternative approaches. Optional.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

Quality of the evidence supporting the recommendation

I. Evidence from at least one properly-designed randomized, controlled trial.
II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one centre), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

[28] Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR. 2009 Sep 4; 58(11). Available from: http://www.cdc.gov/mmwr/pdf/rr/rr5811.pdf.

Table 37. Recommendations for treatment of OIs in HIV-exposed- and HIV-infected infants and children

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
Bacterial infections			
Bacterial pneumonia (*Streptococcus pneumoniae;* occasionally *Staphylococcus aureus, Hib, Pseudomonas aeruginosa*)	• Ceftriaxone: 80–100 mg/kg body weight per day (max. 4 g/day) in 1 or 2 divided doses (**AIII**); OR • Cefotaxime: 150–200 mg/kg body weight (max. 8–10 g/day) per day divided into 3 or 4 doses (**AIII**)	Cefuroxime: 100–150 mg/kg body weight (max. 4–6 g/day) divided into 3 doses (**AIII**)	• Add azithromycin for hospitalized patients to treat other common community-acquired pneumonia pathogens (e.g., *Mycoplasma pneumoniae, Chlamydia pneumoniae*) • Add clindamycin or vancomycin if methicillin-resistant *S. aureus* is suspected (choice based on local susceptibility patterns) • For patients with neutropenia, chronic lung disease other than asthma (e.g., lymphoid interstitial pneumonia, bronchiectasis) or indwelling venous catheter, consider regimen that includes activity against *P. aeruginosa* (e.g., cefepime instead ofceftriaxone) • Consider PCP in patients with severe pneumonia or more advanced HIV disease • Consider evaluation for TB and cryptococcosis
Bartonellosis	Cutaneous bacillary angiomatosis infections: • Erythromycin: 30–50 mg/kg body weight (max. 2 g/day) per day orally divided into 2–4 doses, or if unable to take oral medication, 15–50 mg/kg body weight (max. 2 g/day) per day IV in divided doses 4 times a day (**AII**) • Doxycycline: 2–4 mg/kg body weight (max. 100–200 mg/day) PO QD or IV 1 x QD or divided into 2 doses (**AII**); tetracycines contra-indicated in children <8 years of age *Treatment duration: 3 months*	• Azithromycin: 5–12 mg/kg body weight (max. 600 mg/day) PO 1 x QD (**BIII**) • Clarithromycin: 15 mg/kg body weight (max. 1 g/day) PO QD divided into 2 doses (**BIII**)	• Severe Jarisch-Herxheimer–like reaction can occur in the first 48 hours after treatment • Long-term suppression with erythromycin or doxycycline may be considered in patients with relapse or reinfection (**CIII**)
	CNS infections, bacillary peliosis, osteomyelitis,	Rifampicin: 20 mg/kg body weight (max. 600	

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	severe infections: • Doxycycline: 2–4 mg/kg body weight (max. 100–200 mg/day) per day orally or IV 1 x QD or divided into 2 doses (**AIII**); tetracycines contra-indicated in children <8 years of age *Treatment duration: 4 months*	mg/day) per day orally or IV 1 x QD or divided into 2 doses; can be used in combination with erythromycin or doxycycline in patients with more severe infections (**BIII**)	
Syphilis	Congenital—proven or highly probable disease: • Aqueous crystalline penicillin G: 100,000–150,000 U/kg body weight per day, administered as 50,000 U/kg body weight IV every 12 hrs for the first 7 days of life, then every 8 hours for a total of 10 days (**AII**) • If diagnosed after 1 month of age, aqueous penicillin G, 50,000 U/kg body weight per dose IV every 4–6 hrs for 10 days (**AII**) Acquired: Early stage (primary, secondary, early latent): • Benzathine penicillin: 50,000 U/kg body weight (max. 2.4 million units) IM for 1 dose (**AII**) Late latent stage: • Benzathine penicillin: 50,000 U/kg body weight (max. 2.4 million units) IM once weekly for 3 doses (total 150,000 U/kg body weight; mzx 7.2 million units)(**AIII**)	Congenital: • Alternative for proven or highly probable disease (less desirable if CNS involved): ○ Procaine penicillin G: 50,000 U/kg body weight IM 1 x QD for 10 days (BII) • Infants with possible congenital syphilis (maternal treatment and response adequate, normal physical examination, normal CSF studies, but serum quantitative non-treponemal serologic titre that is the same or 4-fold higher than maternal titre): ○ Benzathine penicillin G: 50,000 U/kg body weight IM in a single dose (max. 2.4 million units) (BII)	• For treatment of congenital syphilis, repeat entire course of treatment if even 1 day of treatment is missed • Children with congenital syphilis should be evaluated at 1, 2, 3, 6, and 12 months of age and have non-treponemal testing at 3, 6, and 12 months after conclusion of therapy or until test becomes negative (**AIII**) • Children with increasing titres or persistently positive titres (even if low levels) at age 6–12 months should be evaluated and considered for retreatment (**AIII**) • Children and adolescents with acquired syphilis should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy (**AIII**)
	Neurosyphilis (including		

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	ocular): • Aqueous penicillin G: 200,000–300,000 U/kg body weight IV every 6 hours (max. 18–24 million units per day) for 10–14 days (**AII**)		
Mycobacterial infections			
MTB	Intensive phase (8 wks) (**AI**): • Isoniazid: 10–15 mg/kg body weight (max. 300 mg/day) PO 1 x QD; PLUS • Rifampicin: 10–20 mg/kg body weight (max. 600 mg/day) PO 1 x QD; PLUS • Pyrazinamide: 20–40 mg/kg (max. 2 g/day) body weight PO 1 x QD; PLUS • Ethambutol: 15–25 mg/kg body weight (max. 2.5 g/day) PO 1 x QD (**AI**) Continuation phase (for drug- susceptible TB) (**AI**): • Daily: o Isoniazid: 10–15 mg/kg body weight (max. 300 mg/day) PO 1 x QD; PLUS o Rifampicin: 10–20 mg/kg body weight (max. 600 mg/day) PO 1 x QD (**AI**) • Intermittent: o Isoniazid: 20–30 mg/kg body weight (max. 900 mg/day) PO 1 x QD, 3 x QW; PLUS o Rifampicin: 10–20 mg/kg body weight (max.	• Alternative drug for rifampicin is rifabutin: 10–20 mg/kg body weight (max. 300 mg/day) PO 1 x QD (same dose is for intermittent 2 or 3 x QW regimen) (**BIII**) • Alternative drug for ethambutol is streptomycin: 20–40 mg/kg body weight (max. 1 g/day) IM PO 1 x QD (or 20 mg/kg as intermittent 2 or 3 times weekly regimen) (**BIII**) • Ethionamide: 15–20 mg/kg body weight orally (max. 1 g/day) divided into 2 or 3 doses per day should be used for TB meningitis (**AIII**). Drug-resistant TB: • Resistance to isoniazid alone: o Discontinue isoniazid o Rifampicin PLUS pyrazinamide PLUS ethambutol (ethionamide or streptomycin can be substituted for ethambutol if *M. tuberculosis* isolate is susceptible to these agents)	• Directly observed therapy should be standard of care for children with TB (**AII**) • Potential drug interactions should be carefully reviewed • In HAART-naive child, initiate therapy for TB 2–8 weeks before starting antiretroviral drugs (**BII**); for children already receiving HAART in whom TB is diagnosed, the child's ARV regimen should be reviewed and altered, if needed, to ensure optimal treatment for both TB and HIV and to minimize potential toxicities and drug-drug interactions (**AIII**) • For children with severe immunosuppression (CD4 percentages <15% for children >6 yrs old, <100 cell/μL), continuation phase for drug-susceptible TB should include either daily or thrice-weekly treatment; twice-weekly regimens should *not* be used because they may lead to rifamycin resistance in immunosuppressed patients (**AII**) • Pyridoxine should be administered if isoniazid or cycloserine is administered (**AII**) • Adjunctive treatment with corticosteroids is indicated for children with CNS disease (**AII**) and can be considered for children with pleural or pericardial effusions, severe miliary disease, and significant endobronchial disease (**BIII**) • Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and colour discrimination (**AIII**)

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	600 mg/day) PO PO 1 x QD 3 x QW (**AI**); ○ Administration of the drugs twice weekly can be considered only for children who are not immuno-suppressed (i.e., CD4 percentage >15% or >100 cells/μL who are >6 years old) (**CIII**) *Treatment duration (drug-sensitive TB)* (**AIII**): • Pulmonary TB: 9 months for HIV-infected child (6 months if not HIV-infected) • Extrapulmonary TB: 12 months	(**BII**) • Resistance to rifampicin alone: ○ Discontinue rifampicin ○ Isoniazid PLUS pyrazinamide PLUS ethambutol PLUS streptomycin for first 2 mos, followed by continuation phase of isoniazid PLUS pyrazinamide PLUS ethambutol to complete 12- to 18-month course (**BIII**) ○ For older adolescents: Isoniazid PLUS pyrazinamide PLUS ethambutol PLUS a fluoroquinolone for 2 months, followed by isoniazid PLUS ethambutol PLUS a fluoroquinolone to complete 12- to 18-month course (**BIII**) • Multidrug resistance: ○ Therapy should be based on resistance pattern (of child or of source case when child's isolate is not available), and children should be managed in consultation with an expert (**AIII**) Treatment duration (drug-	• Thiacetazone can cause severe or fatal reactions in HIV-infected children, including rash and aplastic anaemia, and should not be used (**EIII**) • For drug-resistant strains, ≥2 drugs to which the isolate is susceptible should be administered (minimum of 3 drugs should be administered through the continuation phase of therapy) • Second-line drugs for MDR-TB: ○ Amikacin: 15–30 mg/kg body weight (max. 1 g/day) IM 1 x QD ○ Capreomycin: 15–30 mg/kg body weight (max. 1 g/day) IM 1 x QD ○ Ciprofloxacin: 10–15 mg/kg body weight PO 2 x QD (max. 1.5 g/day); levofloxicin: (500–1,000 mg PO 1 x QD); OR moxifloxacin: 400 mg PO 1 x QD (fluoroquinolones are not labeled for use in children <18 years old because of concerns about potential effects on cartilage; use in younger persons requires assessment of potential risks and benefits) (**CIII**) ○ Cycloserine: 10–20 mg/kg body weight (max. 1 g/day) PO 1 x QD ○ Ethionamide/prothionamide: 15–20 mg/kg body weight (max. 1 g/day) PO in 2–3 divided doses ○ Kanamycin: 15–30 mg/kg body weight (max. 1 g/day) IM 1 x QD ○ Para-aminosalicylic acid: 200–300 mg/kg body weight PO divided into 3–4 doses per day (max. 10 g/day) ○ Streptomycin: 20–40 mg/kg body weight (max. 1 g/day) IM PO 1 x QD

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
		resistant TB) (**AIII**): • *Single drug—isoniazid-resistant TB: 9–12 months* (**BII**) • *Single drug—rifampicin-resistant TB: 12–18 months* (**BIII**) • *MDR-TB: 18–24 months after culture conversion in children with bacteriologic confirmation; ≥12 months in children who were culture-negative at treatment initiation*	
Mycobacterial infections			
MAC	Initial treatment (≥2 drugs) (**AI**): • Clarithromycin: 7.5–15 mg/kg body weight (max. 500 mg/dose) PO 2 x QD (**AI**); PLUS • Ethambutol: 15–25 mg/kg body weight (max. 2.5 g/day) PO 1 x QD (**AI**), followed by chronic suppressive therapy • For severe disease, add rifabutin: 10–20 mg/kg body weight (max. 300 mg/day) PO 1 x QD (**CI**)	• Azithromycin (10–12 mg/kg body weight [max. 500 mg/day] PO 1 x QD if intolerant to clarithromycin) (**AII**) • If rifabutin cannot be administered (or if a fourth drug is needed for patients with more severe symptoms or disseminated disease): Ciprofloxacin (10–15 mg/kg body weight PO 2 x QD [max. 1.5 g/day]); OR • Levofloxicin (500 mg orally PO 1 x QD); OR • Amikacin (15–30 mg/kg body weight IV in 1 or 2 divided doses [max. 1.5 g/day]) (**CIII**)	• Combination therapy with a minimum of 2 drugs is recommended (**AI**) • Clofazamine is associated with increased mortality in HIV-infected adults and should not be used (**EII**) • Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and colour discrimination (**AIII**). • Fluoroquinolones (e.g., ciprofloxacin, levofloxacin) are not labeled for use in children <18 years because of concerns about potential effects on cartilage; use in younger persons requires an assessment of potential risks and benefits (**CIII**) • Chronic suppressive therapy (secondary prophylaxis) is recommended in children and adults after initial therapy (table 29)
Fungal infections			
Aspergillosis	Voriconazole: 6–8 mg/kg body weight per dose IV or 8 mg/kg body weight (max. 400 mg) per dose PO 2 x QD on day 1, followed by 7 mg/kg body	• Amphotericin B deoxycholate: 1.0–1.5 mg/kg body weight IV 1 x QD (**AIII**) • Lipid formulations of amphotericin B: 5	• Potential for significant pharmacokinetic interactions between PIs or NNRTIs with voriconazole and should be used cautiously in these situations • Consider therapeutic drug

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	weight (max. 200 mg) per dose IV or PO 2 x QD (**AI**) *Treatment duration: ≥12 weeks, but duration should be individualized according to the patient's clinical response*	mg/kg body weight IV 1 x QD (**AIII**) • Caspofungin: 70 mg/m^2 body surface area (max. 70 mg) IV as loading dose, then 50 mg/m^2 body surface area (max. 50 mg) IV 1 x QD (**CIII**)	monitoring and dosage adjustment if necessary
Candidiasis	Oropharyngeal disease: • Fluconazole: 3–6 mg/kg body weight (max. 400 mg/dose) PO 1 x QD (**AI**) • Itraconazole cyclodextrin oral solution: 2.5 mg/kg body weight PO 2 x QD (max. 200 mg/day) (**AI**) • Clotrimazole trouches: 10 mg troche PO 4 x QD (**BII**) • Nystatin suspension: 4–6 mL PO 4 x QD; OR one to two 200,000 U flavored pastilles orally 4–5 x QD (**BII**) *Treatment duration: 7–14 days* Oesophageal disease: • Fluconazole: 6 mg/kg body weight orally once on day 1, then 3–6 mg/kg body weight (max. 400 mg/dose) PO 1 x QD (**AI**) • Itraconazole cyclodextrin oral solution: 2.5 mg/kg body weight PO 2 x QD or 5.0 mg/kg body weight PO 1 x QD (**AI**) *Treatment duration: minimum of 4–21 days*	Oropharyngeal disease (fluconazolerefractory): • Itraconazole cyclodextrin oral solution: 2.5 mg/kg body weight PO 2 x QD (max. 200–400 mg/day) (**AI**) • Amphotericin B oral suspension: 1 mL (100 mg/mL) PO 4 x QD (**BII**) Oesophageal disease: • Amphotericin B: 0.3–0.5 mg/kg body weight IV 1 x QD (**BII**) Invasive disease: • Fluconazole (5–6 mg/kg body weight IV or PO 2 x QD) (max. 600 mg/day) for minimum 4 weeks (if uncomplicated *C. albicans* candidemia) (**AI**) • Lipid formulations of amphotericin B: mg/kg body weight IV 1 x QD (**BII**) • Amphotericin B (according to preferred therapy dose) PLUS flucytosine: 100–150 mg/kg body weight orally divided into 4 doses for severe invasive disease, especially involving	• Itraconazole cyclodextrin oral solution should not be used interchangeably with itraconazole capsules • Itraconazole capsules are generally ineffective for treating oesophageal disease (**DII**) • Central venous catheters should be removed when feasible in HIV-infected children with fungemia (**AII**) • Fluconazole should not be used for empiric treatment of fungemia because resistance of non-*albicans Candida* species to fluconazole has been reported (**EIII**) • In uncomplicated catheter-associated *C. albicans* candidemia, an initial course of amphotericin B followed by fluconazole to complete treatment can be used (**BIII**) • Amphotericin B initiation doses: o Mild-to-moderate disease: initiate at 0.25–0.5 mg/kg body weight IV 1 x QD, then increase as tolerated to 0.5–1.5 mg/kg body weight IV 1 x QD (**BIII**) o Severe disease: Initiate treatment at target daily dose (**BIII**) • After children with invasive disease have stabilized and their fever has resolved while on daily therapy, amphotericin B can be administered as 1.5 mg/kg body weight IV once every other day (**BIII**) • Lipid formulation of amphotericin B may be used in patients with renal insufficiency or infusion-related toxicity to amphotericin B

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	Invasive disease: • Amphotericin B: 0.5–1.5 mg/kg body weight IV 1 x QD (**AI**) *Treatment duration: Based on presence of deep tissue foci and clinical response; in patients with candidemia, treat until 2–3 weeks after last by positive blood culture* (**AIII**)	the CNS (**CIII**)	(**BII**) • Voriconazole has been used to treat oesophageal candidiasis in a small number of immunocompromised children without HIV infection; because of limited experience in children, data are insufficient to recommend use of this drug for oesophageal or disseminated candidiasis (**CIII**) • Caspofungin has been used to treat oesophageal and invasive candidiasis in adults; however, data in children are limited and definitive paediatric dose has not been defined (**CIII**) • Flucytosine dose should be adjusted to keep drug levels 40–60μg/mL
Coccidioides spp.	Diffuse pulmonary or disseminated nonmeningitic disease: • Amphotericin B: 0.5–1.0 mg/kg body weight IV 1 x QD until clinical improvement (minimum of several weeks) (**AII**) Meningeal infection: • Fluconazole: 5–6 mg/kg body weight IV or PO 2 x QD (max. 800 mg/day) (**AII**)	Diffuse pulmonary or disseminated nonmeningitic disease (in stable patient): • Fluconazole: 5–6 mg/kg body weight IV or PO 2 x QD (max. 800 mg/day) (**BIII**) • Itraconazole: 5–10 mg/kg body weight IV or PO 2 x QD for 3 days, followed by 2–5 mg/kg body weight PO 2 x QD (max. 400 mg/day) (**BIII**) Meningeal infection (unresponsive to fluconazole): • Amphotericin B PLUS intrathecal amphotericin B (**CI**)	• Surgical debridement of bone and lung lesions may be helpful • Some experts add triazole to amphotericin B therapy and continue triazole once amphotericin B is stopped (**BIII**) • May consider voriconazole, capsofungin, or posaconazole (or combinations thereof), although experience in children is limited, and definitive paediatric dose has not been defined (**CIII**) • Options should be discussed with an expert in treating coccidioidomycosis • Chronic suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is recommended for children after initial induction therapy (table 29)
Fungal infections, continued			
Cryptococcus neoformans	CNS disease: • Acute therapy (minimum 2-week induction followed by consolidation therapy) o Amphotericin B: 0.7–1.0 mg/kg	CNS disease: • Acute therapy (minimum 2-week induction followed by consolidation therapy): o Liposomal amphotericin B:	• In patients with meningitis, CSF culture should be negative before initiation of consolidation therapy • Overall in vitro resistance to antifungal agents used to treat cryptococcosis remains uncommon; newer azoles (voriconazole, posaconazole, ravuconazole) are all

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	body weight (or liposomal amphotericin B, mg/kg body weight) IV QD; PLUS ○ Flucytosine: 100 mg/kg body weight PO QD divided 4 x QD (**AI**); OR ○ Liposomal amphotericin B: 4–6 mg/kg body weight IV 1 x QD (especially in children with renal insufficiency or infusion-related toxicity to amphotericin B); PLUS ○ Flucytosine: 100 mg/kg body weight PO QD divided 4 x QD (**AII**) • Consolidation therapy (followed by chronic suppressive therapy): ○ Fluconazole: 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (max. 800 mg) QD IV or PO for a minimum of 8 weeks (**AI**) Localized disease including isolated pulmonary disease (CNS not involved): • Fluconazole: 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (max. 600 mg) IV or PO QD (**AIII**) *Treatment duration:*	4–6 mg/kg body weight IV once daily (especially in children with renal insufficiency or infusion-related toxicity to amphotericin B) (**AII**) ○ Amphotericin B: 0.7–1.5 mg/kg body weight IV once daily (if flucytosine not tolerated) (**BI**) ○ Fluconazole: 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (max. 800 mg) IV or orally daily; PLUS ○ Flucytosine, 100 mg/kg body weight orally daily divided 4 times a day (**BII**) (offered only if amphotericin B-based therapy not tolerated) Consolidation therapy (followed by chronic suppressive therapy): • Itraconazole: 5–10 mg/kg per day once or twice daily (max. 200 mg/dose) for a minimum of 8 wks (**BI**); a loading dose (calculated twice daily dose is administered 3 times daily) for the first 3 days (max. 200 mg/dose, 600 mg/day) (see comment on itraconazole under	very active in vitro against *C. neoformans*, but published clinical experience is limited about their use for cryptococcosis • Liquid preparation of itraconazole (if tolerated) is preferable (but more expensive) over tablet formulation because of better bioavailability (**BIII**) • Serum concentrations of itraconazole should be monitored to optimize drug dosing • Amphotericin B may increase toxicity of flucytosine by increasing cellular uptake or impairing its renal excretion or both • Flucytosine dose should be adjusted to keep drug levels at 40–60 μg/mL • Oral acetazolamide should not be used to reduce intracranial pressure in cryptococcal meningitis (**DIII**) • Chronic suppressive therapy (secondary prophylaxis) with fluconazole is recommended for children after initial therapy (table 29)

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	Length of initial therapy for non-CNS disease depends on site and severity of infection and clinical response Disseminated disease (CNS not involved) or severe pulmonary disease: • Amphotericin B: 0.7–1.0 mg/kg body weight; OR • Amphotericin liposomal: 3–5 mg/kg body weight; OR • Amphotericin lipid complex: 5 mg/kg body weight IV 1 x QD (with or without flucytosine) (**AIII**) *Treatment duration: Length of initial therapy for non-CNS disease depends on site and severity of infection and clinical response*	'Other options or issues' in this table) Localized disease including isolated pulmonary disease (CNS not involved) • Amphotericin B: 0.7–1.0 mg/kg body weight; OR • Amphotericin liposomal: 3–5 mg/kg body weight; OR • Amphotericin lipid complex: 5 mg/kg body weight IV QD (**AIII**) Disseminated disease (CNS not involved) or severe pulmonary disease: • Fluconazole: 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (max. 600 mg) IV or orally 1 x QD (**AIII**)	
Histoplasma capsulatum	Mild disseminated disease: • Itraconazole oral solution: Initial loading dose of 2–5 mg/kg body weight per dose (max. 200 mg) PO 3 x QD for first 3 days of therapy, followed by 2–5 mg/kg body weight (max. 200 mg) per dose 2 x QD for 12 months (**AII**) Moderately severe to severe disseminated disease: • Acute therapy (minimum 1- to 2-wk induction, longer if clinical improvement is delayed, followed by consolidation	Moderately severe to severe disseminated disease or CNS infection: • Acute therapy (minimum 1- to 2-week induction, longer if clinical improvement is delayed or at least 4–6 weeks if CNS involved, followed by consolidation therapy): o Amphotericin B deoxycholate: 1 mg/kg body weight IV 1 x QD (**AIII**)	• Urine antigen should be monitored to identify relapse • Serum concentrations of itraconazole should be monitored and reach 1 μg/mL at steady-state; levels exceeding 10μg/mL should be followed by dose reduction • Urine antigen should be monitored to identify relapse • A high relapse rate with CNS infection occurs in adults, thereby requiring longer therapy; treatment in children is anecdotal and expert consultation should be considered • Chronic suppressive therapy (secondary prophylaxis) with itraconazole is recommended for children after initial therapy (table 29)

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	therapy) o Lipsomal amphotericin B, 3 mg/kg body weight IV 1 x QD (**AI**) • Consolidation therapy (followed by chronic suppressive therapy): o Itraconazole oral solution: initial loading dose of 2–5 mg/kg body weight per dose (max. 200 mg) orally 3 x QD for first 3 days of therapy, followed by 2–5 mg/kg body weight (max. 200 mg) per dose 2 x QD for 12 months (**AII**) CNS infection • Acute therapy (4–6 weeks, followed by consolidation therapy): o Lipsomal amphotericin B, 5 mg/kg body weight IV 1 x QD (**AII**) • Consolidation therapy (followed by chronic suppressive therapy): o Itraconazole oral solution: initial loading dose of 2–5 mg/kg body weight per dose (max. 200 mg) orally 3 x QD for first 3 days of therapy, followed by 2–5 mg/kg body weight (max. 200 mg) per dose		

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	2 x QD for ≥12 months and until histoplasmal antigen is no longer detected (**AII**)		
PCP	Co-trimoxazole: 15–20 mg/kg body weight TMP; PLUS 75–100 mg/kg body weight SMX 1 x QD IV or orally in 3–4 divided doses (**AI**) (after acute pneumonitis resolved in mild-to-moderate disease, IV co-trimoxazole may be changed to oral) *Treatment duration (followed by chronic suppressive therapy): 21 days* (**AII**)	Alternative therapeutic regimens (if patient is co-trimoxazole-intolerant or clinical treatment fails after 5–7 days of co-trimoxazole therapy): • Pentamidine: 4 mg/kg body weight IV 1 x QD is first choice alternative regimen (**AI**) (pentamidine may be changed to atovaquone after 7–10 days IV therapy **[BIII]**) • Atovaquone: 30–40 mg/kg body weight (max. 1,500 mg/day) 1 x QD PO in 2 divided doses with food for patients from birth to 3 months and >24 months of age (**BI**); for infants aged 3–24 months, an increased dose of 45 mg/kg body weight QD in 2 divided doses with food is needed (**AII**)	• Dapsone: 2 mg/kg body weight PO 1 x QD (max. 100 mg/day) PLUS TMP: 15 mg/kg body weight orally per day divided into 3 doses has been used in adults (**BI**), but data in children are limited (**CIII**) • Primaquine base: 0.3 mg/kg body weight PO 1 x QD (max. 30 mg/day), PLUS clindamycin: 10 mg/kg body weight IV or orally (max. 600 mg IV and 300–450 mg orally) every 6 hours has been used in adults (**BI**), but data in children are not available (**CIII**). • Indications for corticosteroids (**AI**): PaO2 <70 mmHg at room air or alveolar-arterial oxygen gradient >35 mm Hg • Prednisone dose: 1 mg/kg body weight PO 2 x QD for 5 days, then 0.5–1.0 mg/kg body weight PO 2 x QD for 5 days, then 0.5 mg/kg body weight PO 1 x QD for days 11–21 • Chronic suppressive therapy (secondary prophylaxis) with co-trimoxazole is recommended for children and adults after initial therapy (table 29) (**AI**)
Parasitic infections			
Crypto-sporidiosis	Effective HAART—immune reconstitution may lead to microbiologic and clinical response (**AII**)	No consistently effective therapy exists for cryptosporidiosis in HIV-infected persons; optimized HAART and a trial of nitazoxanide can be considered: • Nitazoxanide (data from immunocompetent children) (**BI**), HIV-uninfected; (**CIII**), HIV-infected) in combination with effective HAART:	• Supportive care: Hydration, correct electrolyte abnormalities, nutritional support (**AIII**) • Antimotility agents (e.g., loperamide) should be used with caution in young children (**CIII**)

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
		○ 1–3 years: 100 mg PO 2 x QD ○ 4–11 years: 200 mg PO 2 x QD ○ ≥12 years: 500 mg PO 2 x QD *Treatment duration: Trial of <14 days*	
Malaria	Uncomplicated *Plasmodium falciparum* OR unknown malarial species from chloroquine-resistant area (all other malarial areas or unknown region): • Atovaquone-proguanil (Malarone™) (paediatric tablets 62.5 mg/25 mg; adult tablets 250 mg/100 mg adult tablets) (**AI**) ○ 5–8 kg: 2 paeds tablets x 3 days ○ 9–10 kg: 3 paeds tablets x 3 days ○ 11–20 kg: 4 paeds tablets or 1 adult tablet x 3 days ○ 21–30 kg: 2 adult tablets x 3 days ○ 31–40 kg: 3 adult tablets x 3 days ○ >40 kg: 4 adult tablets x 3 days Chloroquine-sensitive region (north of the Panama Canal): • Chloroquine phosphate: 16.6 mg/kg (10 mg/kg body weight base) (max. 1,000 mg) orally once, then 8.3 mg/kg body weight (max. 500 mg) orally at 6, 24, 48 hours (total dose = 41.6	Uncomplicated *P. falciparum* OR unknown malaria species, chloroquine-resistant (all other malarial areas or unknown region): • Mefloquine (Larium™) (250 g tablets only): 15 mg/kg body weight (max. 750 mg) orally once, then 10 mg/kg body weight (max. 500 mg) orally 12 hrs later • Quinine sulphate: 10 mg/kg body weight (max. 650 mg) orally every 8 hours for 3–7 days; PLUS • Clindamycin: 20 mg/kg body weight daily orally divided into 3 doses every 8 hours for 7 days Severe malaria: • Quinidine: 6.25 mg base/kg body weight IV loading dose over 1–2 hours, then 0.0125 mg/kg/minute infusion, *(treatment duration: 7 days for patients who have been in southeast Asia or Oceania; otherwise 3 days*) • Doxycycline: 100 mg per dose orally every 12 hrs for 7 days, OR • Clindamycin: 20 mg/kg body weight	• Chloroquine phosphate is the only formulation of chloroquine available in the U.S.; 10 mg of chloroquine phosphate = 6 mg of chloroquine base • In combination with quinine, an alternative to clindamycin is doxycycline in persons >8 years of age • Doxycycline: 2.2 mg/kg (max. 100 mg) PO 2 x QD for 7 days • Papua New Guinea has widespread chloroquineresistant *P. vivax*; thus, patients with malaria who have traveled there should be treated as having chloroquine-resistant malaria • Before primaquine is administered, glucose-6-phosphate dehydrogenase status *mus*t be verified • Primaquine typically is administered after the initial chloroquine blood-phase therapy, not in combination • Quinidine gluconate is a class 1a anti-arrhythmic agent not typically stocked in paediatric hospitals • Do not give quinidine gluconate as an IV bolus; administration of quinidine gluconate IV should be monitored and cardiac monitoring is required • Adverse events that can result from use of quinidine gluconate at treatment doses include severe hypoglycemia, prolongation of the QT interval, ventricular arrhythmia, and hypotension • Artesunate is available only from CDC quarantine stations (as of July 2007); contact the CDC's malaria hotline: 770-488-7788, from 8 am to 4:30 pm EST, or 770-488-7100, after hours and on weekends and holidays • The most updated prevention and

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	mg/kg (**AI**) chloroquine phosphate [max. 2,500 mg] = 25 mg/kg chloroquine base) (**AI**) *P. vivax*, *P. ovale*, *P. malariae* (all areas except Papua New Guinea and Indonesia) • Initial therapy (followed by antirelapse therapy) • Chloroquine phosphate: 16.6 mg (10 mg/kg body weight base) (max. 1,000 mg) orally once, then 8.3 mg/kg body weight (max. 500 mg) orally at 6, 24, 48 hours (total dose = 41.6 mg/kg body weight chloroquine phosphate [max. 2,500 mg] = 25 mg/kg body weight chloroquine base) (**AI**) • Antirelapse therapy for *P. ovale*, *P. vivax*: o Primaquine: 0.5 mg base/kg body weight (max. 30 mg base) PO QD for 14 days (**AI**) Severe malaria: • Quinidine gluconate: 10 mg/kg body weight IV loading dose over 1–2 hours, then 0.02 mg/kg/minute infusion for >24 hours, PLUS *(treatment duration: 7 days for patients who were in southeast Asia or Oceania; otherwise 3*	PO QD, divided into 3 doses every 8 hours for 7 days • Artesunate: 2.4 mg/kg body weight IV bolus at 0, 12, 24 hours, then 1 x QD for 7 days; when patient is able to take an oral regimen, can switch to either artesunate: 2 mg/kg body weight PO 1 x QD; PLUS • Doxycycline: 100 mg per dose orally every 12 hrs, OR mefloquine, 15 mg/kg body weight (max. 750 mg) orally once, then 10 mg/kg body weight (max. 500 mg) orally once 12 hours later	treatment recommendations for specific malarial regions are available at the CDC's website (http://www.cdc.gov/malaria/pdf/treatmenttable.pdf) • If regional supplies are not available, they can be obtained from Eli Lilly Company, telephone: 800-821-0538; the CDC's malaria hotline may be of assistance as well (770-488-7788, from 8 am to 4:30 pm EST, or 770-488-7100, after hours and on weekends and holidays)

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	days) • Doxycycline: 100 mg per dose orally every 12 hours for 7 days, OR • Clindamycin: 20 mg/kg body weight PO QD divided into 3 doses every 8 hours for 7 days; quinidine gluconate 10 mg = 6.25 mg quinidine base (**AI**)		
Microsporidiosis	• Effective HAART—immune reconstitution may lead to microbiologic and clinical response (**AII**) • For disseminated (not ocular) and intestinal infection attributed to microsporidia other than *Enterocytozoon bienuesi*: o Albendazole: 7.5 mg/kg body weight (max. 400 mg/dose) per dose PO 2 x QD (**AII**) *Treatment duration: continue until immune reconstitution after initiation of HAART* (**AIII**) • For ocular infection: o Topical fumagillin bicylohexylammonium (Fumidil B): 3 mg/mL in saline (fumagillin 70 μg/mL) eye drops—2 drops every 2 hours for 4 days, then 2 drops 4 x QD (investigational use only in US)		• Supportive care: Hydration, correct electrolyte abnormalities, nutritional support (**AIII**) • Antimotility agents (e.g., loperamide) should be used with caution in young children (**CIII**) • Fumagillin (adult dose: 20 mg/dose orally 3 x QD for 2 weeks), OR TNP-470 (a synthetic analogue of fumagillin; unavailable in the US) is recommended for treatment of infections because of *Enterocytozoon bienuesi* in HIV-infected adults; data on dosing in children are unavailable (**CIII**)

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	(**BII**); PLUS o Albendazole: 7.5 mg/kg body weight (max. 400 mg/dose) PO 2 x QD for management of systemic infection (**BIII**) *Treatment duration: continue indefinitely to prevent recurrence or relapse* (**BIII**)		
Toxoplasma gondii	Congenital toxoplasmosis (**AII**): • Pyrimethamine: o Loading dose is 2 mg/kg body weight PO 1 x QD for 2 days, then 1 mg/kg body weight PO 1 x QD for 2–6 months, then 1 mg/kg body weight orally 3 times weekly; PLUS o Leucovorin (folinic acid): 10 mg orally or IM with each dose of pyrimethamine; PLUS o Sulfadiazine: 50 mg/kg body weight PO 2 x QD *Treatment duration: 12 months* (**AII**) Acquired toxoplasmosis, acute induction therapy (followed by chronic suppressive therapy) (**AI**): • Pyrimethamine: loading dose is 2 mg/kg body weight (max. 50 mg) PO 1 x QD for 3 days, then 1 mg/kg body weight (max. 25 mg) PO 1 x	For sulfonamide-intolerant patients: • Clindamycin: 5–7.5 mg/kg body weight (max. 600 mg/dose) orally or IV per dose 4 x a day can be substituted for sulfadiazine combined with pyrimethamine and leukovorin (**AI**)	Congenital toxoplasmosis: • For infants born to mothers with symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of the mother's treatment during pregnancy (**BIII**) Acquired toxoplasmosis: • Pyrimethamine use requires CBC monitoring at least weekly while patient is on daily dosing and at least monthly while on less than daily dosing (**AIII**) • Co-trimoxazole (5 mg/kg body weight TMP PLUS 25 mg/kg body weight SMX per dose IV or PO 2 x QD) has been used as an alternative to pyrimethamine-sulfadiazine in adults (**BI**) but has not been studied in children (**CIII**) • Atovaquone—(adults: 1.5 g PO 2 x QD with food) in regimens combined with pyrimethamine-leukovorin; with sulfadiazine alone; or as a single agent in patients intolerant to both pyrimethamine and sulfadiazine—has been used in adults (**BII**), but these regimens have not been studied in children (**CIII**) • Azithromycin (adults: 900–1,200 mg/day) also has been used in adults—combined with pyrimethamine-sulfadiazine (**BII**)—but these have not been studied in children (**CIII**) • Corticosteriods (e.g., prednisone or

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	QD; PLUS • Sulfadiazine: 25–50 mg/kg body weight (max. 1.0–1.5 g/dose) orally per dose 4 x QD; PLUS • Leucovorin: 10–25 mg PO QD, followed by chronic suppressive therapy *Treatment duration (followed by chronic suppressive therapy): ≥6 weeks (longer if clinical or radiologic disease is extensive or response is incomplete at 6 weeks)* (**BII**)		dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or when the child has focal lesions with significant mass effects; they are to be discontinued as soon as clinically feasible (**BIII**) • Anti-convulsants should be administered to patients with a history of seizures (**AIII**) and continued through acute treatment, but they should not be used prophylactically (**DIII**) • Chronic suppressive therapy (secondary prophylaxis) is recommended for adults and children after initial therapy (**AI**)
Viral infections			
CMV	Symptomatic congenital infection with neurologic involvement: • Ganciclovir: 6 mg/kg body weight IV every 12 hours for 6 weeks (**BI**) Disseminated disease and retinitis (induction therapy (followed by chronic suppressive therapy): • Ganciclovir: 5 mg/kg body weight IV every 12 hours for 14–21 days (may be increased to 7.5 mg/kg body weight IV 2 x QD), then 5 mg/kg per day for 5–7 days per week for chronic suppression (**AI**) CNS disease (followed by chronic suppressive therapy): • Ganciclovir: 5 mg/kg body weight IV every 12 hours; PLUS • Foscarnet: 60 mg/kg	Disseminated disease and retinitis (induction therapy followed by chronic suppressive therapy): • Foscarnet: 60 mg/kg body weight IV every 8 hours for 14–21 days, then 90–120 mg/kg once a day for chronic suppression (**AI**) Alternative for retinitis (followed by chronic suppressive therapy): • IV ganciclovir PLUS • IV foscarnet (at above induction doses)—may be considered as initial induction therapy in children with sight-threatening disease (**BIII**) • Older children: o Ganciclovir intraocular implant; PLUS o Oral ganciclovir: 30 mg/kg 3 x QD (**BIII**); OR o If child is old	• Valganciclovir is used in adults to treat CMV retinitis: o Induction dosing in adults is 900 mg orally twice daily for 14–21 days, followed by once daily dosing as chronic suppressive therapy (**AI**); data on dosing in children are unavailable (**CIII**) o Valganciclovir liquid formulation is not commercially available and because the pharmacokinetics, bioavailability, safety, and shelf-life of extemporaneously compounded valganciclovir are not known, such 'homebrew' formulations should not be used (**EIII**) • Cidofovir is also used to treat CMV retinitis in adults: o Induction dosing in adults is 5 mg/kg body weight IV once weekly for 2 weeks followed by chronic suppressive therapy (**AI**); data on dosing in children are unavailable (**CIII**) o This drug must be administered with probenecid and IV hydration • Intravitreal injections not practical for most children (**DIII**) • Intraocular implant should not be

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	body weight IV every 8 hours, continued until symptoms improve (**BII**), followed by chronic suppression	enough to receive adult dosing, oral valgan-ciclovir: 900 mg PO 1 x QD (**CIII**)	used in children <3 years of age because of small size of eyes (**EIII**) • Combination ganciclovir and foscarnet is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease in children is unknown, particularly those receiving optimized HAART • Chronic suppressive therapy (secondary prophylaxis) is recommended for children after initial therapy of disseminated disease or retinitis (table 29) (**AI**)
HBV	Treatment for both HIV and HBV: • 3TC: 4 mg/kg body weight orally (max. 150 mg/dose) 2 x QD as part of a fully suppressive HAART regimen (**BII**) • Include TDF (300 mg PO 1 x QD) as part of HAART regimen with 3TC for older children who can receive adult dosing (**BII**) • If child is on HAART containing 3TC or FTC and has detectable HBV DNA (assume 3TC/FTC resistance): o If child is old enough to receive adult dosing, continue 3TC (or FTC) (**CIII**); if child is old enough to receive adult dosing and is not on TDF, add TDF (300 mg orally once daily) to HAART regimen (**BII**); OR add adefovir (10 mg	• Interferon-alfa: 10 million units/m^2 body surface area subcutaneously 3 x weekly for 6 months (sometime used for retreatment of failed lower-dose interferon therapy) (**CII**) • Alternative for 3TC: FTC 6 mg/kg body weight (max. 200 mg) 1 x QD (**BIII**)	• Indications for treatment include (**BII**): o Detectable serum HBV DNA, with or without positive HBeAg, for >6 months; and o Persistent (>6 months) elevation of serum transaminases (twice or more the upper limit of normal); or o Evidence of chronic hepatitis on liver biopsy • Interferon-alfa is contra-indicated in children with decompensated liver disease; significant cytopenias; severe renal, neuropsychiatric, or cardiac disorders; and autoimmune disease (**EII**) • Choice of HBV treatment options for HBV/HCV co-infected children depends on whether concurrent HIV treatment is warranted • 3TC and FTC have similar activity (and have cross-resistance) and should not be administered together • Adefovir is not approved for use in children but is under study in HIV-uninfected children for treatment of chronic HBV; it can be considered for older HIV-infected children who can receive adult dosage • IRIS may be manifested by dramatic increase in transaminases as CD4 counts rise within the first 6–12 weeks of HAART; distinguishing between drug-induced hepatotoxicity or other causes of hepatitis and IRIS may be difficult

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	orally once daily) to HAART regimen (**BII**) o If child is not old enough to receive adult dosing, administer 6-month course of interferon-alfa as above in addition to HAART regimen (**BII**); continue 3TC (or FTC) (**CIII**) Treatment for HIV alone: • HAART regimen that avoids the use of 3TC, FTC, or TDF (**BIII**)		• In children receiving 3TC, FTC, and/or TDF, clinical and laboratory exacerbations of hepatitis (flare) may occur if the drug is discontinued; thus, once anti-HBV/HIV therapy has begun, it should be continued unless contra-indicated or until the child has been treated for >6 months after HBeAg seroconversion and can be closely monitored on discontinuation (**BIII**) • If anti-HBV therapy is discontinued and a flare occurs, reinstitution of therapy is recommended because a flare can be life threatening (**BIII**) • Entecavir and telbivudine have been approved for use in adults with HBV; no data exist on safety or efficacy of these medications in children
HCV	Interferon-alfa PLUS ribavirin combination therapy (**BIII**): • Interferon-alfa–2a or –2b: 3–5 million units/m^2 body surface area subcutaneously or IM 3 times weekly (max. 3 million units/dose); PLUS • Ribavirin (oral): 15 mg/kg body weight QD in 2 divided doses (fixed dose by weight recommended): o 25–36 kg: 200 mg am and pm o >36–49 kg: 200 mg in am and 400 mg in pm o >49–61 kg: 400 mg in am and pm o >61–75 kg: 400 mg in am and 600 mg in pm o >75 kg: 600 mg in am and pm *Treatment duration: 48*	For children in whom ribavirin is contra-indicated (e.g., unstable cardiopulmonary disease, preexisting anaemia or haemoglobinopathy): • Interferon-alfa–2a or –2b: 3–5 million units/m^2 body surface area (max. 3 million units/dose) subcutaneously or IM 3 x weekly (**BII**)	• Length of treatment for HIV/HCV-co-infected children is unknown and based on recommendations for HIV/HCV-coinfected adults (**BIII**) • Treatment of HCV in children <3 years generally is not recommended (**DIII**) • Indications for treatment are based on recommendations in HIV/HCV-co-infected adults; because HCV therapy is more likely to be effective in younger patients and in patients without advanced disease or immunodeficiency, treatment should be considered for all HIV/HCV-infected children >3 years who have no contra-indications for treatment (**BIII**) • IRIS may be manifested by dramatic increase in transaminases as CD4 counts rise within the first 6–12 weeks of HAART; distinguishing between drug-induced hepatotoxicity or other causes of hepatitis and IRIS may be difficult • Interferon-alfa is contra-indicated in children with decompensated liver disease, significant cytopenias, severe renal or cardiac disorders, and autoimmune disease (**EII**)

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	weeks, regardless of HCV genotype (**BIII**)		• Ribavirin is contra-indicated in children with unstable cardiopulmonary disease, severe preexisting anaemia, or haemoglobinopathy (**EII**) • Didanosine combined with ribavirin may lead to increased mitochondrial toxicities; concomitant use is contra-indicated (**EIII**) • Ribavirin and AZT both are associated with anaemia and when possible should not be administered together (**DII**) • Pegylated interferon-alfa is not approved for use in children although it is under study; in adults with chronic HCV warranting treatment, pegylated interferon-alfa–2a (180 μg) or –2b (1.5 μg/kg) subcutaneously once weekly PLUS ribavirin is the treatment of choice (**AI**)
HSVs	Neonatal CNS or disseminated disease: • Acyclovir: 20 mg/kg body weight IV per dose 3 x daily for 21 days (**AI**) Neonatal skin, eye, or mouth disease: • Acyclovir: 20 mg/kg body weight IV per dose 3 x daily for 14 days (**AI**) CNS or disseminated disease in children outside the neonatal period: • Acyclovir: 10 mg/kg body weight IV 3 x daily for 21 days (**AII**) Moderate-to-severe symptomatic gingivostomatitis: • Acyclovir: 5–10 mg/kg body weight per dose IV 3 x daily (**AI**) • After lesions began to	Acyclovir-resistant HSV infection: • Foscarnet: 40 mg/kg body weight per dose IV 3 x daily or 60 mg/kg body weight per dose IV twice daily (**AI**) Mild symptomatic gingivostomatitis: • Acyclovir: 20 mg/kg body weight (max. 400 mg/dose) per dose orally 3 times daily for 5–10 days (**AI**)	• For neonatal CNS disease: Repeat CSF HSV DNA polymerase chain reaction (PCR) should be performed at days 19–21 of therapy; do not stop acyclovir until repeat CSF HSV DNA PCR is negative (**BIII**) • Valacyclovir is approved for use in adults and adolescents with mucocutaneous HSV at a dosage of 1 g orally twice daily (**AI**); no paediatric preparation exists and data on dosing in children are limited, though it could be used by older children able to receive adult dosing • Famciclovir is approved for use in adults and adolescents with mucocutaneous HSV infection at a dosage of 500 mg orally twice daily (**AI**); no paediatric preparation exists and data on dosing in children are unavailable, though it could be used by older children able to receive adult dosing • Suppressive secondary prophylaxis can be considered for children with severe and recurrent gingivostomatitis (**AI**)

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	regress, change to oral acyclovir (**AI**); continue therapy until lesions completely heal For genital herpes: • In children <45 kg: Acyclovir: 20 mg/kg body weight (max. 400 mg/dose) per dose orally 3 times daily for 5–14 days (**AI**) • In adults and adolescents: Acyclovir: 400 mg/dose orally twice daily for 5–14 days (**AI**)		
HPV	• Podofilox solution/gel (0.5%) applied topically twice daily for 3 consecutive days weekly for <4 weeks (patient applied) (**BIII**) • Imiquimod cream (5%) applied topically at night for 3 nonconsecutive nights per week for up to 16 weeks and washed off 6–10 hours after each application (patient applied) (**BII**) • Trichloroacetic acid applied topically weekly for up to 3–6 weeks (health care provider applied) (**BIII**) • Podophyllin resin, 10%–25% suspension in tincture of benzoin, applied topically and washed off several hours after; later repeated weekly for 3–6	• Individual external genital wart lesions can be removed by cryotherapy or electro-dessication; may be repeated every 1–2 weeks (**BIII**) • Veragen, patient self-applied 3 x daily for up to 16 weeks (**CIII**) • Laser ablation or surgical excision for recalcitrant cases	• Adequate topical anaesthetics to the genital area should be administered before application of caustic modalities • Intralesional interferon-alfa generally is not recommended because of high cost, difficult administration, and potential for systemic side effects (**DIII**) • Cidofovir topical gel (1%) is an experimental therapy studied in HIV-infected adults but is not commercially available and has limited use in children; systemic absorption can occur (**CIII**) • Prevention of HPV complications best achieved by HPV vaccination, ideally in childhood/adolescence prior to sexual debut • HAART has not been consistently associated with reduced risk for HPV-related cervical abnormalities in HIV-infected women • Laryngeal papillomatosis generally requires referral to a paediatric otolaryngologist and treatment is directed at maintaining the airway rather than removal of all disease; adjuvant therapy with interferon-alfa or intralesional cidofovir is being used investigationally for invasive disease (**CIII**)

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	weeks (**CIII**)		• Abnormal Pap test cytology should be referred to colposcopy for diagnosis and management
VZV	Chickenpox: • No or moderate immune suppression and mild varicella disease (oral **[BIII]**): o Acyclovir: 20 mg/kg body weight orally per dose (max. 800 mg/dose) 4 x daily for 7–10 days or until no new lesions for 48 hours (**AI**) • Severe immune suppression (CDC immunologic category 3 [969A]), IV [**AIII**]): o Acyclovir: 10 mg/kg body weight IV per dose 3 x daily for 7–10 days or until no new lesions for 48 hours (**AI**) Zoster: • Trigeminal nerve involvement or extensive multidermatomal zoster (IV [**AII**]): o Acyclovir: 10 mg/kg body weight IV per dose 3 x daily until cutaneous lesions and visceral disease are clearly resolving, then can switch to oral acyclovir to complete 10- to 14-day course (**AII**) • Progressive outer	For patients not responding to acyclovir: • Foscarnet: 40–60 mg/kg body weight IV per dose 3 x daily for 7–10 days (**AI**)	• Some experts base IV acyclovir dosing in children aged ≥1 year on body surface area (500 mg/m^2/dose IV every 8 hours) instead of on body weight. • Valacyclovir is approved for use in adults and adolescents who have zoster at a dosage of 1 g orally twice daily for 7–10 days (**AII**); no paediatric preparation is available and data on dosing in children are limited, though it could be used by older children able to receive adult dosing • Famciclovir is approved for use in adults and adolescents who have zoster at a dosage of 500 mg orally 3 x daily for 7–10 days (**AII**); no paediatric preparation is available and data on dosing in children are limited, though it could be used by older children able to receive adult dosing • Involving an ophthalmologist experienced in managing children with VZV retinitis is strongly recommended (**AIII**)

Treatment regimen			
Infection	**Preferred therapies and duration**	**Alternative therapies**	**Other options or issues**
	retinal necrosis: o Ganciclovir: 5 mg/kg body weight IV every 12 hrs; PLUS o Foscarnet: 90 mg/kg body weight IV every 12 hrs; PLUS o Ganciclovir: 2 mg/0.05mL intravitreal twice weekly, AND/OR foscarnet: 1.2 mg/0.05mL intravitreal twice weekly (**AIII**) • Acute retinal necrosis: o Acyclovir: 10 mg/kg body weight IV 3 x daily for 10–14 days, followed by oral valacyclovir, 1 g per dose 3 x daily for 4–6 weeks (for children old enough to receive adult dose); alternative oral acyclovir: 20 mg/kg body weight for 4–6 weeks (**AIII**)		

2.13 POSITIVE HEALTH, DIGNITY AND PREVENTION: POSITIVE LIVING FOR PERSONS WITH HIV

The concept of 'Positive Health, Dignity and Prevention' (PHDP) links issues of HIV treatment, prevention, support, and care within a human rights framework. PHDP, which was defined by PLHIV, is guided by the following values and principles:

- PLHIV must be leaders in the design, programming, implementation, research, and monitoring and evaluation of all programmes and policies affecting us.
- A human rights approach is the foundation of PHDP.
- Preventing HIV transmission is a shared responsibility of all individuals, irrespective of HIV status.
- Sexual and reproductive health and rights therein must be recognised and exercised by everyone, regardless of HIV status.

The core elements of PHPD are:

- Managing sexual and reproductive health: Practicing safer sex, avoiding other STIs, reducing the chance of unwanted pregnancies, and planning for safe conception and a healthy pregnancy.
- Delaying HIV progression: Increasing access to effective HIV management (HAART is potentially the best prevention strategy currently available), supporting healthy nutrition and adequate exercise, and reducing harmful behaviours.
- Promoting shared responsibility to reduce the risk of HIV transmission: Increasing the self-esteem and confidence of PLHIV to protect their own sexual health and avoid passing on the infection.

Effective implementation of PHDP:

- Requires a supportive and protective legal and policy environment, free of stigma and discrimination.
- Promotes holistic health and wellness, including equitable access to voluntary HIV testing, treatment, care, and support services.
- Improves and maintains the health and well-being of PLHIV, which in turn contributes to the improvement and maintenance of the health and well-being of their partners, families, and communities.
- Addresses psychosocial, economic, educational, and socio-cultural vulnerabilities, including gender and sexuality.
- Is responsive to the needs of key populations and is respectful and tailored to specific contexts and the diversity among PLHIV.

2.13.1 Positive Prevention

Within the framework of PHDP, Positive Prevention calls for a shared responsibility among PLHIV, their clinicians, and society at large to reduce the risk of HIV transmission and promote sexual health. Clinicians can play a key role in encouraging their patients to practice Positive Prevention. Firstly, clinicians have accurate information to help PLHIV manage their illness, and, because they are respected as health authorities, their advice can have a profound impact on PLHIV. Further, over the course of their regular interactions with PLHIV, clinicians can create a relationship that encourages trust, giving PLHIV a safe place to discuss issues. Lastly, as a hub

of resources, clinicians can connect patients to community support and reinforce community interventions.

Clinicians should, therefore:

- Know the facts about Positive Prevention and explain them to HIV-infected patients in lay terms.
- Incorporate Positive Prevention messages into HIV-infected patients' routine clinical visits, encouraging and motivating them to practice prevention.
- Maintain an open dialogue with all HIV-infected patients about prevention knowledge and plans.
- Assist HIV-infected patients to access Positive Prevention-related support.

Table 38. Exposure risks (average, per episode, involving HIV-infected source patient not on HA**ART)**

Type of exposure	Risk of HIV transmission
Percutaneous (blood)[a]	0.3%
Mucocutaneous (blood)[b]	0.09%
Receptive anal intercourse[c]	0.25–2.75%
Insertive anal intercourse[d]	0.06%
Receptive vaginal intercourse[e]	0.1–0.2%
Insertive vaginal intercourse[f]	0.03–0.14%
Receptive oral (male)[g]	0.06%
Female-female orogenital[h]	4 case reports
IDU needle sharing[i]	0.67%
Mother-to-child/vertical (no prophylaxis)[j]	24–40%[k]

[a] *Bell DM (1997); see works cited.*
[b] *Ippolito G et al (1993); see works cited.*
[c] *Vittinghoff E et al (1999); see works cited.*
[d] *ibid.*
[e] *CDC/MMWR (1998 Sep 4); see works cited.*
[f] *Rates in Europe and the US. Royce RA et al (1997); see works cited.*
[g] *Vittinghoff E et al (1999); see works cited.*
[h] *Rothenberg RB et al (1998); see works cited.*
[i] *CDC/MMWR (1998 Sep 4); see works cited.*
[j] *ACTG 076*
[k] *24% w/o breastfeeding, up to 40% with breastfeeding*

Table 39. Positive Prevention strategies

Components of Positive Prevention	HIV transmission facts	Strategies	Outcomes
Prevent transmission of the HIV virus to the uninfected	• Worrisome increase in new infections especially in adolescents, men who have sex with men (MSM), sex workers and other most-at-risk-populations (MARP) • Significant variation in risk of HIV transmission associated with different sexual acts	• Encourage and support safer sex practices • Promote 'Know Your Status' campaign; PITC; opt- out testing for STI clients, antenatal clients, MARPs • Support disclosure among partners, partner notification, and HIV counselling for couples	• Increased adherence to safer sex practices • Increased disclosure among partners • Increased awareness of serostatus • Decrease in new HIV infections
Prevent the possibility of HIV super-infection	• Documented evidence exists that HIV-1 infected clients can be re-infected by different strains of HIV-1; for a patient on HAART, the new HIV strain may not be sensitive to the specific ARVs the patient takes, resulting in treatment failure • Progression of HIV disease is more rapid in patients infected with multiple HIV strains	Educate and counsel patients to use safer sex practices, even among individuals who are both HIV-infected	Reduced rates of super-infection with HIV
• Prevent other STIs • Screen all PLHIV for syphilis at baseline and at least annually, if sexually active • Screen all clients for other STIs, if available	• STIs increase risk of both acquisition and transmission of HIV • For PLHIV, contracting other STIs may accelerate progression of HIV disease	• Encourage consistent and correct use of condoms as well as partner notification • Conduct regular STI screening for PLHIV • Educate HIV-infected patients on safer sex practices	• Decreased incidence of STIs • Improved wellness in PLHIV
Prevent other infectious diseases	PLHIV may be more prone to contracting other infectious diseases due to immunosuppression	• PLHIV should ensure proper food handling techniques, avoid direct contact with animal excreta, avoid unnecessary visits to hospitals, and take aggressive precaution in outbreaks (e.g. influenza) • Provide appropriate OI prophylaxis and vaccinations for HIV-infected patients (see	Reduced illness and hospitalization-related development of OI and other infectious diseases

		table 13)	

Sources:

1. *World Health Organization. Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings. Geneva: WHO; 2008. Available from: http://www.who.int/hiv/pub/prev_care/OMS_EPP_AFF_en.pdf.*
2. *The Global Network of People Living with HIV/AIDS. Advancing the sexual and reproductive health and human rights of PLHIV—a guidance package. Amsterdam: GNP+; 2009. Available from: http://www2.ohchr.org/english/issues/women/docs/WRGS/UN%20Agencies/UNAIDS3.pdf.*
3. *Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV. MMWR. 2003 Jul 18; 52(12). Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm.*

2.13.2 Family Planning for PLHIV

Key components of family planning for PLHIV include[29]:

- Integrated family planning services within preventive and curative sexual and reproductive health care, as well as within primary health care, including cancer care and prevention (especially cervix and breast).
- Education and counselling for informed contraception decision-making.
- Availability of and access to contraceptive supplies.

The benefits and potential impact of family planning[30]:

- It promotes gender equity and empowers women and families.
- It has the potential to reduce 32% of maternal deaths, and 10% of newborn, infant, and child deaths.
- It has the potential to decrease 71% of unwanted pregnancies—resulting in the elimination of 53 million unintended pregnancies, 22 million fewer unplanned births, 25 million fewer induced abortions, and 7 million fewer miscarriages.
- Consistent and correct use of condoms can prevent 80% of sexually transmitted HIV.
- If all the women at risk of unintended pregnancy used modern contraceptive methods, the decline in unintended pregnancies and unsafe abortions would reduce the cost of post-abortion care to about US$230 million a year.
- It slows population growth, which contributes towards significantly reducing poverty and hunger thereby helping achieve national and international developmental goals.

Family planning counselling must be integrated in all the phases of HIV care and treatment. HIV-infected women must receive counselling so they can choose the contraceptive methods that best suit their HIV status and needs—i.e., the stage of their disease and therapy, their personal preferences, and the best, updated scientific evidence on method safety. Regardless of the method chosen, however, information on HIV- and STI transmission and the need for dual protection should be emphasised during counselling.

Family planning counselling for PLHIV should include the following:

- HIV-infected men can be offered a permanent contraceptive method (i.e., vasectomy).

[29] World Health Organization. Packages of interventions for family planning, safe abortion care, maternal, newborn and child health. Geneva: WHO; 2010. Available from: http://whqlibdoc.who.int/hq/2010/WHO_FCH_10.06_eng.pdf.

[30] Ibid.

- HIV-infected women of child-bearing age can be offered a permanent (i.e., tubal ligation) or semi-permanent (i.e., intrauterine device [IUD]) contraceptive method.
- HIV-infected women considering hormonal contraception, especially injectable methods, should be counselled about the potentially increased risk of acquiring and transmitting HIV-1[31].
- With hormonal contraceptives, potential drug interactions should be explored.
- Dual protection with condoms MUST be emphasised and supported.

2.13.2.1 Pre-conception Counselling for PLHIV

HIV-infected women who plan to get pregnant should receive pre-conception counselling on the importance of receiving adequate nutrition and adhering to HAART, among other things.

For HIV-infected- as well as serodiscordant couples, counselling and support must be provided to prevent HIV transmission during the attempt to get pregnant. The risk of transmission per act of unprotected receptive vaginal intercourse is summarized in Table 43. If the subject with HIV is on HAART with an undetectable HIV viral load, the risk drops significantly but is not completely eliminated. In any case, unprotected sex should be discouraged due to the risk of HIV transmission. Even when both members of a couple have HIV, it is possible for them to reinfect each other with different strains of HIV.

For couples in which the male partner has HIV, sperm washing or insemination from a donor are recommended whenever available. Insemination from a non-HIV-infected donor eliminates any risk of transmission during conception, but it also eliminates the opportunity of an HIV-infected man achieving genetic fatherhood. For couples in which the female partner has HIV, the couple should be educated to use self-insemination on the fertile days of the woman's cycle.

[31] Heffron et al (2011); see works cited.

Table 40. Summary of key family planning interventions[32]

Interventions at home/community level	Key supplies and commodities needed

Health education for women, men, families, and communities:
• Increase awareness on the benefits of safe sex, family planning, and birth spacing—pre-pregnancy, during pregnancy, and after childbirth
• Enable adolescents, women, and men to access various reproductive health services through integrated and linked services
• Offer counselling and distribute contraceptive methods, including emergency contraception
• Promote awareness of the signs of domestic and sexual violence and where to go for referral
	• Counselling, health education, and promotion materials
	• Job aids
	• Contraceptive methods:
	  ○ Condoms for STI/HIV and pregnancy prevention
	  ○ Oral contraceptives, including emergency contraception
	  ○ Injectables

Interventions at first level health facilities	**Key supplies and commodities needed**
Engage in all of the above, plus offer: • Counselling and provision of the full range of family planning methods • HIV testing and counselling in generalized epidemics • Dual protection (female and male condoms) • Screening for, recognition, and possible management of STIs • HIV testing and counselling • Screening for and management of signs/symptoms of domestic violence and sexual assault • Screening for cancer—cervix and breast • Identifying the initial needs of an infertile couple and referring them to appropriate care • Managing or referring problems	All of the above plus: • Decision-making aids for clients • Full range of contraceptive methods (including vasectomy) • Oral and parenteral antibiotics • Laboratory tests kits for STI/HIV • Surgical equipment to insert/remove implants • Sphygmomanometer
Interventions at referral facilities	**Key supplies and commodities needed**
Engage in all of the above, plus offer: • Treatment for medical conditions, drug side effects and/or complications • Management of methods of choices, if not provided at first level of care (e.g., tubal ligation/vasectomy/insertion and removal of implants, difficult removal of devices). • Appropriate management for infertile couples, including HIV discordant couples	All of the above plus: • Appropriate operating theatre for surgical methods • Surgical equipment

2.13.3 Psychosocial Support for PLHIV

The various aspects of a person's life (physical, psychological, social, and spiritual) are affected when someone is infected with HIV. Psychosocial support is about addressing any problems in these areas that PLHIV, their partners, families, and caregivers may be experiencing. Psychosocial support can help them cope more effectively, thereby improving the quality of their lives as well as potentially preventing further transmission of HIV infection. Given that HIV is presently incurable, ongoing counselling may be critical in ensuring adherence to treatment.

The services of social workers and counsellors should be made readily available to PLHIV; referrals to a psychiatrist should be made in the appropriate cases. PLHIV should be offered

[32] World Health Organization. Packages of interventions for family planning, safe abortion care, maternal, newborn and child health. Geneva: WHO; 2010. Available from: http://whqlibdoc.who.int/hq/2010/WHO_FCH_10.06_eng.pdf.

referrals to local and regional support groups[33] that help individuals with HIV. Also, PLHIV should be informed of their human and legal rights with respect to stigma and discrimination.

Counselling helps PLHIV cope with emotional issues. Counsellors should:

- Assess each patient's emotional state and the availability of friends and family for emotional support.
- Deliver important care information in small amounts of easily understood terms.
- Screen for anxiety, depression, suicidal ideation, and substance use.

Psychosocial support also involves helping patients develop self-management skills, such as:

- Problem solving around various issues.
- Asking for support around medication issues.
- Connecting with the health care team.
- Planning for the future.
- Setting treatment goals.
- Dealing with difficult emotions.
- Practicing good nutrition and self-care (see section 2.13.4 HIV and Nutrition).

Connecting with peer educators and patient advisory groups is an important part of psychosocial support. They can:

- Provide comprehensive, individualized client-based education.
- Encourage clients to actively participate in treatment decisions.
- Encourage clients to involve family- and other members from their support system.

Clinicians should assess HIV-infected patients' attitudes, especially:

- What each patient believes about his or her health.
- Likelihood of engagning in risk-taking behaviours.

Other support services PLHIV might need to be connected to (if available) include:

- Supplemental food
- Housing
- Transportation to the HIV clinic

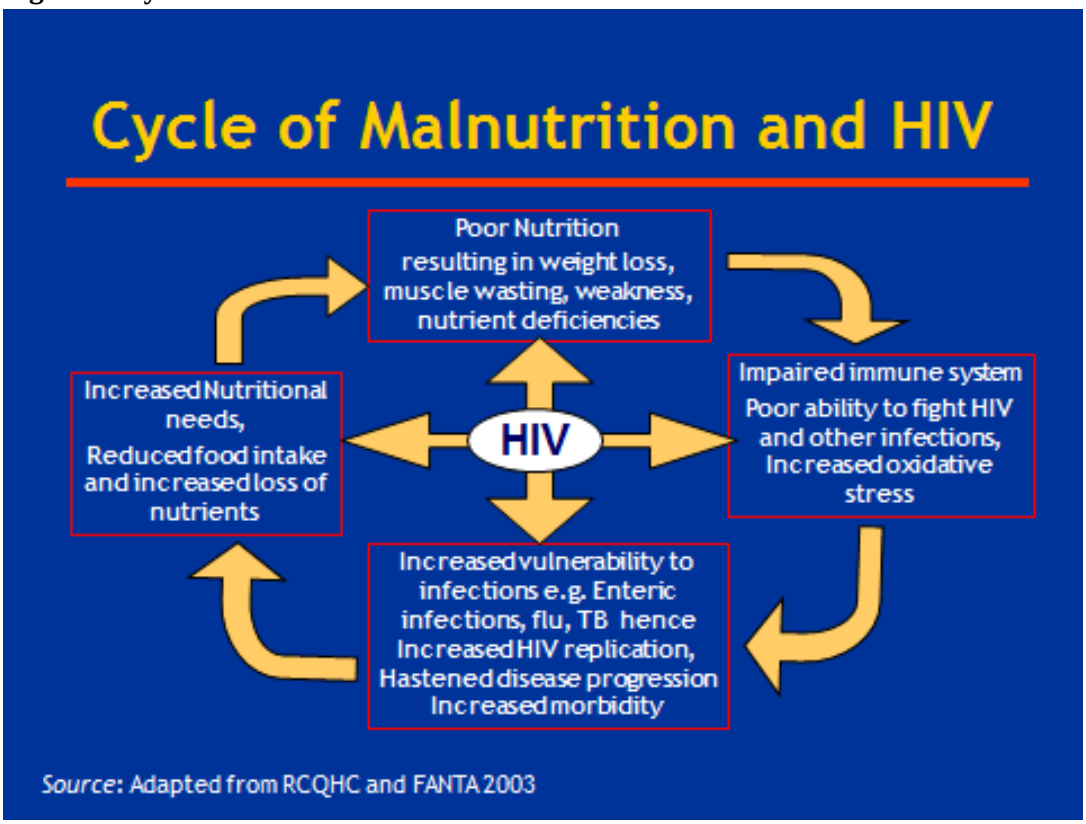
2.13.4 HIV and Nutrition

Proper nutrition is critical for maintaining a strong immune system. HIV infection destroys the immune system and malnutrition hastens the progression to AIDS. Timely screening and assessment on effective nutrition can ensure PLHIV have access to adequate dietary intake, thus influencing disease outcomes. Clinicians are encouraged to familiarize themselves with the HIV nutrition resources and guidelines available in 'Healthy Eating for Better Living', a manual for clinicians published by the Caribbean Food and Nutrition Institute (CFNI)[34].

[33] Examples of regional support groups include CRN+ and Caribbean HIV Alliance.

[34] Pan American Health Organization. Healthy eating for better living: A manual for healthcare workers. Available from: http://www.paho.org/english/cfni/CFNI-HealthCareWorkersManual.pdf.

Figure 6. Cycle of malnutrition and HIV



Source: Food and Nutrition Technical Assistance. Session 2: Link between nutrition and HIV/AIDS. In: Nutrition and HIV/AIDS: A training manual. Uganda: Regional Centre for Quality of Health Care, FANTA, and the LINKAGES Project. Available from: http://www.fantaproject.org/focus/preservice.shtml.

The goals of nutrition care and support for PLHIV include:

- Improve nutritional status:
    - Maintain weight and prevent weight loss
    - Preserve muscle mass
- Ensure adequate nutrient intake
    - Improve eating habits and diet
    - Replenish stores of essential nutrients
- Prevent food- and water-borne illnesses
- Enhance quality of life
    - Treat OIs
    - Manage symptoms affecting food intake
- Provide palliative care

2.13.4.1 Medication and Nutrition

All PLHIV should be referred to a nutritionist or dietician for help in managing their nutritional needs, which can be complex. Drug-drug and drug-food interactions may affect nutrient absorption and metabolism and/or lead to a reduced food intake. Any such situation should be addressed immediately to prevent weight loss and malnutrition, as well as to improve medication efficacy and thereby patient adherence to treatment.

Additionally, food reduces the absorption of the following drugs:

- Isoniazid
- Rifampicin
- Indinavir
- AZT (especially in high-fat diet)

Further, many PIs cause changes in lipid levels and insulin resistance, and high-fat diets increase the bioavailability of TDF. Patients' intake of saturated fats and sugars should therefore be reduced. PIs may also cause osteoporosis or bone disorders; calcium supplementation—1,500 to 2,000 mg daily—is recommended. Patients on didanosine should discontinue alcohol, as it can cause pancreatitis, as should patients on isoniazid, as it may increase the risk of hepatitis.

2.13.5 Routine Health Care Maintenance in HIV-infected Adults and Adolescents

Given access to HAART, PLHIV are experiencing fewer HIV-related complications and having increased life expectancy. As a result, they are also experiencing medical conditions that affect the general population and should therefore be managed and monitored for all relevant age- and gender-specific health problems. The following tables outline interventions for health maintenance in PLHIV, including vaccines.

Table 41. Routine health care maintenance in HIV-infected adults[35]

Intervention/vaccine	Recommendation	Comments
Influenza	1 dose annually	
Pneumococcal (polysaccharide) (PPSV)	2 doses, at least five years apart	
Tetanus, diphtheria, pertussus (Td/Tdap)	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years	Tdap = diphtheria and tetanus toxoids and acellular pertussis Td = diphtheria and tetanus toxoids
Blood pressure check	Perform annually in all patients	
Prostate-specific antigen	Discuss pros and cons with patient and consider annually in men aged ≥ 50 years	Controversial, discouraged by US Preventive Services Task Force; testing may be advisable in men at higher risk of prostate cancer (e.g., black patients and those with family history)
Digital prostate examination	Consider annually in all men >50	Controversial; testing at an earlier age might be advisable in men at higher risk of prostate cancer (e.g., black patients and those with family history)
Anal cancer screening	Consider anoscopy and annual digital rectal examination	Controversial; incidence of anal cancer significantly elevated in HIV-infected patients, especially MSM and HPV-infected women—appropriate screening methodology not yet defined
Ophthalmologic examination	Perform dilated examination every 6–12 months in patients with CD4 count <50cells/mL	Examination with tonometry is advised every 2–3 years in all patients aged ≥ 50 years
Depression screening	Perform annually in all patients	Use conventional mental health interview

[35] Adapted from Aberg et al (2009); see works cited.

Intervention/vaccine	Recommendation	Comments
		or standardized test
Fasting glucose	Perform every 6–12 months in all patients	Consider testing 1–3 months after starting or modifying HAART; haemoglobin A1c should be obtained every 6 months in patients with diabetes
Fasting lipid profile	Perform every 6–12 months in all patients	Consider testing 1–3 months after starting or modifying HAART
Syphilis serology (rapid plasma reagin [RPR], VDRL)	Perform annually	More frequent testing may be indicated in patients at high risk for STIs
Gonorrhoea, chlamydia and trichomoniasis testing	Perform annually	More frequent testing may be indicated in patients at high risk for STIs
TST	Perform annually	No need to repeat in patients with prior positive purified protein derivative test; additional TB testing may be indicated depending on potential exposure
Colonoscopy	Perform at age 50 years and every 10 years thereafter in all patients	More frequent testing is indicated in patients with a history of adenomatous polyps; testing at an earlier age may be advised in patients with a strong family history of colon cancer Alternative approach to colorectal cancer screening: annual stool guiaic x 3, if positive, then refer for colonoscopy
Mammography	Perform annually in all women age 50 years or older	Some authorities advise initiating screening at age 40 based on an individual risk/benefit assessment
Cervical Pap test	Perform annually in all women after 2 normal Pap tests documented during the first year after HIV diagnosis	More frequent testing is indicated in women with a history of atypical squamous cells of unknown significance or cervical dysplasia
Patient education	Address regularly in all patients	Issues may include sexual behaviour and drug counselling, dietary teaching, weight reduction, smoking cessation, and seat belt use

Immunizations

Immunizations for HIV-infected adults in the OECS are the same as those for HIV-uninfected adults, with the following exceptions:

- MMR and varicella should not be administered to severely immunosuppressed persons (e.g., CD4 less than 200, or recent Opportunistic Infection), as MMR and varicella are live attenuated vaccines
- Pneumococcal vaccination (polysaccharide PPSV 23-valent vaccine, and/or conjugate PCV 7-valent vaccine) are recommended for HIV-infected adults, given the increased susceptibility of PLHIV to pneumococcal pneumonia.

2.13.6 Helping PLHIV to Avoid Exposures to Opportunistic Pathogens

2.13.6.1 Environmental and Occupational Exposures

Certain activities or types of employment might increase the risk for exposure to TB—e.g., volunteer work or employment in health care facilities, correctional institutions, and homeless shelters, as well as other settings identified as 'high risk' by local health authorities. PLHIV should consult with their clinicians about whether to continue with such activities. The patient's specific duties in the workplace, the prevalence of TB in the community, and the degree to which TB infection control precautions are being taken in the environment should all factor into the decision. It also has bearing on the frequency with which the patient should be screened for TB.

Childcare providers and parents of children in childcare are at increased risk for acquiring CMV infection, cryptosporidiosis, and other infections (e.g., HAV and giardiasis) from children. The risk of acquiring various infections can be diminished by receiving a HAV vaccination and by practicing good hygiene, like handwashing after contact with faeces or urine (e.g., during nappy-changing) or saliva. All children in childcare facilities also are at increased risk for acquiring these same infections; parents and other caretakers of HIV-infected children should be advised of this risk.

Occupations involving contact with animals (e.g., veterinary work and employment in pet stores, farms, or slaughterhouses) might pose a risk for cryptosporidiosis, toxoplasmosis, salmonellosis, campylobacteriosis, or *Bartonella* infection. However, the available data are insufficient to justify a recommendation against work in such settings. Contact with young farm animals, especially animals with diarrhoea, should be avoided to reduce the risk for cryptosporidiosis.

Activities that involve stirred-up dust or disturbed soil can also pose various risks. Handwashing after gardening or other contact with soil might reduce the risk for cryptosporidiosis and toxoplasmosis. In areas endemic for histoplasmosis, patients should avoid creating dust when working with surface soil; cleaning chicken coops heavily contaminated with compost droppings; disturbing soil beneath bird-roosting sites; cleaning, remodelling, or demolishing old buildings; and cave exploring. In areas endemic for coccidioidomycosis, when possible, patients should building excavation sites or dust storms.

2.13.6.2 Sexual Exposures

Patients should use a latex condom during every act of sexual intercourse to reduce the risk of acquiring CMV, HSV, HPV, human herpes virus-8 (HHV-8), a super-infection with another HIV strain, and/or other sexually transmitted pathogens. Condom use will also reduce the risk of transmission of HIV and other sexually transmitted pathogens to others. Data regarding the use and efficacy of female condoms are incomplete, but these devices should be considered as a risk-reduction strategy.

Patients should avoid sexual practices that might result in oral exposure to faeces (e.g., oral-anal contact) to reduce the risk for intestinal infections (e.g., cryptosporidiosis, shigellosis, campylobacteriosis, amebiasis, giardiasis, and HAV). Latex condom use alone may not reduce the risk of acquiring these faecal-orally transmitted pathogens, especially those that have low infectious doses. Persons wishing to reduce their risk of exposure might consider using dental dams or similar barrier methods for oral-anal and/or oral-genital contact, changing condoms after anal intercourse, and wearing

latex gloves during digital-anal contact. Frequently washing hands and genitals with warm soapy water during and after activities that may bring these body parts in contact with faeces may further reduce risk of illness.

Immunization against HBV is recommended for all susceptible (anti-HBc-negative) HIV-infected patients. Immunization against HAV is recommended for all susceptible MSM, as well as others with indications for HAV vaccine.

2.13.6.3 Injection Drug Use Exposures

Injection drug use is a complex behaviour that puts HIV-infected persons at risk for HBV and HCV; additional, possibly drug-resistant strains of HIV; and other blood-borne pathogens. Providers should assess the patient's readiness to change this practice and provide education and support directed at recovery. Patients should be counselled to stop using injection drugs and to enter and complete substance-abuse treatment, including relapse-prevention programmes. If they are continuing to inject drugs, patients should be provided with the following harm-reduction guidance:

- Never reuse or share syringes, needles, water, or drug preparation equipment.
- If injection equipment has been used previously, clean it with bleach and water before use[36].
- Use only sterile syringes obtained from a reliable source (e.g., pharmacies or syringe exchange programmes).
- To prepare drugs, use sterile (e.g., boiled) water; if this is not possible, use clean water from a reliable source (e.g., fresh tap water). Also, use a new or disinfected container ('cooker') and a new filter ('cotton').
- Clean the injection site with a new alcohol swab before injection.
- Safely dispose of syringes after one use.

All susceptible injection drug users should be immunized against HBV and HAV.

2.13.6.4 HIV and Aging Populations[37]

The prevalence of HIV disease among the elderly is increasing, primarily due to the fact that PLHIV are living longer HAART. Many PLHIV appear to experience 'accelerated aging' and are being diagnosed with diseases and disorders more commonly associated with older populations.

The elderly population should also receive HIV prevention messages, including safer sex and HIV risks. They should also be offered HIV tests to timely identify HIV infection. An HIV test must be considered for older clients with symptoms and signs of HIV disease and co-morbid conditions that might indicate an increased risk for HIV infection. For example, elderly patients who have chronic HBV or recent history of STIs should be screened for HIV. If prior negative tests for HIV infection have been recorded, renewed testing should be performed in the event that ongoing risk factors are elicited during the visit. Reactivation of TB, recurrent HSV infections, severe or recurrent HZV, recurrent pneumonias, meningitis, gastrointestinal parasitosis, mucocutaneous candida and fungal infections or molluscum contagiosum may also

[36]Department of Health and Human Services. HIV prevention bulletin: Medical advice for persons who inject illicit drugs. 1997; May 8. Available from: http://cdcnpin.org/Reports/MedAdv.pdf.

[37] Adapted from: Belize Ministry of Health. Clinical Management Guidelines for HIV/AIDS, August 2011

indicate the presence of HIV infection. Abnormalities on physical exam that can point to an HIV diagnosis include facial seborrhea, angular chelitis, thrush, gingivitis, aphthous ulcers, hairy leukoplakia of tongue (highly indicative), diffuse lymphadenopathy, hepatosplenomegaly, onychomycosis and other dermatophytoses. Laboratory abnormalities—such as anaemia, leukopenia (especially lymphopenia), thrombocytopenia, and elevated total protein—can also suggest HIV infection, in the absence of other diagnoses.

Before initiating HAART in the elderly, baseline investigations must include screening for metabolic conditions like diabetes, cardiovascular disease, nephropathy dyslipidemias, osteoporosis, and other preexisting conditions. It is likely that care will include managing other co-morbid conditions commonly associated with aging, such as hypertension, diabetes, and hyperlipidemia. The drug-drug interaction between the HAART regimen and any medication used to ameliorate the co-morbidity must be monitored carefully. Further, laboratory monitoring will be important to identify any emerging co-morbidities and/or exacerbation of existing conditions.

2.14 POSITIVE LIVING FOR INFANTS AND CHILDREN WITH HIV

HIV-infected children treated optimally with HAART and OI prophylaxis, and given appropriate nutritional and other supportive therapies can grow up to lead normal adult lives. In developed countries, such children are now growing up to consider university educations, buying houses, marrying, and even having children. The long-term prognoses of paediatric HIV/AIDS can therefore be excellent.

2.14.1.1 Routine Clinical and Laboratory Monitoring for Children on HAART

- Determine baseline haemoglobin level (and white cell count, if available) at the initiation of HAART.
- For infants and children on AZT-containing regimens, measure haemoglobin at week 8, post-initiation, or more frequently if symptoms indicate.
- Monitor infants' and children's growth, development, and nutrition monthly.
- Laboratory monitoring for toxicity should be symptom directed.

2.14.1.2 CD4 Count Monitoring

- Measure CD4 count at the time of HIV diagnosis and every 3–4 months thereafter.
- Monitor CD4 count with increasing frequency as it approaches the threshold for starting HAART.
- Measure CD4 count if new clinical staging events develop, including growth faltering and neurodevelopmental delay.
- Where capacity for CD4 count measurement is limited, target its use to assessing the significance of clinical events.

2.14.1.3 Viral load monitoring

- Viral load determination is desirable, but not essential, prior to initiating HAART.
- Measure viral load every 6 months after initiating HAART.
- Viral load monitoring is useful to detect virologic failure, which occurs before immunological and clinical failure.

2.14.1.4 Immunizations for HIV-infected Infants and Children

Immunization recommendations for HIV-infected children in the OECS are the same as immunization recommendations for non-HIV infected children, with the following exceptions:

- BCG is contra-indicated;
- MMR and Varicella vaccines should not be administered to children who are severely immuno-compromised (CD4% less than 15%)
- Inactivated Polio Vaccine (IPV) is preferred over Oral Polio Vaccine (OPV)
- Pneumococcal vaccination (polysaccharide PPSV 23-valent, and/or conjugate PCV 7-valent) is recommended for HIV-infected infants and children given their vulnerability to pneumococcal pneumonia. See http://www.cdc.gov/mmwr/pdf/rr/rr5811.pdf for details regarding paediatric pneumococcal vaccination options.

2.14.1.5 Nutrition

- Routinely assess nutritional status—including weight and height—at scheduled visits, particularly after HAART has been initiated.
- Provide 25–30% additional energy to children on or off HAART who are symptomatic, have conditions requiring increased energy (e.g., TB, chronic lung disease, chronic OIs, or malignancies) or have weight loss or evidence of poor growth.
- Manage severely malnourished children per the guidelines for uninfected children and provide them with 50–100% additional energy.
- Provide one recommended daily allowance of micronutrients per day; if this cannot be obtained through diet or there is evidence of deficiency, then supplementation should be given.
- Provide infants and children with a high-dose vitamin A supplement every 6 months between the ages of 6 and 59 months, as per the guidelines for uninfected children.
- Manage diarrhoea with zinc supplementation, as per the guidelines for uninfected children.

2.14.1.6 Growth and Development

Monitoring the growth and development of paediatric patients is of paramount importance. Even though a child who is nonadherent to HAART may have normal growth and development, failure in these parameters is usually indicative of poor virologic control. Growth charts and Tanner scores are important tools in the care of paediatric patients.

2.14.1.7 Disclosure of Status to Children

Status disclosure is an important aspect of care. As children approach adolescence, they participate more in their own care; understanding their condition can make the difference between treatment success and failure. It also makes them aware of their parents' diagnoses and therefore needs to be handled with appropriate sensitivity. Disclosure is also important in HIV prevention as paediatric patients become adolescents and sexuality develops.

2.14.1.8 The Effect of Stigma and Severe on Adherence

Stigma and severe poverty remain major causes of poor ARV adherence. Many patients refuse to be seen at clinics and will not allow health care workers to visit their homes. Some liquid ARVs require refrigeration, which can be problematic because firstly, many families do not own refrigerators, and secondly, some may not want other household members to know that their child is on medication. The health care team must be aware of such issues and be willing to devise innovative approaches to deliver care successfully.

2.15 POST-EXPOSURE PROPHYLAXIS

2.15.1 Overview of Post-exposure Prophylaxis

HIV post-exposure prophylaxis (PEP) refers to the set of services that are provided to an individual who has been exposed to HIV in order to mitigate that exposure. These services comprise first aid; counselling that includes an assessment of risk for HIV; HIV testing; and, depending on the outcome of the exposure assessment, a possible prescription of a 28-day course of ARVs, with appropriate support and follow-up.

Any individual could potentially encounter 'non-occupational exposure' to HIV, for example, though sexual encounters—consensual or assault—and needle sharing among injecting drug users. 'Occupational exposure' to HIV may occur among clinicians, laboratory personnel, emergency rescue staff, waste-disposal workers, law enforcement personnel, and fire-fighters, all of whom may be exposed to blood and other potentially infectious body fluids while performing their duties. The levels of risk for contracting HIV infection related to a particular exposure experienced are summarized in table 43. Anyone who has sustained an exposure to HIV should be counselled on the level of risk and informed that PEP, with a timely course of antiretroviral therapy (ART), can reduce, although not eliminate, the risk of HIV transmission.

Because PEP is not 100% effective, it is imperative for all workplaces where HIV exposure is possible to stress the importance of primary prevention as well as offer risk prevention counselling.

Table 43. Estimated probability of HIV transmission associated with various exposures to HIV[a]

Exposure	Average per-episode risk
Occupational	
Percutaneous (blood)	0.3%
Mucocutaneous (blood)	0.09%
Non-occupational[b]	
Receptive anal intercourse	1–2%
Insertive anal intercourse	0.06%
Receptive vaginal intercourse	0.1–0.2%
Insertive vaginal intercourse	0.03–0.14%
Receptive oral (male)	0.06%
Needle-sharing	0.6%

[a] *Assumes HIV-infected source patient/partner.*
[b] *Risk may be higher in sexual assaults due to trauma.*

2.15.2 Occupational Exposures

Management of an occupational exposure to HIV includes the following sequence of steps:
1. Decontaminate the exposure site and administer first aid.

2. Assess risk and establish eligibility for PEP.
3. Administer PEP medication, if indicated.
4. Conduct a baseline laboratory evaluation, including HIV testing (with counselling and informed consent).
5. Carefully document the exposure incident and promptly report it to the employee's supervisor.
6. Ensure follow-up by scheduling further testing and offering support, as indicated.

These steps are explained in further detail below.

2.15.2.1 Step 1. Decontaminate the Exposure Site and Administer First Aid

First aid as well as decontamination of the exposure site should be performed immediately. The goal is to reduce contact time with the source person's blood, body fluids, or tissues. Exact management will vary according to the scenario, as described below.

- <u>If skin is broken during an injury with a used needle or sharp instrument:</u>
  - Do not squeeze or rub the injury site.
  - Wash the site immediately using soap or a mild disinfectant solution that will not irritate the skin. The WHO recommends using a chlorhexidine gluconate solution.
  - If running water is not available, clean the site with a gel or other hand-cleaning solution, whatever is typically available.
  - Do not use strong solutions, such as bleach or iodine, to clean the site because these may irritate the wound and make the injury worse.

- <u>If splash contact occurs on unbroken skin:</u>
  - Wash the area immediately. If running water is not available, clean the area with a gel or other hand-rub solution, whatever is typically available.
  - Do not use strong disinfectants.
  - Unbroken skin is an excellent barrier to HIV in blood and other potentially infectious bodily fluids. PEP ART is not recommended in this setting.

- <u>If the eye sustains splash contact:</u>
  - Irrigate the exposed eye immediately with water or normal saline.
  - Sit in a chair, tilt the head back, and have a colleague gently pour water or normal saline over the eye, pulling the eyelids up and down to make sure the eye is cleaned thoroughly.
  - If contact lenses are worn, leave them in place while irrigating the eye, as they form a protective barrier. Once the eye has been cleaned, remove the contact lenses and clean them as normal; this will make them safe to wear again.
  - Do not use soap or disinfectant on the eye.

- <u>If splash contact occurs to the mouth:</u>
  - Spit the fluid out immediately.
  - Rinse the mouth thoroughly, using water or saline, and spit again. Repeat this process several times.
  - Do not use soap or disinfectant in the mouth.

2.15.2.2 Assess Risk and Establish Eligibility for PEP

The purpose of risk assessment is to determine the severity of the exposure and whether any immediate health care action (such as the provision of PEP) is required. Risk should be assessed as soon as possible after every incident, no matter what time of day the exposure occurs. After-hours or weekend exposures may require evaluation in an emergency department or urgent care centre.

Risk assessment begins with establishing whether or not the incident represents a true exposure to HIV. If the risk is considered significant, PEP should be initiated as soon as possible, within 72 hours of exposure. In cases where risk cannot assessed rapidly, regardless of the reason, the first dose of PEP ART can be given as a precautionary measure. If subsequent assessment determines that the exposure was not significant, PEP should be discontinued.

Table 44 lists examples of exposures and non-exposures to HIV. Table 45 lists criteria for initiating PEP ART. Table 46 lists situations in which PEP ART is NOT recommended.

Table 44. Exposures versus non-exposures to HIV

Exposures

• Transfusion of blood or blood components
• IV, intramuscular or subcutaneous injury with a needle contaminated with a potentially infectious body fluid,38 whether or not the injury results in visible bleeding
• Any mucous membrane or break in the skin (e.g., non-healed wound or dermatologic condition that compromises the integrity of the skin) exposed to a potentially infectious body fluid
• Human bites:
  o Exposure to the individual doing the biting if the skin was broken resulting in visible bleeding;
  o Exposure to the bitten individual if the skin was broken and visibly bleeding AND the individual who was doing the biting was bleeding in the mouth at the time of the bite.

Non-exposures
• Intact skin or healed wound/skin lesion contaminated with potentially infectious body fluid. IV, intramuscular or subcutaneous injury with a needle contaminated with a fluid that is not potentially infectious. • Mucous membrane or break in the skin exposed to a fluid that is not potentially infectious and not visibly bloody.

Table 45. Recommended eligibility criteria for PEP in occupational settings[a]

1. <72 hours has elapsed since exposure. 2. The exposed individual is not known to be HIV infected. 3. The person who is the source of exposure is living with HIV or has an unknown HIV status. 4. Exposure was to blood, body tissues, visibly bloodstained fluid, concentrated virus, CSF, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, or amniotic fluid. 5. The skin was penetrated with spontaneous bleeding or deep puncture, or a significant amount of fluid was splashed on a mucous membrane, or non-intact skin sustained prolonged contact with an at-risk substance. 6. The skin was penetrated by a recently used hollow bore needle or other sharp object that was visibly contaminated with blood.

[a] *Note that ALL criteria must be met for initiation of PEP ART.*

[38] For exposures to HIV, potentially infectious body fluids include blood, amniotic fluid, spinal fluid, pleural fluid, pus, or any fluid that is visibly bloody. Saliva, urine, and feces are not considered to be potentially infectious for HIV unless visibly bloody.

Table 46. Negative indications for PEP[a]

1. The exposure occurred >72 hours previously. 2. The exposed person was already HIV-infected from a previous exposure. 3. The exposure does not pose a risk of transmission: a. Skin remained intact during and after exposure to potentially infectious body fluids. b. Exposure was to non-infectious bodily fluids (e.g., faeces, saliva, urine, sweat) and those fluids were not visibly bloody. c. Exposure was to bodily fluids from a person known to not be infected with HIV, unless that person is identified as high risk for recent HIV infection and thus likely to be within the window period.

[a] *PEP is not indicated if ANY of these criteria are met.*

2.15.2.2.1 Assessment of the Source Person

Whether to use PEP or seek out the source person should be decided on a case-by-case basis considering the type of exposure and the clinical and/or epidemiological likelihood that the source person is HIV infected.

If the exposure is assessed as posing zero- or a very low risk of HIV transmission, the source person does not need to be identified and tested because PEP would not be prescribed, even if the source person were found to be HIV-infected.

If the exposure is severe enough to warrant the consideration of PEP, standard precautions require that all source people be regarded as potentially HIV-infected. In such circumstances, the source person should be identified and tested and counselled[39]. PEP should not be delayed pending the source person's test results, even in settings where rapid testing techniques are not available. If the results come back negative, PEP should generally be discontinued unless it is possible that the source person is in the 'window period' between acute HIV infection and seroconversion.

2.15.2.3 Step 3. Administer PEP Medication, if Indicated

The standard PEP regimen should comprise two nucleoside-analogue reverse-transcriptase inhibitors. Three-drug regimens, comprised of two nucleoside-analogue RTIs plus a boosted PI, can be considered in situations where ARV resistance is known or suspected. The recommended duration for PEP is 28 days. Additionally, the patient should be counselled about the efficacy of PEP.

The preferred and alternative two-drug PEP regimens are listed in table 47 below.

Table 47. Preferred and alternative two-drug PEP regimens

Preferred regimen	Alternative regimen
TDF (300 mg once daily) + 3TC (300 mg once daily)	AZT + 3TC (dose: Combivir FDC—one tablet twice daily)

If drug resistance is suspected and a third drug is considered necessary, that drug should be a boosted PI, not an NNRTI. NVP is contra-indicated for PEP due to the risk of toxicity. EFV is not recommended because of its initial neuropsychiatric side effects. If the resistance profile of the source person is known, this should be taken into account when selecting PEP medicines.

[39] It is important to remember that testing of the source person requires consent. However, the exposed worker should not be involved in obtaining consent from the source person for HIV testing.

Table 48. Preferred and alternative three-drug PEP regimens

Preferred regimen	Alternative regimen
TDF + 3TC + LPV/r	AZT + 3TC + ATV with an RTV boost
	TDF + 3TC + either LPV or ATV with an RTV boost

2.15.2.4 Step 4. Conduct a Baseline Laboratory Evaluation, Including HIV Testing

The rationale for testing the exposed worker for HIV soon after the exposure occurs is to establish a baseline against which future test results can be compared. Testing should be done as soon as the appropriate conditions arise. As with any HIV testing, patient confidentiality should be respected, informed consent should be given, and pre- and post-test counselling offered. And again, PEP should never be delayed if HIV testing and counselling are not immediately available.

In occupational settings, performing an HIV test immediately after exposure might not be feasible. If necessary, the baseline test can be performed up to several days after exposure and still be a valid indicator of the exposed individual's HIV status at the time of exposure, even if PEP ART has commenced. For example, if a starter pack of PEP ART (1–7 day supply) was given immediately after exposure, the HIV test may be offered to the individual when he or she returns for the remainder of the PEP medicine, or, if a full course of medicine was prescribed, during follow-up visits.

For those taking PEP ART, other laboratory tests should be performed to determine a baseline in case of ARV toxicity, and to screen for other infections spread by occupational exposure. These tests include: serum haemoglobin; basic chemistry panel; liver function; urine pregnancy test for women who might be pregnant; HBV surface antigen, surface antibody, and core antibody; and HCV antibody. Ideally, these tests are obtained at around the same time that PEP is started, but these tests should not delay the initiation of PEP ART.

2.15.2.5 Step 5. Document and Report the Exposure Incident

The employee's supervisor should be notified of the incident and a detailed, accurate incident report that respects the exposed employee's privacy should be written. As a rule, incident reports should always be completed. Their purpose is to support health and safety reviews—which should be done post-exposure to determine whether any unsafe practices or equipment in the workplace need to be addressed—as well as compensation claims, should they arise.

The incident report can be written immediately after the exposure but the priority should be to evaluate and treat the exposed employee.

2.15.2.6 Step 6. Ensure Follow-up

Any worker who may have been exposed to HIV must be offered fully confidential follow-up services, preferably coordinated by the clinical care coordinator or the infection control coordinator. The coordinator would be responsible for getting blood test results; arranging post-test counselling, including information on the potential of secondary HIV transmission as well as on ways to reduce future exposure risk; reminding the worker when their follow-up blood tests are due; monitoring their adherence to PEP medications; monitoring any adverse drug reactions;

and treating side effects. In addition, the coordinator should see that all necessary forms and reports—including an incident report—have been completed, and ensure all documentation relating to the incident is stored in a confidential manner.

A follow-up appointment for the exposed employee should be arranged within one week of the exposure, to assess adherence to PEP medications, determine whether there is clinical evidence of drug toxicity, and act upon any new information related to the exposure or the source person that may have become available.

Serologic (antibody) HIV testing should be repeated at 4–6 weeks and again at 3 and 6 months. If seroconversion occurs, the exposed worker should be promptly notified and immediately referred for care with a physician experienced in managing HIV infection.

2.15.3 Sexual Assault

For people who have been sexually assaulted, the recommended steps at the initial post-assault visit are as follows:

1. Provide initial crisis intervention.
2. Involve local law enforcement.
3. Conduct a general health exam.
4. Collect forensic evidence.
5. Assess the risk of HIV transmission.
6. Provide the first dose of PEP ART, if appropriate.
7. Offer HIV pre-and post-test counselling and perform rapid testing, if available.
8. Evaluate and test for other infections transmitted through sexual exposures.
9. Offer empiric treatment for gonorrhoea, chlamydia, and trichomonas.
10. Conduct baseline laboratory tests.
11. Provide pregnancy testing and emergency contraception to women of childbearing age.
12. Ensure follow-up.

2.15.3.1 Step 1. Provide Initial Crisis Intervention

This includes emotional support and first aid.

2.15.3.2 Step 2. Involve Local Law Enforcement

If law enforcement is not already involved, contact them and report the incident.

2.15.3.3 Step 3. Conduct a General Health Exam

A general health exam should review the patient’s overall status as well as record any injuries sustained.

2.15.3.4 Step 4. Collect Forensic Evidence

If forensic evidence is to be collected, it should first be confirmed whether the patient was forced to perform oral sex; if so, an oral swab should be obtained before any medicine is taken.

2.15.3.5 Step 5. Assess the Risk of HIV Transmission

The risk of becoming infected with HIV from sexual assault may be higher than from consensual sex. This is because the presence of physical trauma tends to increase transmission risk. Risk also varies by sexual act; for example, receptive anal- and vaginal intercourse are riskier than oral intercourse (see table 49). Additionally, STIs elevate transmission risk, as does being an adolescent girl—the immaturity of the vaginal and cervical cells increase susceptibility to HIV infection—and being a female who uses Depo-Provera (medroxyprogesterone acetate).

As in occupational exposure, PEP following sexual assault is most effective if given as soon as possible (and no later than 72 hours) after the exposure. People who have been sexually assaulted who present later than 72 hours post-assault would normally not be considered eligible for PEP. However, in the case of ongoing sexual assault that occurs over a number of hours or days, the 72-hour time limit should be applied to the most recent potential exposure.

If the source person is of unknown HIV status, providing PEP after a sexual assault is generally recommended. Whenever feasible (and following informed consent), HIV testing of source people is strongly recommended.

Table 49. Recommended PEP eligibility criteria among people who have been sexually assaulted

1. <72 hours has elapsed since exposure.
2. The exposed individual is not known to be HIV infected.
3. The source of exposure is HIV-infected or is of unknown HIV status.
4. There is a defined risk of exposure, e.g.,
   - The exposed individual received oral sex with ejaculation or vaginal or anal intercourse without a condom or with a condom that broke or slipped.
   - There was contact between the perpetrator's blood or ejaculate and the exposed person's mucous membrane or some non-intact skin.
   - The exposed individual was drugged or otherwise unconscious at time of assault and is uncertain about the nature of the potential exposure.
   - The person was gang raped.

[a] *Note that ALL criteria must be met for initiation of PEP ART.*

2.15.3.6 Step 6. Provide the First Dose of PEP ART, if Appropriate

The standard PEP regimen should comprise two nucleoside-analogue RTIs. Three-drug regimens, comprised of two nucleoside-analogue RTIs plus a boosted PI, can be considered in situations where ART resistance is known or suspected. The recommended duration for PEP is 28 days. Additionally, the patient should be counselled about the efficacy of PEP.

Table 50. Standard PEP ART

Preferred regimen	Alternative regimen
• TDF + 3TC • Adult dose: 300 mg of TDF once daily + 300 mg of 3TC once daily • Paediatric dose is weight-based (see section 2.10); if <12 years old or <35 kg weight, use alternative regimen	• AZT + 3TC • Adult dose: Combivir FDC, one tablet twice daily • Paediatric dose is weight-based (see section 2.10)

If drug resistance is suspected and a third drug is considered necessary, that drug should be a boosted PI, not an NNRTI. NVP is contra-indicated for PEP due to the risk of toxicity. EFV should not be given to women who are pregnant or are of childbearing age because it is

teratogenic. If the resistance profile of the source person is known, this should be taken into account when selecting PEP medicines.

Table 51. PEP ART in situations where ARV Resistance is suspected in the Source Patient

Preferred regimen	Alternative regimens
TDF + 3TC + LPV/r • Adult dose: 300 mg of TDF once daily + 300 mg of 3TC once daily + (2 tablets of LPV/r [200/50 mg] twice daily or 4 tablets of LPV/r once daily) • Paediatric doses are weight-based (see Paediatric HAART section); if <12 years old or <35kg weight, use alternative regimen	AZT + 3TC + LPV; or ATV with a RTV boost

2.15.3.7 Step 7. Offer HIV Pre-and Post-test Counselling and Perform Rapid Testing

Offer HIV pre-and post-test counselling and perform rapid testing, if available.

2.15.3.8 Step 8. Evaluate and Test for Other Infections Transmitted through Sexual Exposures

Infections to test for include chlamydia; gonorrhoea; syphilis; HSV; HBV surface antigen, surface antibody, and core antibody; and HCV antibody.

2.15.3.9 Step 9. Offer Empiric Treatment for Gonorrhoea, Chlamydia, and Trichomonas

Positive test results for gonorrhoea, chlamydia, and trichomonas do not need to be obtained before starting treatment for these STIs.

2.15.3.10 Step 10. Obtain Baseline Laboratory Tests

If PEP ART is given, obtain tests for CBC, liver function, creatinine, and estimated glomerular filtration rate.

2.15.3.11 Step 11. Provide Pregnancy Testing and Emergency Contraception

All women of childbearing age who are raped should be offered a pregnancy test as part of sexual assault care services. If the initial pregnancy test is negative, patients should be offered a second pregnancy test a month later to determine whether they have become pregnant from the assault. Women who are not pregnant at the time of presentation should be offered emergency contraception, which can be given up to 120 hours (5 days) after a sexual assault.

PEP can be provided whether or not a pregnancy test is available. Women who are pregnant at the time of presentation can still be offered PEP.

Breastfeeding mothers should be advised that if they were infected with HIV due to the assault, the risk of transmitting the virus to their child through breastfeeding is high (considering the high viral load associated with the initial stage of HIV infection). Appropriate counselling should be offered based on exclusive breastfeeding, and safe alternatives to breastfeeding should be discussed when they are acceptable, feasible, affordable and sustainable. Safe sex practices should also be encouraged.

2.15.3.12 Step 12. Ensure Follow-up

A series of follow-up visits should be scheduled to discuss side effects from and adherence to PEP ART; mental health needs; referrals for other support services; and further investigation, prophylaxis, and treatment for STIs and HBV, if warranted. Additionally, HIV tests should be repeated at 4–6 weeks and then again at 3 and 6 months.

2.15.4 HIV Exposure through Consensual Sex

Managing an exposure from consensual sex is the same as for sexual assault, except that law enforcement and forensic evidence are not required. The same sequence of steps should be performed and the same indications for initiating PEP apply.

Table 52. Summary of PEP

Item	Recommended action and notes
Eligibility	• Exposure within 72 hours • Exposed individual not known to be infected with HIV • Significant exposure • Source of exposure is HIV-infected or of unknown HIV status
Informed consent for PEP	• Information about risks and benefits • Consent may be given verbally
Medicine	• Two nucleoside-analogue RTIs (typically TDF + 3TC or AZT + 3TC) • Add a boosted PI to the regimen if drug resistance is likely
Duration of therapy	• 28 days
HIV testing with informed consent and pre- and post-test counselling according to protocols	• Baseline HIV test in exposed person • Follow-up HIV testing 3–6 months after exposure • Rapid HIV test the source person if feasible; use informed consent and standard operating procedures
Additional laboratory evaluations	• Pregnancy testing • Haemoglobin (for AZT-containing PEP regimens) • HBV and HCV screening if available and based on the prevalence of the diseases
Counselling	• For adherence; side effects; risk reduction; trauma or mental health problems; and social support and safety
Referral	• Referrals as appropriate
Record-keeping	• Maintain accurate, confidential records
Clinical follow-up	• Assess and manage side effects • Assess and support adherence

3 CLINICAL GUIDELINES FOR THE MANAGEMENT OF SEXUALLY TRANSMITTED INFECTIONS IN THE OECS

3.1 OVERVIEW

3.1.1 Introduction

These comprehensive treatment guidelines are designed for clinicians in the OECS involved in the treatment, care, and support of patients with STIs. The guidelines are included in this manual because many clinicans who manage the care and treatment of HIV-infected patients are also involved in STIs care and treatment. There are myriad parallel issues between HIV and other STIs, particularly related to vertical transmission and prevention. Moreover, patients with HIV infection are not infrequently infected with a concomitant STI, which can produce a synergistic relationship as they potentiate each other's progression. Hence, it is essential to manage these diseases respective of each other and according to best practices. This argument forms the basis for integrating STI management with HIV treatment, care, and support, and produces a common platform for delivering standardized care throughout the OECS.

The guidelines focus on syndromic management, complemented by aetiological diagnosis, within the context of a limited-resource setting. The goal is to treat multiple infections in one patient. Clinicians are encouraged to use these guidelines to best serve the individual patient and to preserve and protect public health.

3.1.2 Theoretical Approach

The management of STIs in adults, adolescents, and children is generally similar, albeit with a few differences. The primary mode of transmission in infants is MTCT, whether viral—as in the case of perinatal HIV infection—or bacterial—as in the case of gonococcal conjunctivitis. In adults, sexual partners are the main avenues of transmission. Thus, when an STI is found in an infant, active examination and treatment must be done for the infant, the mother, and her partner(s), and prevention counselling must be offered. These steps reduce morbidity and mortality of everyone involved and interrupt the potential for disease transmission, thereby safeguarding both the individual family and public health.

The symptoms of STIs in children and adolescents are very similar to those in adults. Many young adolescents may be asymptomatic and have advanced ascending cervical infections because of the biological immaturity of the genital tract. Physical examination should be done on a case-by-case basis; speculum examination is generally not required for children. The diagnostic methods and offending organisms are standard for all age groups. In terms of treatment, guidelines are generally comparable to those for adults, with a few caveats. Notably, drug dosing must be carefully calculated, taking into account the weight of the child. Proper dosage is acutely linked with adherence—successful treatment often depends on the child's level of ingestion of a prescribed drug. Many children do not like taking medication, thus it must be as feasible as possible for the child to ingest. The clinician must also encourage the caregiver to patiently persevere in order to achieve the desired treatment outcomes.

A comprehensive, patient-sensitive approach is needed in the management of STIs in children and adolescents. During the treatment process, a detailed history must be taken, including investigation of interactions between the child and household members and/or friends, to explore the possibility of incest or child abuse. When the only evidence is the isolation of an offending organism and/or the identification of antibodies to a sexually transmissible agent, the findings should be carefully confirmed and considered. It is the clinician's duty to report sexual abuse and rape cases to the appropriate authorities. Case management should be done in consultation with key persons, including parents, paediatricians, and social workers. Parents have legal authority over their children and should be informed of all pertinent issues related to their children's treatment and care. Children's rights vary from country to country, which also must be taken into consideration. Psychological and social support services are important in case of sexual abuse and rape.

3.1.3 Goals in STI Management

The first line of STI mangement includes promptly educating, evaluating, and treating persons who are infected and infectious, to interrupt disease transmission. The second line of STI management is to identify, evaluate, and possibly empirically treat those whose infections were potentially transmitted by the initially-identified patient. This reduces complications of their disease and stanches the spread of infection, thereby reducing morbidity and mortality from STIs in the community.

3.1.4 Role of the Clinician in STI Prevention

A focus on prevention is a cost-effective strategy that reduces STI-related morbidity and mortality in the individual and in the community. Physicians and nurses must be cognizant of their roles in STI prevention:

1. Assessing a patient's risk when attending clinic or private practice, and testing accordingly.
2. Providing referrals for prevention and/or risk reduction counselling.
3. Talking to patients about testing for STIs, including blood-borne infections.
4. Diagnosing and treating patients infected with STIs.
5. Talking to patients about pre-exposure vaccination, where possible.
6. Providing or referring for partner management services.
7. Reporting STI and/or HIV/AIDS cases in accordance with national statutory requirements.
8. Keeping STI and/or HIV reports confidential.

These roles are best carried out in the context of a multidisciplinary team approach that incorporates physicians, nurses, pharmacists, social workers, laboratory technicians, and adjunctive health care providers.

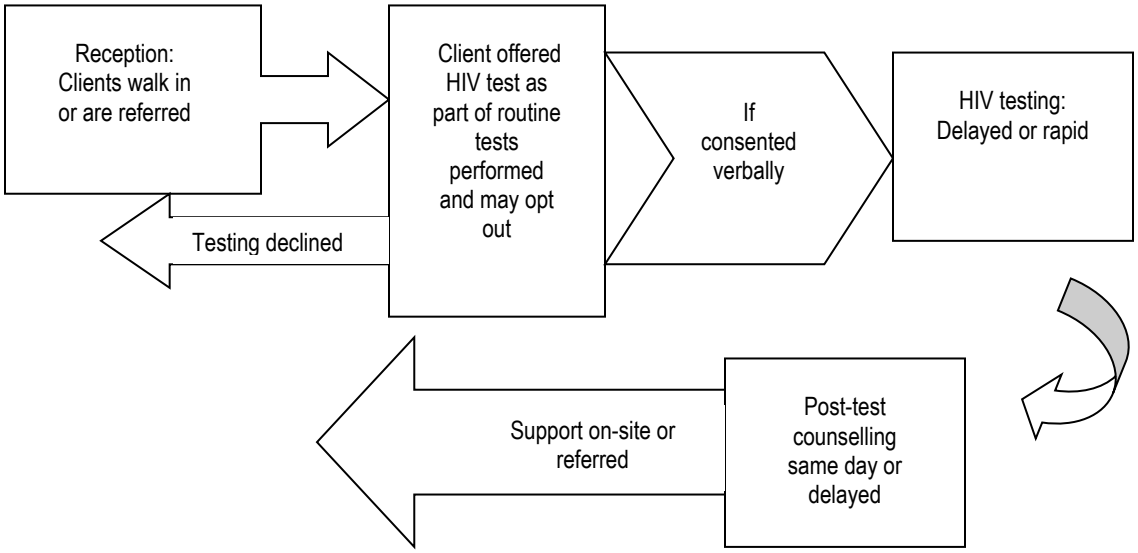
3.1.5 Counselling

Counselling for STIs and HIV—an important component of disease management—is done in conjunction with testing through a VCT- or PITC approach. Counselling is often the first point of contact for many persons infected with an STI, whether asymptomatic or symptomatic. At this first encounter, the health care worker should establish the patient's trust and build upon it by actively listening and showing empathy and understanding. Setting this precedent helps the health care worker to identify STI risk factors as well as gives them credibility in providing the patient guidance on STI prevention, condom use, and partner notification.

VCT and PITC testing have slightly different approaches. VCT relies on an individual volunteering for testing. In PITC, a health care provider initiates counselling and offers the individual STI and/or HIV testing based on the level of risk to the individual or within a community. In fact, in communities with a high prevalence of HIV and/or STIs (compared to the national average), routine testing is preferred, which requires health care providers to implement PITC. In the OECS, PITC is the preferred approach, given efforts to scale up testing to the general population.

The figure below delineates the process of PITC.

Figure10. PITC protocol



In PITC, consent for testing is verbal and does not require a written consent form.

The main focus of PITC is post-test counselling—patients who test positive for HIV or other STIs are referred for treatment; those who test negative receive counselling on prevention.

During post-test counselling for STIs, it is imperative that the following be addressed:

- The importance of informing partner(s) or spouse about the STI diagnosis (either the patient or the health care provider informs the partner[s] or spouse).
- Assessing the patient's risk for HIV and having the patient decide whether or not to undergo HIV testing.
- Educating the patient on (and helping them come to terms with) worrisome complications of STIs, such as infertility and congenital syphilis.
- If necessary, helping the patient deal with incurable STIs (e.g., HSV), which may be transmitted to the partner(s) or spouse.
- Preventing future infections, including strategies for discussing condom use with the partner(s) or spouse.
- Confidentiality, disclosure, and the risk of violence or stigmatizing reactions from spouse, partner(s), family, and/or friends.

- Empowering patients to take control of their lives and responsibilities for disease prevention.

In many STI service-oriented clinics, there may not be time to initiate an in-depth counselling session that covers the aforementioned topics. Patients often need a detailed risk assessment and reduction plan based on their personal histories. Some may need emotional support, particularly if they have been diagnosed with recurrent STIs and have displayed high-risk behaviours. Furthermore, the patient should also be provided condoms and educational materials. Responding to patients' needs requires time, a trust-promoting environment, and a health care worker experienced in counselling. Therefore, it may be more appropriate for STI clinicans to focus on treating the patient, and then refer them to relevant counselling services rather than to try to engage in all of the important aspects of counselling during one clinical visit.

3.2 INITIAL EVALUATION OF THE STI PATIENT

The initial evaluation of the STI patient is foundational to acute and chronic treatment and care. It commences with a thorough history and physical examination, guiding clinical investigation and resulting in a differential diagnosis. In the clinical care setting, the treatment strategy for STIs may differ between communities and countries, usually due to resource availability and cost considerations.

For the purpose of these guidelines, the primary treatment strategy is syndromic management, which should be supported by aetiological diagnosis based on microbiological testing to confirm the STI.

3.2.1 Steps for Initial Evaluation of the STI Patient

For individuals seeking evaluation for an STI, appropriate care consists of the following:

1. History taking, including behavioural, demographic and medical risk assessment:
    a. Detailed sexual history
    b. Substance use/recreational drug use
    c. Symptoms and review of systems
    d. Prior STIs and treatments
2. Physical examination, particularly of the genital area, done with sensitivity and understanding
3. Initial investigations, as indicated by the history and physical examination
4. Diagnosis, established either through syndromic or laboratory-based methodologies
5. Treatment that is prompt, optimal, and based on the presumed or established diagnosis
6. Patient education and counselling, including information on:
    a. Nature of infection
    b. Adherence to therapy
    c. Importance of partner notification and partner treatment
    d. Risk reduction and prevention of further STI transmission
7. HIV risk perception and assessment
8. Clinical follow up, when appropriate and feasible

Confidentiality with respect to all communication and documentation must be maintained throughout the entire process.

3.2.1.1 Step 1. History Taking

Taking a patient's comprehensive history is the most important step in the initial evaluation because it guides all subsequent physical examinations and investigations. The style of history taking depends on the clinician. However, there are key components that must be included when eliciting a proper history from a patient presenting symptomatically or asymptomatically with an STI. Above all, the clinician must use active listening skills as well as maintain confidentiality at all times. In addition, the following information should be collected:

Background:

- Basic: Name, address, occupation, marital status
- (For women) Gynaecological: Last menstrual period, gravida, Pap test

- Past medical history: Co-morbid diseases, hospitalizations, immunizations, transfusions, surgeries
- Current history: Medications, allergies
- Social history: Alcohol, drugs, incarceration, transactional sex, domestic violence
- Travel history
- Date of last HIV test

Presenting problems:
- Chief complaint
- Details of chief complaint
- Associated symptoms
- Duration of symptoms linked to onset of sexual activity
- Systemic review
- (For women) douching/vaginal cleansing practices

STI and/or HIV risk assessment questions—the 'Five Ps':
1. Partners—number of sexual partners in last month, 3 months, 12 months
2. Sexual practices—men, women, both; site(s) of exposure
3. Prevention of pregnancy
4. Protection from STI—condom use; if so, how often (also, demonstrate proper use)
5. Past history of STI

3.2.1.2 Step2. Physical Examination

The initial physical examination must be very patient-focused and specific. The antecedent history should serve as a guide for building the differential diagnosis and to verify the patient's primary complaints. There are common elements in the examination of men and women. Focused examinations based on the anatomy, sexual practices and risk behaviours may also be required.

Common elements for men and women:
- Mouth: Oral manifestations, including ulcers, plaques, masses, redness
- Skin: Ulcers, rashes, plaques, raised lesions, nodules, distribution
- Nodes: Distribution—inguinal, femoral, cervical, nature (tenderness, suppurated)
- Abdominal examination: Tenderness, masses, discolouration
- Anal and perianal area
- Genitalia

Women's genitalia:
- Observation and inspection: Vulva, vagina, introitus, perineum, mons pubis, anus (look for discharges, ulcers, plaques, erythema, pigmentation)
- Speculum examination: Vaginal vault—posterior fornix, lateral walls, cervix (look for discharges, erythema, oedema, ulcers)
- Digital examination: Cervix, uterus, adnexa (look for tenderness, masses, position, mobility)

Men's external genitalia:

- Foreskin, glans penis, mons pubis, urethra (look for ulcers, discharges)
- Testis, scrotum (assess size, shape, symmetry, tenderness)
- Anus (look for discharges, tenderness, ulcers, masses)
- Prostate (assess size, median sulcus, tenderness)

Physical examination findings should be matched with the history to ascertain congruency or inconsistencies with the initial diagnosis and to consider new diagnosis, if necessary.

3.2.1.3 Step 3: Initial Investigations

The method of investigation used will depend on the symptoms, sexual risk behaviour, and site exposed during sexual intercourse. Sometimes multiple sites need to be examined in order to confirm infection. It is important to focus investigations on the full range of possible STIs in the differential diagnosis and not just on any individual organism.

Although the gold standard of diagnosis is laboratory confirmation, this may not always be possible. Where syndromic management is used, efforts should be made at intervals to supplement the diagnosis with laboratory testing to confirm the utility of the syndromic approach and to identify resistant organisms. The main investigations used for STI diagnosis are described below.

Swabs:

- Men: Urethral Gram stain, culture and sensitivity (gonorhoea, chlamydia)
- Women:
  - High vaginal: Wet mount examination (trichomoniasis, bacterial vaginosis, candida)
  - Endocervical: Gram stain, culture and sensitivity (gonorhoea, chlamydia)
- Consider anal swabs in both sexes based on symptoms and risk factors

Serology for both men and women:

- VDRL/RPR (syphilis)
- HTLV-1 or -2
- HIV subtype 1 or 2
- HSV-2
- HAV, HBV, HCV, if available

Urinalysis:

- Microscopy culture and sensitivity
- Point of care nucleic acid amplification testing (NAAT), if available

Special considerations for women:

1. Pap test with or without visual inspection with ascetic acid (VIA)
2. Pregnancy test
3. Pelvic ultrasound for pelvic inflammatory disease (PID), where clinical findings are non-diagnostic
4. CBC

Special considerations for men:

- VIA—some providers will apply 3–5% acetic acid (which causes skin to turn white) to detect HPV-infected genital mucosa. However, acetic acid application is not a specific test for HPV infection. Therefore, the routine use of this procedure for screening to detect mucosal changes attributed to HPV infection is not recommended.

3.2.1.4 Steps 4–7. Diagnosis, Treatment, Patient Education, and Follow-up

After receiving the laboratory results from an accredited laboratory (to ensure quality control) and in accord with the history and physical examination, a proper diagnosis and treatment plan can be formulated. Diagnoses and treatment plans will vary by syndrome and specific infectious aetiology, as detailed in the following sections.

3.3 SYNDROMES OF STIs

Persons infected with STIs experience a multitude of symptoms, varying from vaginal discharges to genital ulcers. Many infections are asymptomatic, however, and require active investigation to confirm their diagnosis. The following section focuses on syndromes of STIs, possible aetiologies, methods of diagnosis, treatment, and prevention.

3.3.1 Vaginal Discharges—Vaginitis

Vaginal discharges are one of the most common presenting symptoms in women. Whereas normal discharges are usually clear, white, or milky with no odour, abnormal vaginal discharges usually present with a change in the amount, colour, or smell, as well as presence of irritation, itching, or burning. Although they may be indicative of an STI, these symptoms can also result from an imbalance in vaginal bacteria. Many women may be concerned about the cause of vaginal discharges, especially if they are not sexually active and have recurrent symptoms. However, frequently no causative organism for vaginal discharge can be identified.

When taking the patient's history, it is important to ask about vaginal cleansing practices—studies indicate that some women in the region wash up into the vagina with soaps or other products and less frequently use vaginal douches. These practices can change the vaginal pH balance, thereby increasing the risks of: vaginal discharges, worsening cervicitis, and higher levels of infection. All vaginal cleansing practices, including douching, that attempt to clean up into the vagina should be discourged

The most common causes of vaginal discharges in symptomatic women are:

1. Bacterial vaginosis (40–45%)—*Provotella, Mobilincus, Gardnerella vaginalis, Ureaplasma, Mycoplasma*
2. Vaginal candidiasis (20–25%)—*C. albicans, C. tropicalis, and C. glabrata*
3. Trichomoniasis (15–20%)—*T. vaginalis*

3.3.1.1 Diagnostic Process

3.3.1.1.2 Differential Diagnosis

1. Normal physiological discharge
2. Atrophic vaginitis
3. Cervicitis
4. Vulvo-vaginitis
5. Pinworm infestation
6. Foreign body
7. Condom allergy
8. Cervical polyp
9. Contact dermatitis
10. Vaginal cancer
11. Cervical cancer
12. Excessive desquamation of normal vaginal epithelium

3.3.1.1.3 Investigations

The work-up for a patient with vaginal discharges depends on the risk factors for infection. All women presenting with a vaginal discharge should be given a pelvic examination, though the patient's age may require the clinician to modify the examination techniques used. Where a child presents with a vaginal discharge and clinical examination proves difficult or impossible, examination under anesthesia by a gynaecologist may be required.

Studies that should be included for a patient with vaginal discharge are (depending on clinic capacity for in-house microscopy):

- Swab: High vaginal swab, endocervical swab, wet mount, Gram stain.
  - Serology: For HIV, HTLV-1 or -2, HAV, HBV, HCV, VDRL.
- Saline wet mount: Place a drop of vaginal discharge on a slide with 1–2 drops of 0.9% isotonic sodium chloride solution and examined under high power (×400).
  - Clue cells are indicative of bacterial vaginosis; test is 60% sensitive and 98% specific.
  - Hyphae and budding yeast suggest vaginal candidiasis.
  - Motile trichomonads indicate *T. vaginalis* infection; test is 80–90% sensitive.
- Whiff test: Place 1–2 drops of potassium hydroxide (KOH) on a slide with vaginal discharge; a characteristic amine odour suggests bacterial vaginosis, but this test is not highly sensitive. It may be positive with *Trichomonas* vaginitis.
- KOH mount: Place 1–2 drops of KOH on a slide with vaginal discharge; the KOH will destroy the bacterial cell wall of the presenting organisms, leaving yeast in the form of pseudohyphae and branches chains that remain clearly visible for diagnosing candidal infection.
- PH testing: Use litmus paper to determine vaginal pH; a pH >4.5 is often found in patients with trichomoniasis or bacterial vaginosis (84–97% sensitivity, 57–78% specificity). Recent intercourse, douching, cervical mucus, and blood can lead to false positive results.
  - Bacterial vaginosis—pH is 5.0–6.0
  - Vaginal candidiasis—pH is <4.5
  - *T. vaginalis* infection—pH is 5.0–7.0
    - Nucleic acid amplification testing: For clinics with capacity for nucleic amplification testing, vaginal swabs and urine samples can provide easy, quick, patient-friendly ways to diagnose STIs. This test is highly sensitive for *Trichomonas* infection and bacterial vaginosis, more so than Gram stain. Diagnosing vaginitis on clinical signs and symptoms alone can be difficult because of their similarity to those of most STIs. A combination of diagnostic methods and clinical signs and symptoms can greatly enhance the process. Table53 illustrates various criteria used to diagnose vaginal syndromes.

Table 53. Vaginal syndromes

Condition	Symptoms	Discharge	Vulvar/ vaginal inflammation	PH	Amine[a]	Microscopy
Normal exam	None	Variable clear or white	None	≥ 4.5	None	Lactobacilli
Vulvo-vaginal candidiasis	Vulvar irritation	White clumpy 'cottage cheese'	Vaginal epithelium, introitus, vulva	≤ 4.5	None	White blood cells (WBC), fungal elements (branched hyphae and pseudo hyphae)
Trichomonal vaginitis	Profuse discharge	Profuse frothy, green, or yellow	Vaginal and vulvar	>4.5 (often >5.0)	Maybe	WBC, trichomonads
Bacterial vaginosis	Malodour	Moderate, thin, homogenous grey	None	>4.5	Yes	Clue cells, few lactobacilli

[a] *Fishy odour with 10% KOH*

Diagnosis of vaginitis will depend on the availability of resources, but testing can be readily performed in a clinic with microscopy and the appropriate reagents.

a. Risk Assessment for Other STIs with Similar Symptoms

It can be difficult to determine whether a woman presenting with avaginal discharge needs expanded treatment for asymptomatic cervicitis. Peforming a risk assessment on the patient can minimize such a conundrum as well as increase the specificity and positive predictive value for it. It is important that the risk assessment be adapted to the local population. Here are some of the risk factors that may be taken into consideration when developing a risk assessment score for the patient:

Clinical signs:
- Cervical muco-pus, erosions, or friability on examination
- Bleeding between menses or in sexual intercourse

Demographic and behavioural:
- Age <21 years
- Number of partners within the previous 3 months
- New partner within the previous 3 months
- Whether current partner has an STI
- Partner condom use

A woman who presents with the obvious clinical signs of muco-pus and cervical friability on examination and/or had unprotected sex would be at higher risk for cervical infection and hence would need to be treated for cervicitis. Optimal coverage for chlamydia and *N. gonorrhoeae* as well as bacterial vaginosis and trichomoniasis would be warranted. In this way, the risk assessment can serve as a valuable tool for defining treatment for cervicitis versus vaginitis in times of uncertainty.

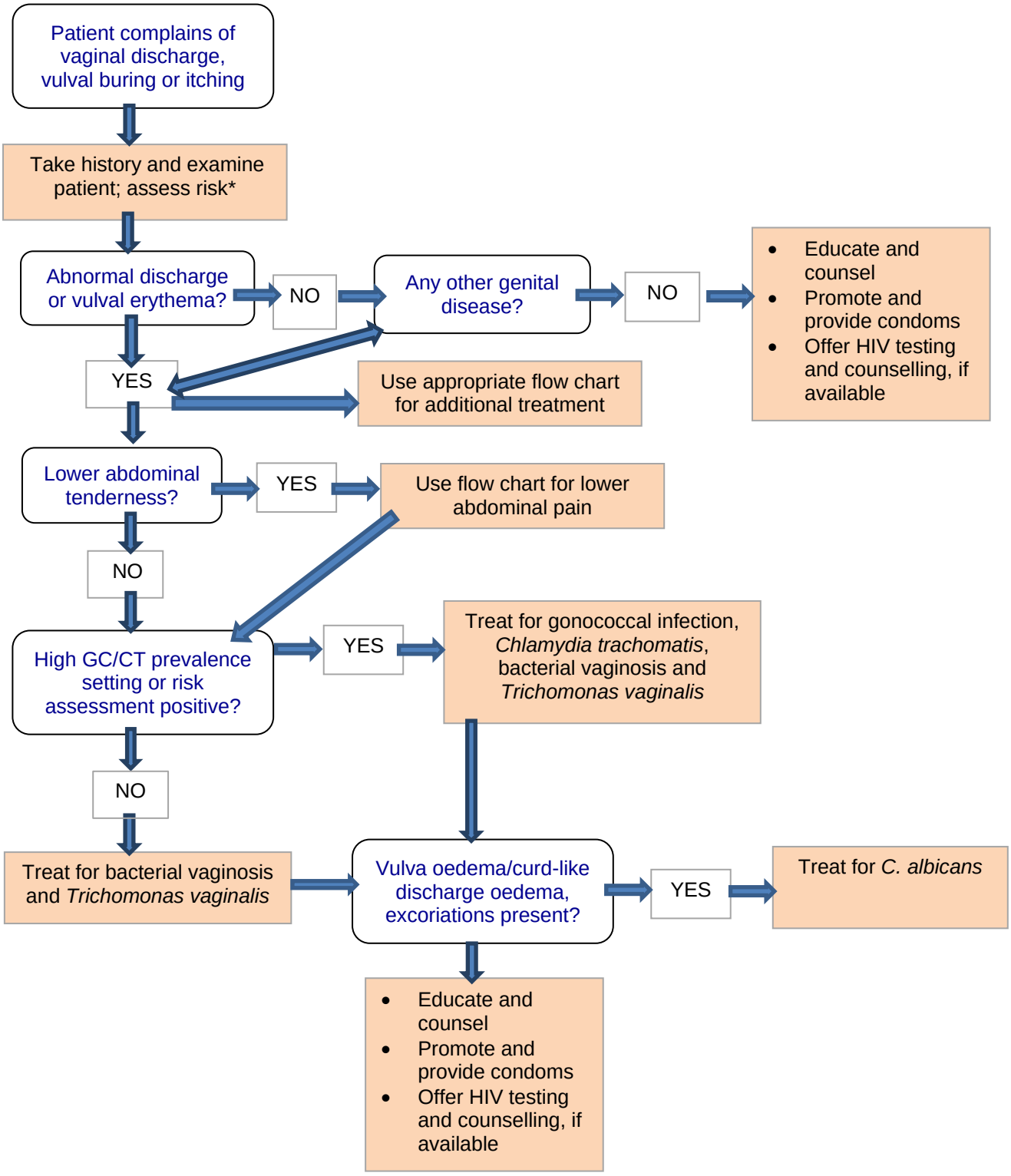
b. Treatment

Vaginal discharges may be an indication of either vaginal or cervical infection, or both. Distinguishing between the two infections can be difficult, especially in adolescents, for whom vaginal discharge is poorly predictive of cervical infection. The two presenting syndromes are thus often considered for treatment using syndromic management. This approach should be supported by aetiologically based microbiological testing using swab, urine, and serology samples for diagnosis. Adjunctive education, testing, and counselling are also essential in the comprehensive management of the patient.

c. Syndromic Management

The figure below provides an algorithm for the syndromic management of vaginal discharges.

Figure 11. The syndromic management approach for vaginal discharge



Source: World Health Organization. Guidelines for the management of sexually transmitted infections. Geneva: WHO; 2003. Available from: http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf.

d. Specific Causes

i. Bacterial Vaginosis

Bacterial vaginosis is the most prevalent cause of vaginal discharges in women. It results from a relative loss of lactobacillus in the vagina and an overgrowth of other bacteria. The typical presentation is in the form of a thin, homogenous, malodourous discharge, which can be greyish white or yellowish in colour. The discharge is often uncomfortable due to its amount and odour. Related vaginal pain or vulvar irritation is uncommon. In a nationally representative survey in the US, most women with bacterial vaginosis were found to be asymptomatic.

Bacterial vaginosis is associated with having multiple male or female partners or a new sex partner, douching, not using a condom, and having few vaginal lactobacilli. Women who have had gynaecologic surgeries, such as dilation and curettage, may also be at high risk for bacterial vaginosis. Women who have never been sexually active can also be affected; whether bacterial vaginosis is a sexual pathogen is unknown. Pregnant women with bacterial vaginosis may experience obstetrical complications like pre-term delivery and low birth weight.

1. Diagnosis

Bacterial vaginosis can be diagnosed using clinical criteria (i.e,. Amsel's diagnostic criteria) or Gram stain (gold standard). Amsel's criteria are:

1. Homogenous, thin vaginal discharge (colour and amount may vary)
2. Presence of clue cells (>20%) on microscopic examination
3. pH of vaginal fluid >4.5
4. A fishy odour of vaginal discharge before or after addition of 10% KOH (whiff test)

Detection of three of these four criteria establishes the diagnosis of BV in 90% of affected women.

Gram stains are used to diagnose bacterial vaginosis as well as help clearly differentiate the cause, which is especially important for women with recurrent infections. The Gram stain is also used to determine:

1. The relative concentration of lactobacilli
2. Gram-negative and Gram-variable rods and cocci (e.g., *G. vaginalis, Prevotella, Porphyromonas,* and *Peptostreptococci*)
3. Curved Grams negative rods (e.g., *Mobilincus*)

2. Treatment

Although routine treatment of affected women's partners is not indicated, when a woman presents with recurrent symptoms, it may be prudent to treat her partner. Women should abstain from sex during treatment and avoid douching. The use of intravaginal yogurt and/oral probiotics has not been shown to be effective as a treatment.

Table 54. Treatment regimens for bacterial vaginosis

Recommended	Alternative regimens
• Metronidazole: 500 mg orally twice a day for 7 days; OR • Metronidazole gel: 0.75% 1 full applicator (5 g) intravaginally once a day for 5 days; OR • Clindamycin cream: 2% 1 full applicator (5 g) intravaginally at bedtime for 7 days	• Tinidazole: 2 g orally once daily for 2 days; OR • Tinidazole: 1 g orally once daily for 5 days; OR • Clindamycin: 300 mg orally twice a day for 7 days; OR • Clindamycin ovules: 100 mg intravaginally once at bed time for 3 days
Notes: Consuming alcohol should be avoided during treatment and for 24 hours thereafter. *Metronidazole and clindamycin should be avoided during the first trimester* *Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use (refer to clindamycin product labeling for additional information)*	

Treatment for bacterial vaginosis should be avoided during the first trimester of pregnancy unless the benefits outweigh the risks for adverse events. Regimens for pregnant women with bacterial vaginosis include the following:

- Metronidazole: 500 mg orally twice a day for 7 days
- Metronidazole: 250 mg orally 3 times a day for 7 days
- Clindamycin: 300 mg orally twice a day for 7 days

Pregnant women should have a follow-up visit 1 month after completing treatment.

Approximately 30% of women have a relapse of symptoms within 3 months of treatment and 50% within 12 months. In the case of recurrent bacterial vaginosis, consider a longer course of therapy, as 15–20% of women fail initial therapy. After a 10-day initial treatment, use:

- Metronidazole gel: 0.75% twice weekly for 4–6 months to decrease symptoms; OR
- Metronidazole orally: 400 mg twice daily for 3 days at the start and at the end of menstruation

Treatment for bacterial vaginosis in PLHIV is the same as for non-HIV-infected individuals, although they may experience bacterial vaginosis more frequently. Annual screening for bacterial vaginosis may be indicated based on the risk factors; this is important because bacterial vaginosis has been linked to increased HIV acquisition and transmission.

3. Vaginal Candidiasis

Candidiasis is a fungal infection common in women of childbearing age. Pruritus (itching) is the predominant symptom, accompanied by a thick, odourless, white vaginal discharge, sometimes ‘cottage cheese-like’ in appearance, which can extend from inside the vagina to the vulva and inguinal region. Vulvar involvement can cause burning during urination, pain during sex, and noticeable discomfort. Unlike bacterial vaginosis, there is no prominent odour in vaginal candidiasis.

Patients often have a history of recurrent or recent antibiotic treatment. Symptoms of candidiasis often begin just before and after menses and may precede the onset of puberty in young girls. Precipitating factors include immunosuppression, diabetes mellitus, pregnancy, and hormone replacement therapy. Recurrent episodes may indicate underlying immunodeficiency. In HIV-

infected patients, there are often increasing colonization rates of which more non-*albicans* *Candida* species are present. The frequency and severity of episodes correlates strongly with the degree of immunosuppression—lower the CD4 count, the more symptomatic the patient.

4. Diagnosis

The diagnosis of vaginal candidiasis is suggested by:

1. A wet preparation (saline, 10% KOH) or Gram stain of vaginal discharge that demonstrates yeast, hyphae, or pseudohyphae
2. Normal pH of <4.5
3. A culture that yields a yeast species (culturing is recommended if negative KOH, fewer than two symptoms, or chronic symptoms)

5. Treatment

Key points to consider:

- Women presenting with signs and symptoms of candida should be treated.
- Treating sex partners is not typically recommended but may be considered in recurrent cases, particularly if the male partner could have a candida balanitis.
- Treatment of vaginal candidiasis is the same, regardless of HIV status.
- Oral fluconazole is contra-indicated in pregnancy.
- Creams and oil-based lubricant may weaken latex condoms; caution is advised when using condoms during treatment.

For the purposes of treatment, vaginal candidiasis (also referred to as vulvo-vaginal candidiasis) may be broadly classified as either ‘complicated’ or ‘uncomplicated’ and is as follows:

- Uncomplicated (sporadic or infrequent, mild to moderate): Likely to be caused by *C. albicans* and occurring in non-immunocompromised women
- Complicated (recurrent, severe): Caused by a species other than *C. albicans* or occurring in immunocompromised women

The following table describes treatment regimens for uncomplicated and complicated cases.

Table 55. Treatment recommendations for vaginal candidiasis

Uncomplicated vaginal candidiasis	Complicated vaginal candidiasis
• Butoconazole 2% cream: 5 g intravaginally for 3 days • Butoconazole 2% cream: 5 g (butoconazole 1 sustained release), single intravaginal application • Clotrimazole 1% cream: 5 g intravaginally for 7–14 days • Clotrimazole: 100 mg vaginal tablet for 7 days • Clotrimazole: 100 mg vaginal tablet, 2 tablets for 3 days • Miconazole 2% cream: 5 g intravaginally for 7 days • Miconazole: 100 mg vaginal suppository, 1 suppository for 7 days • Miconazole: 200 mg vaginal suppository, 1 suppository for 3 days • Miconazole: 1,200 mg vaginal suppository, 1 suppository for 1 day • Nystatin: 100,000 unit vaginal tablet, 1 tablet for 14 days • Terconazole: 80 mg vaginal suppository, 1 suppository for 3 days	• Recurrent (≥4 symptomatic episodes in 1 year): 7–10 days of topical therapy or a 100 mg or 150 mg oral dose of fluconazole every third day for a total of 3 doses (days 1, 4, and 7); for maintenance, oral fluconazole 100 mg or 150 mg weekly for 6 months • Severe: 7–14 days of topical azole therapy or 150 mg of oral fluconazole repeated in 72 hours; adjunctive use of nystatin cream or low-potency steroid cream may be beneficial • Non-albicans: 7–14 days of nonfluconazole therapy; 600 mg of boric acid in a gelatin capsule vaginally twice daily for 14 days • Immunocompromised: 7–14 days of topical therapy • Pregnant: 7 days of topical agents; fluconazole is contra-indicated
Patients should be informed that oil-based creams and suppositories might weaken latex condoms.	

Patients are instructed to return only if symptoms persist or recur within 2 months of the initial symptoms' onset. Routine treatment of sex partners is not indicated.

2. Cervicitis

Cervicitis is defined as inflammation of the cervix, usually derived from an infectious source. Prompt diagnosis and treatment are important to prevent the spread of infection to the upper genital tract, which can result in endometritis and/or PID.

Symptoms of cervicitis include increased vaginal discharges, dysuria, urinary frequency, and intermenstrual bleeding; however, many women with cervicitis are asymptomatic. Women with cervicitis may also present with cervical ulcers, fever and malaise as well as abnormal changes mediated through HPV. With prolonged infection, symptoms may lead to lower back pain and abdominal pain.

There are two major diagnostic signs that characterize cervicitis (either or both may be present):
1. A purulent or mucopurulent endocervical exudate, visible in the endocervical canal with surrounding erythema and oedema.
2. Sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os.

The most common identifiable causes of cervicitis are the bacterias *Chlamydia trachomatis* (chlamydia) and *Niesseria gonorrhoeae* (gonorrhoea), and the parasite *Trichomonas vaginalis* (trichomoniasis), followed by viral causes such as HSV-2 and HPV. However, in most cases of cervicitis, no organism is isolated.

a. Diagnostic Process

i. Differential Diagnosis

Due to the fact that cervicitis may be an indicator of both upper- and lower-genital tract infections, women who seek medical attention for PID should receive a clinical assessment supported by diagnostic investigations, including:

- Endocervical and high vaginal swab testing for Gram stain, culture, and sensitivity for chlamydia and gonorrhoea.
- Wet mount and microscopy for bacterial vaginosis, trichomoniasis, and candida.
- Serology for type-specific HSV is optional.

Nucleic amplification testing using urine, cervical, or vaginal samples is even more sensitive than Gram stains for identifying *Chlamydia trachomatis* and *N. gonorrhoeae*. On microscopy, a finding of >10 WBC in vaginal fluid—in the absence of trichomoniasis—might indicate endocervical inflammation caused specifically by *C. trachomatis* or *N. gonorrhoeae*.

Table 56. Differential diagnosis of cervicitis

Syndrome	Aetiology
Ectocervicitis	• Trichomonas vaginalis • Bacterial vaginosis • Candida
Endocervicitis	• Chlamydia trachomatis • *N. gonorrhoeae* • *Mycoplasma genitalium*
Discrete lesions	• HSV-1 and -2 • HPV • Cervical polyp
Other causes	• Douching or chemical irritation • Bechet's syndrome • Cervical cancer • No cause identified (30–40% of cases)

b. Treatment

Presumptive treatment for cervicitis is given according to the following critieria:

- Sexually active female ≥25 years of age
- New or multiple partners
- Unprotected sex
- Follow-up cannot be assured

In the syndromic management approach, dual therapy to cover both gonorrhoea and chlamydia is recommended. These two STIs are the most prominent and are usually responsible for ascending pathologies in the female genital tract.

Table 57. Overall management plan for cervicitis

1. Perform an endocervical swab for Gram stain culture and sensitivity
2. Perform a high vaginal swab
3. Perform an in-clinic microscopy of wet mount sample, if available
4. Counsel on prevention, including condom use and demonstration
5. Conduct serology for HIV, HTLV-1 or -2,VDRL, HAV, HBV, HCV
6. Recommend no sexual activity until treatment is completed and until partner has been treated
7. If pregnancy is a factor, consider modifying treatment
8. Follow up with patient in 1–2 weeks when results are available
9. Examine and treat partners for chlamydia and gonorrhoea
10. Perform test of cure for patients diagnosed with gonorrhoea
11. Consider partner-expedited therapy[a] for consorts who are not likely to come in for treatment and have no treatment contra-indications
12. Report cases of gonorrhoea, chlamydia, and trichomoniasis to the local health authority and initiate partner- or provider-initiated contact tracing
13. Test patients with chlamydia and gonorhoea after 3 months have elapsed
14. Provide treatment regimens recommended as below:

Recommended	Alternative
• Metronidazole: 500 mg po BD 7 days; PLUS • Ceftriaxone: 250 mg IM stat; PLUS • Doxycycline: 100 mg po BD 7 days	• Metronidzole 2gm po stat • Cefixime 500 mg po bd • Azithromycin 1 gm po stat

[a] *Partner-expedited therapy: Providing appropriate therapy for the index case's contact(s); this is done especially when the partner cannot be relied upon to come in for examination and treatment.*

c. Specific Causes of Cervicitis

i. Chlamydia

Chlamydia is the most frequently reported infectious disease in the US but is under-reported in OECS countries due to a lack of access to nucleic amplification testing.

Asymptomatic infection is common in men and women. Women may present with a cervical discharge and marked erythema but 80–90% have a normal cervix. Men may present with a clear urethral discharge. Chlamydia is especially important to identify in women owing to the potentially devastating sequelae of PID, ectopic pregnancy, and infertility. In men, untreated chlamydia can lead to infertility.

Patients presenting with symptoms of chlamydia may also have concomitant gonorrhoea, which together, compounds the inflammatory response in the genital tract and facilitates HIV transmission.

1. Diagnostic Process

a. Screening

All sexually active women aged <25 years with positive risk factors (described below) should be screened annually for chlamyida using the local risk-factor assessment criteria:

- Previous case of gonorrhoea or other STI
- New or multiple partners
- Inconsistent condom use

- Commercial sex work
- Drug and alcohol use
- Living in high prevalence areas.

b. Diagnosis

Chlamydia urogenital infection in women can be diagnosed by testing urine or by swabbing the endocervix; the latter is currently the most feasible option for the region. Urethral infection in men can be diagnosed by testing urine or by swabbing the urethra. Rectal chlamydia infections in individuals engaged in receptive anal intercourse can be diagnosed by rectal swabbing. Nucleic acid amplification, cell culture, direct immunofluorescence, enzyme immunoassay (EIA) and nucleic acid hybridization test (NAAT) can all be used to diagnose chlamydia on endocervical specimens and men's urethral swab specimens. NAAT is innovative and of tremendous benefit since it can be used at the point of care.

c. Treatment

Because a laboratory diagnosis of chlamydia may be difficult to obtain in the OECS region, syndromic management for both chlamydia and gonorrhoea is recommended. Moreover, it is fundamentally important that partners of patients with suspected and confirmed chlamydia be treated for both chlamydia and gonorrhoea.

Table 58. Treatment regimen for chlamydia

Recommended	Alternative regimen
• Azithromycin: 1 g orally in a single dose; OR • Doxycycline: 100 mg orally 2 x a day for 7 days	• Erythromycin base: 500 mg orally 4 x a day for 7 days; OR • Erythromycin ethylsuccinate: 800 mg orally 4 x a day for 7 days; OR • Levofloxacin: 500 mg orally 1 x a day for 7 days; OR • Ofloxacin: 300 mg orally 2 x a day for 7 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

Table 59. Treatment regimen for chlamydia during pregnancy

Recommended	Alternative regimen
• Azithromycin: 1 g orally in a single dose; OR • Amoxicillin: 500 mg orally three times a day for 7 days	• Erythromycin base: 500 mg orally 4 x a day for 7 days; OR • Erythromycin base: 250 mg 4 x a day for 14 days; OR • Erythromycin ethylsuccinate: 800 mg orally 4 x a day for 7 days; OR • Erythromycin ethylsuccinate: 400 mg orally 4 x a day for 14 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

ii. Gonorrhoea

Gonorrhoea is one of the most prevalent STIs in the OECS and the second most reported bacterial STI in the US.
The majority of urethral infections in men are symptomatic and require immediate therapy. Many infected men complain of a yellow purulent and often malodouruous discharge with associated dysuria and pain on erection. In prolonged infection, this may lead to testicular pain and swelling. Gonococcal infection in men can lead to infertility and prostatitis.

Infected women tend to have a yellow vaginal discharge; however, because most gonorrhoeal infection is located in the cervix, many women present with little or no symptoms until complications have occurred. Complications include PID, which can result in tubal scarring, ectopic pregnancies, chronic abdominal pain, and Fitz-Hugh-Curtis syndrome.

In gonorrhoea, both partners need to be treated and a thorough history obtained to ascertain all sites of infection based on sexual practices, including the oropharynx, eyes, and anus.

1. Diagnostic Process

a. Diagnosis

Gonorrhoea is traditionally diagnosed through Gram stain. In symptomatic men, because of its high specificity (>99%) and sensitivity (>95%), a Gram stain of a male urethral specimen that demonstrates polymorphonuclear leukocytes with intracellular diplococcic can be considered diagnostic for infection. In asymptomatic men, a negative Gram stain is not sufficient to rule out gonorrhoea because of its low sensitivity. Additionally, Gram stains of urethral, pharyngeal, or rectal specimens are not sufficient to detect infection and are therefore not recommended in asymptomatic men.

A specific diagnosis of gonorrhoea can be obtained by testing endocervical, vaginal, urethral (men only), or urine specimens with culture, nucleic acid hybridization tests, and NAAT methods. Because non-culture tests cannot provide antimicrobial susceptibility results, in cases of suspected or documented treatment failure, clinicians should perform both culture- and microbiological susceptibility testing. A test of cure should be performed after treating gonorrhoea due to the global prevalence of antimicrobial resistance.

All persons who have gonorrhoea should be tested for other STIs, including chlamydia, syphilis and HIV.

b. Treatment

Table 60 describes treatment regimens for gonorrhoea.

Table 60. Treatment regimens for gonorrhoea in adolescents and adults

Uncomplicated infections of the cervix, urethra and rectum	Uncomplicated infections of the pharynx
• Ceftriaxone: 250 mg IM in a single dose; OR, if not an option • Single-dose injectibles cephalosporins regimens (cefotaxime: 500 mg IM); OR • Ciprofloxacin[a]: 500 mg po stat; PLUS • Azithromycin: 1 g orally in a single dose; OR • Doxycycline: 100 mg orally 2 x a day for 7 days	• Ceftriaxone: 250 mg IM in a single dose; PLUS • Azithromycin: 1 g orally in a single dose; OR • Doxycycline: 100 mg orally 2 x a day for 7 days
[a] *In areas with low gonococcal resistance, prevalence of <5% and drug sensitivity testing*	

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

c. Treatment of Gonorrhoea during Pregnancy

As with other patients, pregnant women infected with gonorrhoea should be treated with a recommended or alternate cephalosporin. Azithromycin can be considered for women who cannot tolerate a cephalosporin.

See figure 11 for an algorithmic management of vaginitis.

2. Gonorrhoea in Infants and Children

Mothers are the primary source of gonorrhoea in infants. Mothers of infants who have been diagnosed with gonorrhoea and their sex partners must be evaluated and treated accordingly.

Symptoms in infants may be localized to the eyes—with a purulent discharge, as in the case of neonatal opthalmatorium—or disseminated—leading to gonococcal meningitis, which produces high fevers and seizures.

Sexual abuse is the most frequent cause of gonorrhoea in preadolescent children. In the case of preadolescent girls, vaginitis is the most common presentation, heightening clinical suspicion for higher gential tract infections. Gonococcal-associated PID after vaginal infection is less common in preadolescent girls than in women. It has been found that among sexually abused children, anorectal and pharyngeal infections with gonorrhoea are commonly asymptomatic. Sampling based on the sexual practices in consideration is recommended.

a. Diagnosis

The diagnosis of gonorrhoea in a child follows that of an adult and is based on the sexual practice sustained.

- Urethral or endocervical swab: Urethral or vaginal exposure, respectively
- Pharyngeal swab: Oral exposure
- Anal swab: Anorectal exposure

Swabs must be sent for microscopy, Gram stain, culture, and sensitivity.

For infants, the diagnosis of gonorrhoea requires a culture of the fluid of the organ in question; blood cultures should supplement CSF and synovial fluid aspirate for testing in the case of meningitis and arthritis respectively.

b. Treatment

Optimal treatment for gonorrhoea is based on microbiological testing. However, syndromic treatment before confirmed aetiological diagnosis must be given, with adequate coverage for chlamydia due to the high correlation between the two infections. A list of treatment regimens based on the permutations of gonococcal disease is given in the following table.

Table 61. Treatment of gonorrhoea in infants

Disease condition	Recommended regimen
Gonococcal conjunctivitis	Ceftriaxone: 1 g IM in a single dose

Disseminated gonococcal infection (DGI)	• Ceftriaxone: 1 g IM or IV every 24 hours; OR
	• Alternative regimens:
	  ○ Cefotaxime: 1 g IV every 8 hours; OR
	  ○ Ceftizoxime: 1 g every 8 hours

Gonococcal meningitis and endocarditis	Ceftriaxone: 1–2 g IV every 12 hours
Opthalmia neonatorum caused by *N. gonorrhoeae*	• Ceftriaxone: 25–50 mg/kg IV or IM in a single dose, not to exceed 125mg • Prophylaxis: ○ Erythromycin: 0.5% ophthalmic ointment in each eye in a single application
Prophylactic treatment for infants whose mothers have gonorrhoea	Recommended regimen in asymptomatic cases: • Ceftriaxone: 25–50 mg/kg IV or IM, not to exceed 125 mg in a single dose
DGI and gonococcal scalp abscesses in newborns	• Ceftriaxone: 25–50 mg/kg/day IV or IM in a single dose for 7 days with a duration of 10–14 days, if meningitis is documented; OR • Cefotaxime: 25 mg/kg/IV or IM every 12 hours for 7 days, with a duration of 10–14 days if meningitis is documented
Special considerations	**Regimen**
Children who weigh >45 kg	Treat with one of the regimens recommended for adults (see section 3.3.1.2.3.2)
Children who weigh ≤45 kg and have uncomplicated gonococcal vulvo-vaginitis, cervicitis, urethritis, pharyngitis or proctotitis	Ceftriaxone: 125 mg IM in a single dose
Children who weigh ≤45 kg who have bacteremia or arthritis	Ceftriaxone: 50 mg/kg (maximum dose: 1 g) IM or IV in a single dose daily for 7 days
Children who weigh >45 kg and have bacteremia or arthritis	Ceftriaxone: 50 mg/kg IM or IV in a single daily dose for 7 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

c. Ethics

The social services department must be informed of the possibility of sexual abuse when a diagnosis of gonorrhoea has been made in a child.

3. Lower Abdominal Pain and Pelvic Inflammatory Disease

All sexually active women presenting with lower abdominal pain must be evaluated for the presence of PID. PID is a spectrum of inflammatory disorders that often ascend from the lower- to the upper-genital tract; it can include any combination of cervicitis, endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. Symptoms suggestive of PID include abdominal pain, dyspareunia, bleeding between periods, dysuria, fever, and sometimes nausea and vomiting. Sexually transmitted organisms, such as *N. gonorrhoeae* and *C. trachomatis*, are implicated in many cases. However, microorganisms that comprise the vaginal flora (e.g., anaerobes, *G. vaginalis*, *Hib*, *Mobilincus*, enteric Gram-negative rods) have also been associated with PID. All women who have acute PID should be tested for gonorrhoea, chlamydia, and HIV.

The sequelae of PID can be damaging and lead to ectopic pregnancy, chronic lower abdominal pain, and infertility.

a. Diagnostic Process

i. Diagnosis

PID may be difficult to diagnose because of the wide variation in clinical manifestations; many women with PID have subtle or mild symptoms. Delays in diagnosis and treatment probably contribute to inflammatory sequelae in the upper reproductive tract.

PID becomes highly probable as a diagnosis when one or more of the following symptoms and signs are seen in a woman in whom pregnancy has been excluded:

Symptoms:
- Lower abdominal pain, which is typically bilateral
- Deep dyspareunia
- Abnormal vaginal bleeding, including post coital, intermenstrual and menorrhagia
- Abnormal vaginal or cervical discharge which is often purulent

Signs:
- Lower abdominal tenderness, which is typically bilateral
- Adnexal tenderness on bimanual vaginal examination
- Cervical motion tenderness on bimanual vaginal examination
- Fever (>38°C)

The specificity of diagnosis is enhanced by:
- Temperature >38.3C
- Abnormal cervical or mucopurulent discharge
- Abundant WBCs on saline or wet mount
- Elevated erythrocyte sedimentation rate (ESR) or c-reactive protein (CRP)
- Laboratory documentation of cervical infection with *C. trachomatis* or *N. gonorrhoeae*

It should be noted that no history, examination, or laboratory finding is both sensitive *and* specific. The most specific diagnostic tools are laproscopy, transvaginal ultrasound, MRI, and endometrial biopsy. These are primary used in the hospital setting with complicated cases that

are not settling on standard recommended therapy. Such modalities are not commonly used for diagnosis in OECS countries.

ii. Differential Diagnosis

The differential diagnosis for lower abdominal pain is broad and takes into account adjacent organ systems. Particular attention must be given to surgical emergencies such as ectopic pregnancies and appendicitis which can be life threatening. Therefore, careful evaluation of the patient is imperative for diagnosis. The differential diagnoses for PID are as follows:

- Ectopic Pregnancy
- Appendicitis
- Urinary tract infection
- Endometriosis
- Vaginitis
- Irritable Bowel Syndrome

b. Treatment

If an acute emergency has been ruled out, patients suspected of PID can be treated on an outpatient basis. In general, clinicians should err on the side of overdiagnosis and treat suspected cases. If the patient is sexually active and has pelvic or lower abdominal pain without another cause, then empiric treatment is recommended

Many cases of PID go undiagnosed and untreated, leading to tubal scaring and infertility. To avoid such longterm sequelae—combined with the fact that there are many asymptomatic infections—clinicians should have a high index of suspicion to treat for PID.

i. Issues to Consider for Hospital Admission

Whether hospitalization is necessary rests on the clinician's judgment as well as the patient meeting any one of the following criteria:

- Diagnosis is uncertain
- Surgical emergencies, such as appendicitis and ectopic pregnancy, cannot be excluded
- A pelvic abscess is suspected
- Severe illness precludes management on an outpatient basis—e.g., nausea, vomiting, high fever
- The patient is pregnant
- The patient is unable to follow or tolerate an outpatient regimen
- The patient has failed to respond to outpatient therapy

Table 62 describes how to clinically manage women with lower abdominal pain.

Table 62. Management plan for women with lower abdominal pain

First step

Ascertain the cause of lower abdominal pain; if in doubt, refer to hospital (see above on issues to consider for hospital diagnosis of PID)

Outpatient management for PID

- Perform pregnancy test
- Conduct serology testing for HIV, VDRL, HAV, HBV, HCV
- Perfom high vaginal- and endocervical swabs for culture and sensitivity
- Perfom urinalysis and urine culture
- Conduct ultrasound; if not available, refer
- Perform CBC with differential and ESR/CRP
- Perform a vaginal saline wet mount with pH
- Perform KOH wet mount and whiff test
- Examine and treat any male sex partners from the last 60 days, also treating for gonorrhoea and chlamydia, regardless of aetiology of PID
- Consider partner-expedited therapy[a] for consorts who are not likely to come in for treatment and have no treatment contra-indications
- Recommend no sexual activity until treatment is completed and until partner has been treated
- Notify as per National Guidelines

Follow-up

- Follow up in 1–2 weeks when results are available
- Test the cure in patients diagnosed with gonorrhoea
  - If gonorrhoea, chlamydia, or trichomoniasis are found on microbiological testing, report cases to local health authority and initiate partner or provider-initiated contact tracing
  - Test patients with chlamydia and gonorrhoea after 3 months have elapsed

Recommended treatment for outpatient therapy for PID

- Ceftriaxone: 250 mg IM in a single dose; OR
- Cefoxitin: 2 g IM in a single dose; PLUS
- Probenicid: 1 g orally administered concurrently in a single dose; OR
- Cefotaxime: 500 mg in a single dose; PLUS
- Doxycycline: 100 mg orally 2 x a day for 14 days; WITH or without
- Metronidazole: 500 mg orally 2 x a day for 14 days

Recommended inpatient treatment regimen[c]	Alternative
• Cefotetan 2 g IV every 12 hours; OR • Cefoxitin: 2 g IV every 6 hours; PLUS • Doxycycline: 100 mg orally or IV every 12 hours; PLUS • Metronidazole[b]: 500 mg orally or IV twice daily ***Regimen B*** • Clindamycin: 900 mg IV every 8 hours; PLUS • Gentamicin: Loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours; single daily dosing (3–5mg/kg) can be substituted	• Ampicillin/sulbactam: 3 g IV every 6 hours; PLUS • Doxycycline: 100 mg orally or IV every 12 hours

[a] *Partner-expedited therapy: Providing appropriate therapy for the index case's contact(s); this is done especially when the partner cannot be relied upon to come in for examination and treatment.*

[b] *Patients taking metronidazole should be cautioned about taking alcohol.*

[c] *Therapy should be continued for at least three days after the patient has improved and should then be followed by doxycycline 100 mg PO BD for 14 days*

See appendix 4.3 for drug safety during pregnancy and breastfeeding.

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

4. Urethritis

Urethral discharge in males is a common STI presentation. It is the corollary of cervical discharge in women. The major pathogens causing urethral discharges are *N. gonorrhoeae* and *Chlamydia trachomatis*. Other causes, such as *M. genitalium*, HSV, and *T.vaginalis*, are less likely but should be part of the differential diagnosis. The exact role of ureaplasmas in urethritis is controversial due to the conflicting observations in clinical studies.

Male patients complaining of urethral discharge should be examined; if no discharge is present, the urethra must be gently massaged from the ventral part of the penis towards the meatus.

a. Diagnostic Process

An aetiological diagnosis for the cause of urethritis should be obtained, substantiated by laboratory testing (i.e., urethral swabs for Gram stain, microscopy, culture, and sensitivity) and microscopy, if available. Microscopic examination of a urethral smear may show an increased number of polymorphonuclear leukocytes; more than 5 polymorphonuclear leukocytes per high power field is indicative of urethritis in males. The Gram stain may show Gram-negative intracellular diplococcic, indicating gonorrhoea.

The two most common causes of urethritis—gonorrhoea and chlamydial infection may cause symptoms that are indistinguishable from each other. Quite often, they are concomitant and require simultaneous treatment. If gonorrhoea is not found, then the diagnosis is given as a ‘non-gonococcal urethritis’, and by definition includes all other causes, such as chlamydia.

Persistent or recurrent symptoms of urethritis may result from drug resistance, poor compliance, or reinfection.

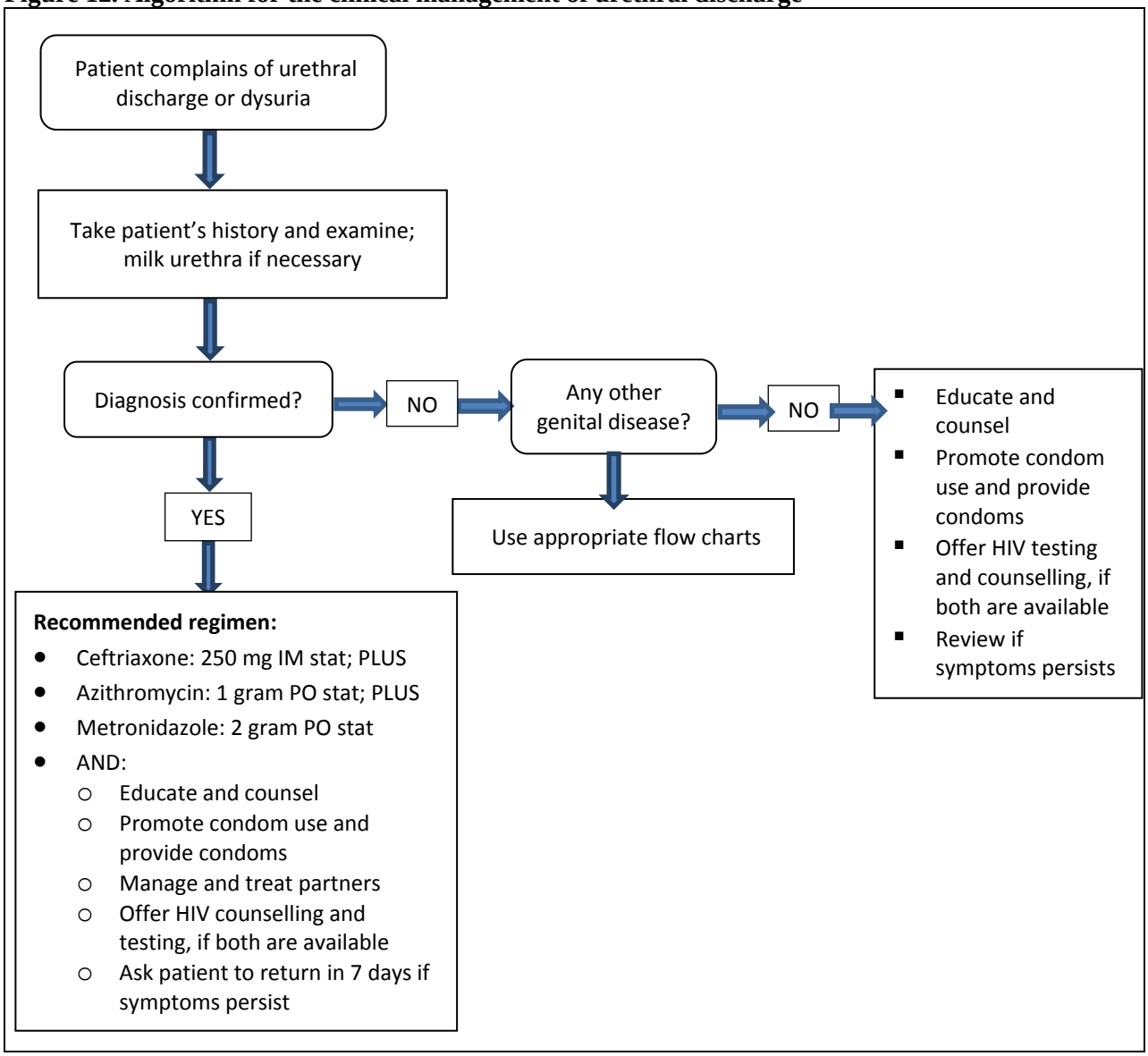
b. Syndromic Management

Table 63 and figure 12 delineate a management plan for urethritis.

Table 63. Management plan for urethritis

<table>
<tr><th colspan="2">Treatment steps</th></tr>
<tr><td colspan="2">• Perform urethral swab for Gram stain culture and sensitivity
• Offer prevention counselling—condoms, condom demonstration
• Conduct serology for HIV, HTLV-1 or -2 , VDRL, HAV, HBV, HCV
• Use recommended treatment regime
• Consider partner-expedited therapy[a] for consorts who are not likely to come in for treatment and have no treatment contra-indications
• Recommend no sexual activity until treatment is completed and until partner has been treated
• Notify as per National Guidelines</td></tr>
<tr><th colspan="2">Follow up</th></tr>
<tr><td colspan="2">• Follow up in 1–2 weeks when results are available
• Test the cure in patients diagnosed with gonorrhoea
o If gonorrhoea, chlamydia or trichomoniasis are found on microbiological testing, report cases to the local health authority and initiate partner or provider-initiated contact tracing
o Test patients with chlamydia and gonorrhoea after 3 months have elapsed</td></tr>
<tr><th>Recommended</th><th>Alternative</th></tr>
<tr><td>• Ceftriaxone: 250 mg IM stat; PLUS
• Azithromycin: 1g PO stat; PLUS
• Metronidazole: 2g PO stat</td><td>• Ciprofloxacin: 500 mg PO stat; PLUS
• Doxycycline: 100 mg PO BD 7 days; PLUS
• Metronidazole: 500 mg PO BD 7 days</td></tr>
<tr><td colspan="2">[a] Partner-expedited therapy: Providing appropriate therapy for the index case's contact(s); this is done especially when the partner cannot be relied upon to come in for examination and treatment.</td></tr>
</table>

Figure 12. Algorithm for the clinical management of urethral discharge



Source : World Health Organization. Guidelines for the management of sexually transmitted infections. Geneva: WHO; 2003. Available from: http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf.

5. Epididymitis

Epididymitis is a clinical condition that is subdivided into acute and chronic syndromes. Acute epididymitis is defined as pain, swelling, and inflammation of the epididymis that has lasted for <6 weeks, whereas chronic epididymitis is characterized by a history of discomfort and/or pain in the scrotum, testis, or epididymis that has lasted >6 weeks. Most acute episodes of epididymitis involve the testis, and lead to a condition often referred to as epididymo-orchitis. Chronic epididymitis is also subcategorized—inflammatory or obstructive chronic epididymitis and/or chronic epididymalgia.

In men <35 years old, epididymitis is often caused by STIs—mainly gonorrhoea and chlamydia—but can be caused by other enteric organisms (e.g., *E. coli*, *Klebsiella*, and

Pseudomonas). It is typically seen in male partners who perform insertive anal sex. Sexually transmitted acute epididymitis is accompanied by a urethritis, which is typically asymptomatic.

For men >35 years old, sexually transmitted epididymitis is uncommon. Bacteruria secondary to obstructive urinary disease (e.g., benign prostatic hyperplasia, bladder outlet obstruction) is more common. Generally in this age group, non-sexually transmitted epididymitis is associated with urinary tract instrumentation or surgery, systemic diseases, and immunosuppresion. A broader differential is therefore required in men >35 presenting with epididymitis.
Unlike acute epididymitis, chronic infectious epididymitis is most frequently seen in granulomatous reactions, like TB. TB lesions are usually secondary to lesions found elsewhere in the body, such as the lungs. The diagnosis should be suspected if the patient has a history of TB, has been exposed to someone with TB, or is not improving despite antibiotic treatment.

In pre-pubertal children with epididymitis, potential aetiological agents may be coliforms, Pseudomonas infection, or mumps virus. Clinically, mumps epididymo-orchitisis usually follows a week of parotid enlargement. Testicular torsion should be considered as a part of the differential diagnosis, as this condition requires immediate surgical referral. Other conditions such as tumors and trauma must also be considered.

a. Diagnostic Process

i. Diagnosis

The diagnosis of epididymitis is made on clinical grounds. Patients who have acute epididymitis typically have unilateral testicular pain and tenderness; palpable swelling of the epididymis is usually present. This swelling can spread to the testis, with associated tenderness in the spermatic cord.

There may also be:
- Urethral discharge
- A secondary hydrocoele
- Erythema and/or oedema of the scrotum on the affected side
- Pyrexia

If, on physical examination, the testes are found to be elevated or rotated, then there must be a high index of suspicion for torsion of the testes. This is even more conclusive when there is a history of trauma. Testicular torsion is a surgical emergency and must be considered in all cases. Notably, it occurs more frequently in adolescents and in men who have no evidence of inflammation. Differentiating between epididymo-orchitis and testicular torsion may be difficult; if any doubt exists, then an urgent urology consult is recommended.

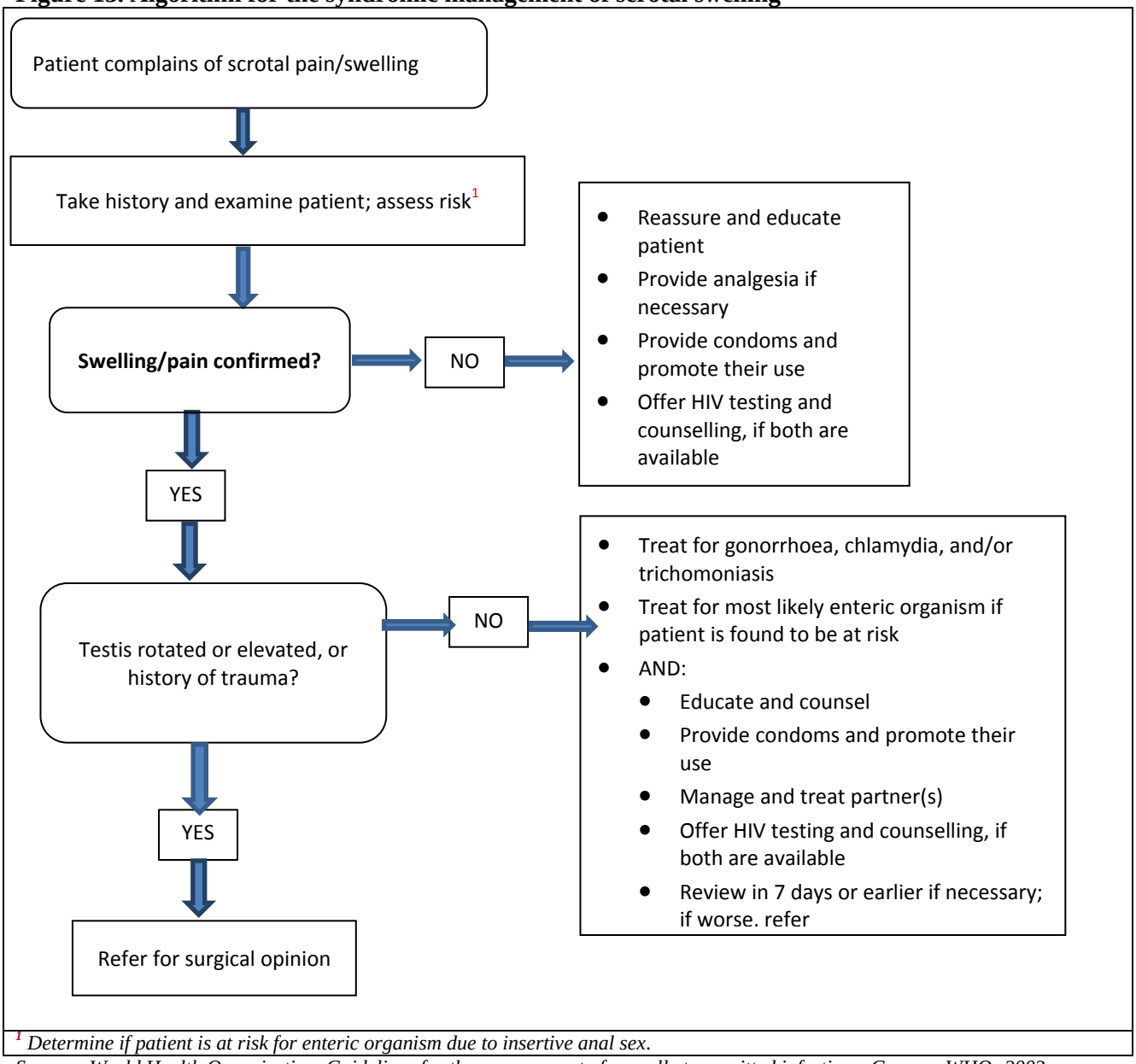
b. Syndromic Management

Table 64. The management of epididymitis and scrotal swelling

Treatment steps
• Conduct a physical examination and take a thorough history • If torsion of the testis cannot be ruled out, refer to a surgeon • Perform urethral swab for gonorrhoea and chlamydia • Collect a first-void urine sample and perform urinalysis for leukocyte esterase or microscopy for >10 WBC per high power field • Conduct serology for HIV, VDRL, HBV, HCV, HTLV 1&2 • Advise bed rest, scrotal elevation, and analgesia • Provide recommended treatment as per protocol • Educate and reassure patient • Counsel on prevention and recommend sexual abstinence during course of therapy • Advise patient to return within 18–24 hours if symptoms have not resolved • Notify as per National Guidelines
Follow-up
• Refer partners of patients with confirmed gonorrhoea or chlamydia if they had sexual intercourse with the infected partner within 60 days preceding onset of symptoms • Educate and counsel on STI prevention • Offer condoms
Recommended regimen
• Ceftriaxone: 250 mg IM in a single dose; PLUS • Doxycycline: 100 mg PO 2 x day for 10 days; PLUS • Metronidazole: 500 mg PO BD for 7 days For acute epididymitis, most likely caused by enteric organisms: • Ceftriaxone: 250 mg IM in a single dose; PLUS • Levofloxacin: 500 mg PO once daily for 10 days; OR • Ofloxacin: 300 mg PO twice a day for 10 days; PLUS • Metronidazole: 500 mg PO BD for 7 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

Figure 13. Algorithm for the syndromic management of scrotal swelling



[1] *Determine if patient is at risk for enteric organism due to insertive anal sex.*

Source : World Health Organization. Guidelines for the management of sexually transmitted infections. Geneva: WHO; 2003. Available from: http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf.

6. Balanoposthitis

Balanoposthitis refers to inflammation of the glans penis (balanitis) and the foreskin (posthitis). Balanitis is uncommon in circumcised males.

Balanoposthitis is a descriptive term referring to various conditions of differing aetiologies affecting the same anatomical sites. Candidal infection is the most common cause of balanoposthitis; other aetiologic agents include *Bacteroides*, *Gardnerella*, and *Streptococcus*. Presenting symptoms include scaly or ulcerated rash, soreness, dyspareunia, itching, inability to retract the foreskin, discharge from the glans, and odour.

Complications are mild, but in immunosuppresed patients—such as diabetics and PLHIV—it can lead to recalcitrant infections, despite therapy. In PLHIV, balanoposthitis can progress to fungal septicemia if left untreated.

a. Diagnostic Process

i. Differential Diagnosis

The diffierential diagnosis of balanoposthitis includes:

- Bowen's disease
- Contact dermatitis, irritant
- Erythroplasia of Queyrat
- Lichen sclerosus et atrophicus
- Zoon's balanitis
- Other predominantly dermatological conditions such as psoriasis, circinate balanitis, allergic/irritant dermatitis, and fixed drug eruption should also be considered

ii. Diagnosis

The diagnosis of balanoposthitis can be made on clinical grounds but requires laboratory confirmation:

- Wet prep of swab taken from the underside of the foreskin using KOH to identify pseudohyphae.
- Sub-preputial swab for bacterial culture.

The presence of aceto-white changes with application of 5% acetoacidic acid suggest HPV infection, which can be seen in association with balanoposthitis.

b. Treatment

Empiric treatment with antifungal is recommended (antibiotic cream is optional); aetiology can only be confirmed from laboratory results (e.g., microscopy and swab culture). Proper hygiene—daily washing with foreskin retraction—and thorough drying of the penis and foreskin is advised.

Table 65. Recommended treatment for balanoposthitis

Recommended regimen
• Clotrimazole: 1% cream applied to the penis or foreskin daily for 7–14 days • Miconazole: 4% cream applied to the penis or foreskin daily 7–14 days; PLUS • Antibacterial ointment (fucidic acid [Fucidin] or mupirocin [Bactroban]) • Metronidazole cream or Bactin ointment applied to affected area 2 x daily for 7–14 days

7. Genital Ulcer Disease

Genital ulcer disease (GUD) is a syndrome of ulcerative, erosive, pustular, or vesicular genital lesion(s), with or without regional lymphadenopathy. It can be caused by a number of STIs as well as conditions not related to STIs; exact aetiology often depends on the prevalence of particular organisms in the local environment.

a. Diagnostic Process

i. Differential Diagnosis

Clinical diagnosis of GUD is often inaccurate, particularly in settings where several aetiologies are common. Moreover, clinical manifestations and patterns of GUDs may be further altered in the presence of HIV infection. Diagnosis is often inadequate when based solely on history and physical examination because of the lack of sensitivity and specificity of the lesion(s), even in so-called 'classic' cases.

The following table provides a differential diagnosis of the most prevalent causes of GUD in the OECS region. It further illustrates the point that clinical distinction between these conditions can be difficult and therefore requires investigation.

Table 66. Differential diagnosis of genital ulcers

Condition	Causative organism	Painful lesions	Lymphadenopathy	No. of ulcers
Herpes	HSV-1 or -2	Yes (vesicular)	Yes	More likely multiple than one
Syphilis	*Treponema pallidum*	No	Yes	More likely one than multiple
Chancroid	*H. ducreyi*	Yes	Yes (suppurative)	One or more
Granuloma inguinale (donavanosis)	*Klebsiella granulaomatis*	No	No	One
Lymphogranuloma venerum (LGV)	*C. trachomatis*— serovars L1, L2, or L3	Yes	Yes ('groove sign' may suppurate)	Often transient and unnoticed

After examination to confirm the presence of genital ulceration, treatment appropriate to local aetiologies should be given. Because of the difficulty of diagnosing GUD on clinical grounds alone, it is essential to provide continual follow-up to confirm the actual cause. A comprehensive treatment regimen is necessary to cover most of the causative organisms of GUD.

Men and women with GUD have an increased risk of acquiring and transmitting HIV. Ulcers generated by these organisms provide a vital break in the skin for HIV to enter. The ensuing inflammatory response also recruits a number of CD4 cells that are subsequently infected by the HIV virus, causing a potentiated proliferation of HIV in the genital tract. Treating GUD early is essential to reducing HIV transmission in the infected individual and their partner(s).

b. Syndromic Management

Table 67. Syndromic management of GUD

Treatment steps
• Conduct a physical examination—including the peri-anal region—and take patient history • Perform serological testing for VDRL, HIV, HBV, HCV, HTLV-1 and -2 • Conduct dark field examination of exudate, if possible • Aspirate any fluctuant glands (avoiding surgical excision) • Perform type-specific serology for HSV-1 and HSV-2 • Perform urethral/endocervical/high vaginal swab for other STIs (and anal, where history suggests) • Provide condoms and offer counselling on their use as well as on STIs • Recommend avoidance of sex for the duration of treatment • Notify as per National Guidelines • Follow syndromic management guidelines
Syndromic recommended regimen
• Azithromycin: 1 g PO in a single dose; PLUS • Aciclovir: 500 mg PO TID for 7 days; PLUS • Benthazine penicilin G: 2.4 megaunits IM in a single dose Review in 7 days: • If lesion is healing, continue treatment • Examine and treat partner(s) • For patients with chancroid, examine and treat partners if sexual contact was within 10 days preceding the onset of patient's symptoms • Provide symptomatic partners of patients with HSV-2 with the same treatment regimen as their partners; offer evaluation, counselling, and type-specific serology to partners who are not symptomatic • Treat based on serological testing and microbiological results from swabs • Notify health authorities for patients diagnosed with syphilis and chancroid

Source : World Health Organization. Guidelines for the management of sexually transmitted infections. Geneva: WHO; 2003. Available from: http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf.

8. Inguinal Buboes

Associated with the clinical picture of a genital ulcer is the concomitant existence of inguinal buboes. Inguinal buboes are often caused by chancroid and LGV. These organisms may produce painful enlargement of the lymph glands in the groin area, which are often fluctuant. It should be noted, however, that other non-STI organisms—such as TB—may also produce similar symptoms. Syndromic treatment is therefore recommended for clinical manifestations of inguinal buboes.

a. Treatment

The recommended syndromic treatment for inguinal buboes can be seen in the table below.

Table 68. Syndromic treatment for inguinal buboes

Recommended regimen
• Ciprofloxacin: 500 mg orally 2 x a day for 3 days; PLUS • Doxycycline: 100 mg orally 2 x a day for 14 days; OR • Erythromycin: 500 mg orally 2 x a day for 14 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

Some cases may require treatment longer than the recommended 14 days. Fluctuant lymph nodes should be aspirated through healthy skin. Incision and drainage or excision of nodes may delay healing and should not be attempted. Where there is doubt or treatment failure, especially with an HIV patient, referral for diagnostic biopsy is advisable.

9. Genital Ulcers

Specific aetiologies of various genital ulcers are described below.

a. Granuloma Inguinale (Donavanosis)

Donovanosis is caused by the intracellular Gram-negative bacterium *Klebsiella granulomatis*, (previously known as *Calymmatobacterium granulomatis*). The disease presents clinically as painless, progressive, ulcerative lesions without regional lymphadenopathy. The lesions are highly vascular; they can easily bleed on contact and are characterized by their beefy red appearance.

i. Diagnostic Process

The causative organism is difficult to culture. Diagnosis requires visualization of dark-staining Donovan bodies on tissue crush preparation or biopsy.

ii. Treatment

Table 69 describes the recommended and alternative treatment regimens for donavanosis.

Table 69. Clinical management of donavanosis

Recommended regimen	Alternative regimen
Doxycycline: 100 mg orally 2 x a day for at least 3 weeks and until all lesions have completely healed	• Azithromycin: 1 g orally once per week for at least 3 weeks and until all lesions have completely healed; OR • Ciprofloxacin: 750 mg orally 2 x a day for at least 3 weeks and until all lesions have completely healed; OR • Erythromycin base: 500 mg orally 4 x a day for at least 3 weeks and until all lesions have completely healed; OR • Co-trimoxazole: one double strength (160 mg/800 mg) tablet orally 2 x a day for at least 3 weeks and until all lesions have completely healed

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

b. Chancroid

Chancroid is caused by the organism *Haemophilus ducreyi*, which is still prevalent in the region. Clinically, it presents as a painful genital ulcer with tender suppurative inguinal adenopathy. A probable diagnosis of chancroid for both clinical and surveillance purposes can be made if all of the following criteria are met:

1) The patient has one or more painful genital ulcers.
2) The patient has no evidence of *T. pallidum* infection by dark field examination of the ulcer exudate or by a serologic testing for syphilis performed at least 7 days after the onset of ulcers.
3) The clinical presentation, appearance of genital ulcers, and, if present, regional lympadenopathy are typical for chancroid.
4) A test for HSV performed on the ulcer exudate is negative.

i. Diagnostic Process

1. Diagnosis

A definitive diagnosis of chancroid requires the identification of *H. ducreyi* on special culture media that is not widely available from commercial sources. Confirmatory diagnosis of chancroid is often challenging in limited resources settings and so it is usually based on clinical grounds.

ii. Treatment

Table 70 describes the recommended treatment regimens for chancroid.

Table 70. Clinical management of chancroid

Recommended regimen
• Azithromycin: 1 g orally in a single dose; OR • Ceftriaxone: 250 mg intramuscularly (IM) in a single dose; OR • Ciprofloxacin: 500 mg orally 2 x a day for 3 days; OR • Erythromycin base: 500 mg orally 3 x a day for 7 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

c. Lymphogranuloma Venerum

LGV is caused by *Chlamydia trachomatis* serovars L1, L2, or L3. The most common clinical manifestation of LGV among heterosexuals is tender inguinal and/or femoral lymphadenopathy that is typically unilateral. An ephemeral genital ulcer papule or pustule sometimes appears at the site of inoculation. By the time the patient seeks medical care, the lesion has often disappeared. In terms of sexual practices, rectal exposure for either men or women can result in proctocolitis, including mucoid and/or haemorrhagic rectal discharge, anal pain, constipation, fever and/or tenesmus. Complications include colorectal fistulae and strictures.

i. Diagnostic Process

Diagnosis is based on clinical suspicion, epidemiologic information, and the exclusion of other aetiologies for proctocolitis, inguinal lymphadenopathy, and genital or rectal ulcers. A lymph node specimen can be tested for chlamydia by culture, direct immunofluorescence, or nucleic acid detection. Chlamydia serology (compliment fixation titres >1:64 can support the diagnosis of LGV in the appropriate clinical context.

ii. Treatment

Table 71 describes the recommended treatment regimens for LGV.

Table 71. Clinical management of LGV

Recommended regimen	Alternative regimen
Doxycycline: 100 mg orally twice a day for 21 days	Erythromycin base: 500 mg orally 4 x a day for at least 3 weeks and until all lesions have completely healed

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

10. *Genital Herpes*

Genital herpes is a chronic, viral infection that often presents with a prodrome of fever and malaise. Early on, it typically manifests as painful vesicular lesions that appear in crops and resolve within 9–14 days. Experiencing lesions may also produce psychological trauma—including anxiety and depression—in the infected individual.

Two types of HSV have been identified as causing genital herpes: HSV-1 and HSV-2. Although most cases of recurrent genital herpes are caused by HSV-2, an increasing number are being attributed to HSV-1. Many persons infected with HSV-2 have not been diagnosed with genital herpes and the diagnosis is often only discovered through serological type-specific testing. In such cases, a mild or unrecognized infection is present, but viruses are shed intermittently in the genital tract. The majority of genital herpes infections are inadvertently transmitted by individuals in such circumstances—those who are unaware that they have the infection or are asymptomatic when transmission occurs.

Pregnant women who have an outbreak of genital herpes in the period immediately prior to delivery are advised to have a caesarean section to avoid transmitting the virus to the infant.

There is a close association between HIV and HSV. The break in the epidermis caused by HSV creates a portal of entry for the HIV virus, thus facilitating the transmission of HIV. Symptoms of recurrent genital herpes infections are often more severe and occur with greater frequency in persons co-infected with HIV and HSV. Treatment with HAART and prophylactic antiviral medication can help to reduce the severity of symptoms.

a. Diagnosis

The diagnosis of genital herpes—often made on clinical grounds—is neither sensitive nor specific. Both virological- and type-specific serological testing are viable options for making a diagnosis. Cell culture and PCR are available in first-world settings for persons who seek medical treatment for genital ulcers or other mucocutaneous lesions. Complementary type-specific HSV-serologic assays based on HSV glycoprotein G2 (HSV-2) and glycoprotein G1 (HSV-1) are also used in some countries. Providers should specifically request serologic type-specific glycoprotein G (gG) -based assays when serology is performed, as other assays do not accurately distinguish HSV-1 from HSV-2 antibodies.

b. Treatment

Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of treatment. In managing genital herpes, the severity and stage of infection must be taken into account, as this may determine the strength and frequency of the regimen used for viral suppression. Additionally, patients must be educated on the natural history of genital herpes, sexual and perinatal transmission, and preventive methods.

Table 72. Summary treatment regimens for the treatment of genital herpes

Disease	Recommended regimen(s) and dose/route	Alternative regimens[a]
First clinical episode of genital herpes	• Acyclovir: 400 mg PO TID x 7–10 days; OR • Acyclovir: 200 mg PO 5/day x 7–10 days; OR • Famciclovir: 250 mg PO TID x 7–10 days; OR • Valacyclovir: 1 g PO BID x 7–10 days	None
Established infection in the HIV-uninfected person: *Suppressive*	• Acyclovir: 400 mg PO BID; OR • Famciclovir: 250 mg PO BID; OR • Valacyclovir: 500 mg PO QD; OR • Valacyclovir: 1 g PO QD	None
Episodic therapy for recurrent episodes	• Acyclovir: 400 mg PO TID x 5 days; OR • Acyclovir: 800 mg PO BID x 5 days; OR • Acyclovir: 800 mg PO TID x 2 days; OR • Famciclovir: 125 mg PO BID x 5 days; OR • Famciclovir: 1,000 mg PO BID x 1 day; OR • Famciclovir: 500 mg once, followed by 250 mg BID x 2 days; OR • Valacyclovir: 500 mg PO BID x 3 days; OR • Valacyclovir: 1 g PO QD x 5 days	None
Established infection in the HIV-coinfected person *Suppressive therpy*	• Acyclovir: 400–800 mg PO BID or TID; OR • Famciclovir: 500 mg PO BID; OR • Valacyclovir: 500 mg PO BID	None
Episodic therapy for recurrent episodes	• Acyclovir: 400 mg PO TID x 5–10 days; OR • Famciclovir: 500 mg PO BID x 5–10 days; OR • Valacyclovir: 1 g PO BID x 5–10 days	None

[a] *To be used if medical contra-indication to recommended regimen.*

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

See figures 14 on algorithmic management of genital ulcers.

11. Syphilis

Syphilis is a systemic disease caused by the spirochaete *Treponema pallidum*. It is divided into a series of overlapping stages, with symptoms varying based on the stage of disease. The stages are based on clinical findings and provide a useful guide for management. Infection is classified as acquired (through sex or blood transfusion) or congenital (MTCT). The breakdown of these subsets is described in subsequent sections.

a. Acquired Syphilis

Acquired syphilis is divided into early and late syphilis. Early syphilis comprises the primary, secondary and early latent stages. Late syphilis refers to late latent syphilis, the latter of which is further divided into gummatous syphilis, neurological syphilis, and cardiovascular syphilis.

Early syphilis:

- Primary: Presents with a primary painless chancre on the genitals that may heal without treatment.
- Secondary: Presents with more disseminated signs and symptoms, including the classic palmar/plantar rash or a desquamating rash of the palms and soles; a papular squamous

eruption that may be generalized on the body; alopecia; iritis; condyloma lata; and generalized lymphadenopathy. Rash may resemble pityriasis rosea, guttate psoriasis, and drug- or viral eruptions. Liver irritation with a raised ALT/AST may occur. Can also present as a neurologic deficit—hearing loss, vision loss, or neuropathy can occur. Have a high index of suspicion and ensure proper evaluation using treponemal and non-treponemal tests.

- Early latent: Latent syphilis acquired within the preceding year is referred to as early latent syphilis. May not be clinical signs but serological markers (VDRL titres) may be elevated.

The early stages of syphilis are more infectious but respond better to treatment.

Late syphilis:

- Late latent syphilis: Has no clinical manifestations. Defined as an infection of >2 years duration without the presence of clinical stigmata of syphilis.
- Tertiary: Term often used synonymously with late symptomatic syphilis (gummatous, nuerological and cardiovascular).

b. Diagnostic Process

i. Diagnosis

Dark field examination detects *T. pallidum* in lesion exudate or tissue and is the definitive method for diagnosing early syphilis. The test is however less reliable in examining rectal and non-penile genital lesions and not suitable for examining oral lesions due to commensal treponemes.

A presumptive diagnosis of syphilis is possible with the use of two types of serological tests:

1. Non-treponemal: VDRL or RPR
2. Treponemal tests: Fluorescent treponemal antibody abosorbed (FTA-ABS) test, *T. pallidum* passive particle agglutination (TP-PA) assay, Treponema Pallidum Hemaglutination Assay(TPHA), various EIAs, and chemiluminescence immunoassays

To correctly diagnose syphilis, more than one type of serological test must be used because each test has its own limitations. For example, false positive non-treponemal test results may occur in persons who are not infected with syphilis—certain medical conditions can produce a variety of similar antibodies and proteins, which then creates a false positive result. Autoimmune conditions (e.g., systemic lupus erythematosus) and other factors (e.g., older age, injection drug use) can also produce false positive results. Persons with a reactive non-treponemal test should also receive a treponemal test to confirm the diagnosis. However, in limited-resource settings, the non-treponemal test is often the only means of laboratory diagnosis; therefore the diagnostic process should also rely on clinical signs and symptoms.

ii. Serological Monitoring

Optimally, clinical monitoring of syphilis requires a combination of treponemal- (TPHA) and non-treponemal tests (VDRL and RPR). As mentioned, serology must be interpreted in light of clinical findings and documented treatment history.

Non-treponemal antibody titres usually correlate with disease activity and are used to help determine the stage of the infection, monitor treatment response, and assess reinfection. A

fourfold titre decrease in non-treponemal test (e.g., from 1:16–1:4 or from 1:32–1:8) is indicative of a positive treatment response. The non-treponemal tests - VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titres are often slightly higher than VDRL titres. Because of this, it is important to compare the same non-treponemal test when determining treatment response for a patient.

VDRL or RPR tests are often negative in late syphilis but this does not exclude the need for treatment. Other treponemal infections, such as yaws or pinta, may give positive serogical test results for syphilis although the RPR or VDRL result is usually of low titre (1:8). Because it is not possible to exclude latent syphilis in this situation, it is recommended that these patients be managed as though they have syphilis.

Treponemal tests, once reactive, usually remain reactive for life regardless of treatment, although some cases will sero-revert if the patient is treated during the primary stage.

iii. Serofast

Some patients, despite undergoing effective treatment for syphilis, continue to have a reactive non-treponemal test, usually with a VDRL or RPR titre of <1:4. They are then considered to be in a serofast state and do not require any further treatment. Many patients who are serofast remain so for life. Regardless of the stage of syphilis, in serofast patients, annual serological monitoring for a period of 5 years is required. However, high-risk patients should undergo periodic serological monitoring every 3–6 months to monitor possible reinfections.

iv. Neurosyphilis

In the case of suspected neurosyphilis, a CSF-VDRL test is the standard serologic test for diagnosis; it requires referral to a hospital for lumbar puncture.

PLHIV may have atypical clinical and laboratory test findings of syphilis, as well as faster rates of disease progression. Not all HIV-infected patients need to undergo lumbar puncture; the primary indications for lumbar puncture in PLHIV are as follows:

- Presentation of neurologic, ophthalmic, or otologic symptoms
- Active tertiary syphilis
- Treatment failure

c. Treatment

i. Treatment and Management of Sexual Partners

It is extremely important that sexual partners of syphilis-infected patients be clinically and serologically evaluated and treated early with a recommended regimen according to the following protocols.

Presumptive treatment:

- Anyone exposed to a case of primary, secondary, or early latent syphilis within 90 days preceding the initial patient’s clinic visit should be treated, even if they are seronegative.
- Anyone exposed for a period >90 days (3 months) must be treated if serological tests are not available and the opportunity for follow-up is uncertain.

Definitive treatment:

- Patients with high non-treponemal serological titres (e.g., VDRL >1:32) indicative of early syphilis should receive treatment.
- Sexual partners of infected persons meeting any of the following criteria:
    - Sexual contact within the last 3 months plus duration of symptoms for patients diagnosed with primary syphilis.
    - Sexual contact within the last 6 months plus duration of symptoms of a person with secondary syphilis.
    - Sexual contact within the last year with a person with early latent syphilis.

Variable treatment:

- Long-term sex partners of patients who have latent syphilis should be evaluated clinically and serologically and treated on the basis of the evaluation.

Treatment for VDRL-negative contacts of primary or secondary syphilis:

- Benzathine penicillin G: 2.4 MU IM stat; OR
- Tetracycline: 500 mg PO QID x 15 days; OR
- Doxycycline: 100 mg PO BD x 15 days

Treatment for VDRL-positive contacts of syphilis:

- Assess disease stage and assign treatment regimen appropriately.
- Although there is very little evidence to inform advice about the time frame for sexual abstinence, advise patients to refrain from sexual contact of any kind until the lesions of early syphilis (if present) are fully healed or until the results of the first follow-up serology are known.

See figures 14 on algorithmic management of genital ulcers.

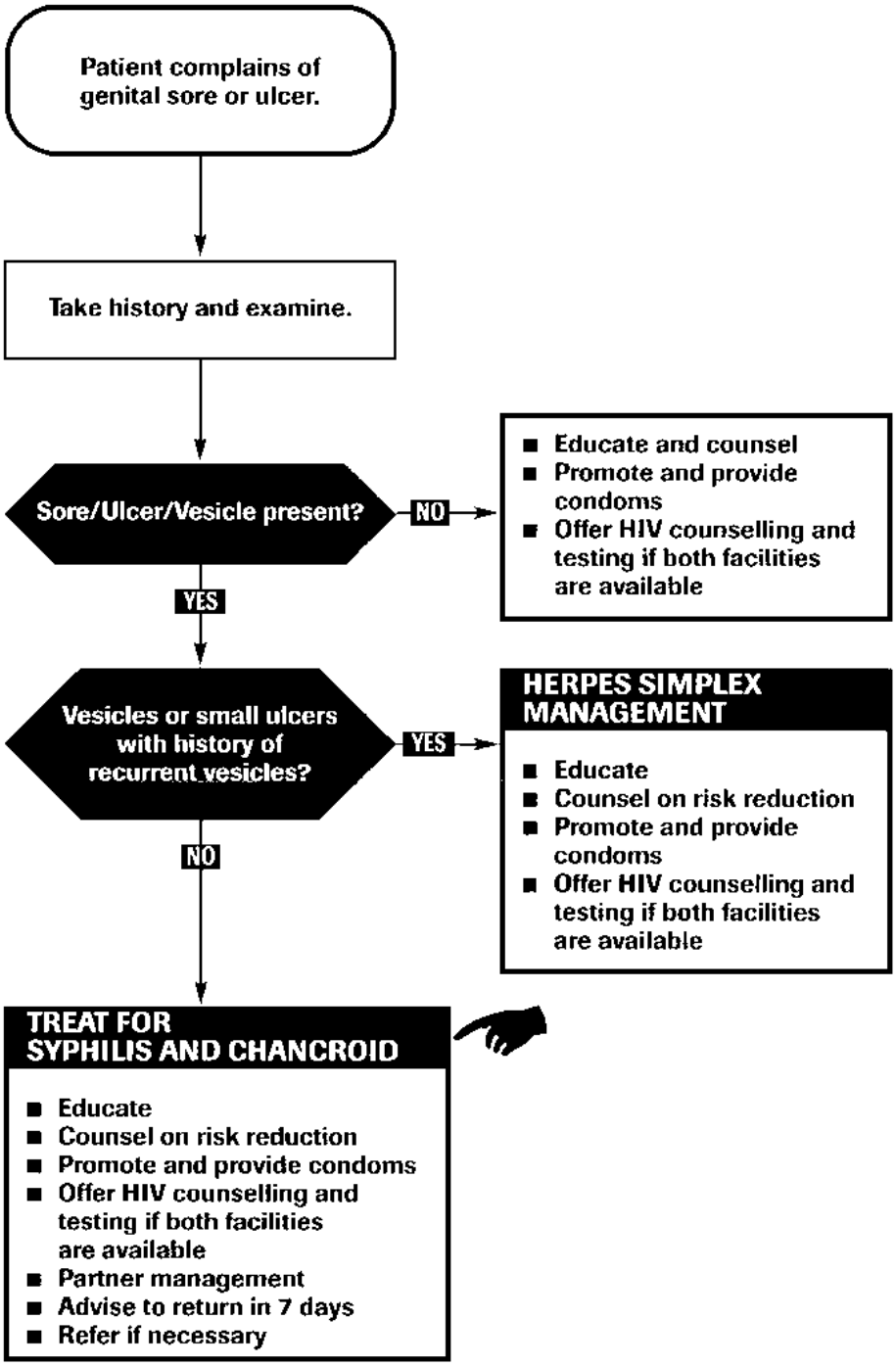
ii. Follow-up

Monitoring treatment response in patients with syphilis can be challenging because definitive criteria for cure or treatment failure have not been established. Clinical and serological evaluations should be performed according to the following schedule:

- Patients with primary and secondary syphilis must be tested at 3 months, 6 months, and 1 year after treatment, then yearly for 5 years if they remain serofast above non-reactive post treatment.
- Patients with tertiary syphilis must be tested at 6 months and 1 year after treatment, then yearly for 5 years if they remain serofast above non-reactive post treatment.

Management of patients with cardiovascular syphilis should include consultation with a cardiologist. These patients should be monitored for many years, as should patients with neurosyphilis.

Figure 14: Algorithm for the syndromic management oig Genital Ulcer Disease (GUD)



Source : World Health Organization. Guidelines for the management of sexually transmitted infections. Geneva: WHO; 2001.

d. Congenital Syphilis

Congenital syphilis is divided into early (first 2 years of life) and late syphilis (becomes apparent later in life). Clinical symptoms in an infant with congenital syphilis may result from immunological stimulation or from direct cellular attack; they include non-immune hydrops, jaundice, hepatosplenomegaly, rhinitis, skin rash, and/or pseudo-paralysis of an extremity. These infants may also have cranial nerves dysfunction with auditory problems as well as learning difficulties later in life.

In keeping with the syphilis elimination programme mandated by PAHO and the OECS, all women should be serologically screened for syphilis early in pregnancy (i.e., at the first visit) and later in the third trimester. (Note: HIV screening should also be performed at these times.) Countries may increase screening for both HIV and syphilis at their discretion.

Screening method may vary but either non-treponemal or treponemal antibody testing can be used. Women with reactive non-treponemal test should have confirmatory testing with treponemal tests titres. Any woman who delivers a stillborn infant after 20 weeks gestation should be tested for syphilis. No infant should leave the hospital without maternal serological status being determined at least once during the pregnancy.

i. Evaluation and Treatment of Infants with Congenital Syphilis during the First Months of Life

The diagnosis of congenital syphilis is complicated by the transplacental transfer of maternal treponemal and treponemal IgG antibodies to the foetus, which may result in the infant's blood returning a false positive serological test results for syphilis. Therefore, the treatment decisions frequently must be made on the basis of:

- Confirmation of maternal syphilis.
- Adequacy of maternal treatment.
- Presence of clinical, laboratory, or radiographic evidence of syphilis in the infant.
- Comparison of maternal (at delivery) and infant non-treponemal serological titres using the same test (either VDRL or RPR, but not comparing one to another) preferably conducted at the same laboratory, as there could be variation in titre assessment.

All infants born to women who have reactive serologic tests for syphilis should be examined thoroughly for evidence of congenital syphilis. The quantitative non-serologic test for syphilis should be performed on the infant's sera, not on cord blood.

The following scenarios describe the evaluation and treatment of infants for congenital syphilis.

Scenario 1:

Infants with proven or highly probable disease and:

1. an abnormal physical examination that is consistent with congenital syphilis; OR
2. a serum-quantitative non-treponemal serologic titre that is fourfold higher than the mother's titres; OR

3. A positive dark field test of body fluid(s).

Recommended evaluations:
- CSF analysis for VDRL, cell count, and protein
- CBC, differential and platelet count
- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver function tests, cranial ultrasound, ophthalmic examination, and auditory brain stem response)

Table 73. Recommended regimen for infants with congential syphilis

Recommended regimen
• Aqueous crystalline penicilin G: 100,000–150,000 units/kg/day administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days; OR • Procaine penicillin G: 50,000 units/kg/dose IM in a single dose for 10 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

If more than 1 day of therapy is missed, the entire course of treatment should be restarted. When possible, a full 10-day course of penicillin should be taken, even if ampicilin was initially provided for sepsis. In all other situations, maternal history of infection with *T. pallidum* and treatment for syphilis must be considered when evaluating and treating the infant.

Scenario 2
Infants who have a normal physical examination and a serum quantitative non-treponemal serological titre ≤fourfold the maternal titre and the mother:
1. was not treated, inadequately treated, or has no documentation of having received treatment;OR
2. was treated with erythromycin or another penicillin regime; OR
3. received treatment <4 weeks before delivery.

Recommended evaluations:
- CSF analysis for VDRL, cell count, and protein
- CBC, differential and platelet count
- Long-bone radiograph

A complete evaluation is not necessary if 10 days of parental therapy was administered, although such evaluations might still prove useful.

Table 74. Recommended regimen for infants with congential syphilis

Recommended regimen
• Aqueous crystalline penicillin G: 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days; OR • Procaine penicillin G: 50,000 units/kg/dose IM in a single dose for 10 days; OR • Benzathine penicillin G 50,000 units/kg/dose IM in a single dose

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

If the mother has untreated early syphilis at delivery, 10 days of parental therapy can be considered.

Scenario 3

Infants who have a normal physical examination and a serum quantitative non-treponemal serological titre ≤fourfold the maternal titres and the mother:

1. was treated during pregnancy, treatment was appropriate for the stage of infection and administered >4 weeks before delivery; AND
2. has no evidence of reinfection or relapse.

Recommended evaluations:

- None required

Table 75. Recommended regimen for infants with congential syphilis

Recommended regimen
• Benzathine penicillin G: 50,000 units/kg/dose IM in a single dose[a]
[a] *Another approach involves not treating the infant but rather providing close serological follow up in those whose mother's non-treponemal titres decreased four fold after appropriate therapy for early syphilis or remained stable or low for late syphilis*

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

Scenario 4

Infants who have a normal physical examination and a serum quantitative non-treponemal serological titre ≤four fold the maternal titre and the mother:

1. had adequate treatment before pregnancy; OR
2. had a treponemal serological titre that remained low and stable before and during pregnancy and at delivery (VDRL <1:2; RPR<1:4).

Recommended evaluations:

- None required

Table 76. Recommended regimen for infants with congential syphilis

Recommended regimen
No treatment is required; however, benzathine penicillin G (50,000 units/kg/dose IM in a single dose) might be considered, particularly if follow-up is uncertain

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

ii. Evaluation and Treatment of older Infants and Children

Older infants (aged >1 month) and children who are identified as having reactive serological tests for syphilis should be assessed for congenital or acquired syphilis through a review of maternal serology and records. Any child at risk for congenital syphilis should receive a full evaluation and testing for HIV infection.

Recommended evaluations:

- CSF analysis for VDRL, cell count, and protein
- CBC, differential, and platelet count

- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver function tests, cranial ultrasound, ophthalmic examination, and auditory brain stem response)
-

Table 77. Recommended regimen for infants with congential syphilis

Recommended regimen
• Aqueous crystalline penicillin G: 200,000–300,000 units/kg/day/IV, administered as 50,000 units/kg every 4–6 hours for 10 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

1. Penicillin Allergy and Desensitization

Because data are insufficient regarding the use of antimicrobiological agents (e.g., ceftriaxone) other than penicillin to treat syphilis, infected infants and children who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should be desensitized to it, if necessary, then treated with penicillin. (Note: If a non-penicillin agent is used, close serologic- and CSF follow-up are indicated.) To ascertain sensitivity to penicillin, a skin test to a penicillin determinant, such as benzylpenicilloyl poly-L-lysine (Pre-Pen), is advised. Allergic reactions can range from a mild rash to severe angioedema and anaphylaxis (e.g., upper-airway obstruction, bronchospasm, and hypertension). Given that an anaphylactic reaction can cause death, every effort should be made to avoid administering penicillin to penicillin-allergic patients, unless they first undergo acute desensitization to eliminate anaphylactic sensitivity. Desensitization should only take place in facilities with resuscitation equipment and trained personnel.

Table 78. Oral desensitization protocol for patients with a positive skin tests for penicillian allergy[a]

Penicillin V suspension dose[b]	Amount[c] (units/mL)	mL	Units	Cumulative dose (units)	Reaction/treatment
1	1,000	0.1	100	100	
2	1,000	0.2	200	300	
3	1,000	0.4	400	700	
4	1,000	0.8	800	1,500	
5	1,000	1.6	1,600	3,100	
6	1,000	3.2	3,200	6,300	
7	1,000	6.4	6,400	12,700	
8	10,000	1.2	12,000	24,700	
9	10,000	2.4	24,000	48,700	
10	10,000	4.8	48,000	96,700	
11	80,000	1.0	80,000	176,000	
12	80,000	2.0	160,000	336,000	
13	80,000	4.0	320,000	656,700	
14	80,000	8.0	640,000	1,296,700	

Note: Observation period was 30 minutes before parental administration of penicillin.
[a] Wendele GD (1985); see works cited.

Reprinted with permission from the New England Journal of Medicine.
[b] *Interval between doses = 15–30 minutes; elapsed time = 4–8 hours; cumulative dose = 1.3 million units.*
[c] *The specific amount of drug was diluted in approximately 30 ml of water and then administered orally.*

12. Ophthalmia Neonatorum

Opthalmia neonatorum is defined as conjunctivitis that occurs within the first 4 weeks of life. It is a relatively common illness, occurring in 1–12% of newborn infants. The cause may be bacterial, viral, or chemical in nature. In terms of STIs, bacterially, gonorrhoea and chlamydia are predominant causes of opthalmia neonatorum, although rates of chlamydia are estimated to be higher than those of gonorrhoea (2–40%, compared to <1%, respectively, in Canada and the US). Virally, HSV transmission during delivery can be a cause of opthalmia neonatorum, though it is rare. Non-sexually transmitted bacteria—such as *Staphylococcal-*, *Streptococcal-*, *Haemophilus-* and other Gram-negative bacterial species—account for 30–50% of ophthalmia cases. Chemical conjunctivitis caused by the instillation of silver nitrate account for the majority of the rest of the cases.

The clinical presentation of opthalmia neonatorum varies. In most instances, opthalmia neonatorum presents as a mild illness. Chemical-induced conjunctivitis secondary to silver nitrates usually appears within the first day of life and spontaneously resolves within 2 days. In cases of gonorrhoea, infants present with a purulent conjunctival discharge with surrounding erythema and oedema 2–7 days after birth. Such infants may have difficulty opening their eyelids;and if left untreated, this may lead to corneal ulceration, perforation of the globe of the eye, and blindness. Newborns with chlamydia conjunctivitis may experience varying degrees severity—from mild hyperemia with scant mucoid discharge to eyelid swelling, chemosis, and pseudomembrane formation after 5–14 days. They may also have concomitant pneumonia. HSV is another cause of conjunctivitis; it has an incubation period ranging from 6–14 days. HSV may lead to corneal ulceration, corneal scaring, and disseminated CNS involvement. If neonatal conjunctivitis is not adequately recognized and treated, it may lead to blindness.

a. Diagnostic Process

i. Differential Diagnosis

- Viral conjunctivitis
- Periorbital cellulitis
- Glaucoma primary or secondary
- Nasolacrimal duct obstruction

1. Laboratory Studies

- Conjunctival scraping Gram stain and either Giemsa Stain or calcofluor white stain
- Culture on chocolate agar and/or Thayer-Martin for *N. gonorrhoeae*
- Culture on blood agar for other bacteria
- If available, DNA PCR nucleic amplification testing using eye swab samples for gonorrhoea and chlamydia
- Histologic findings may also aid in the diagnosis of conjunctivitis and include the following:
  - Chemical conjunctivitis—neutrophils, occasional lymphocytes on Gram stain
  - Bacterial conjunctivitis—bacteria, neutrophils on Gram stain

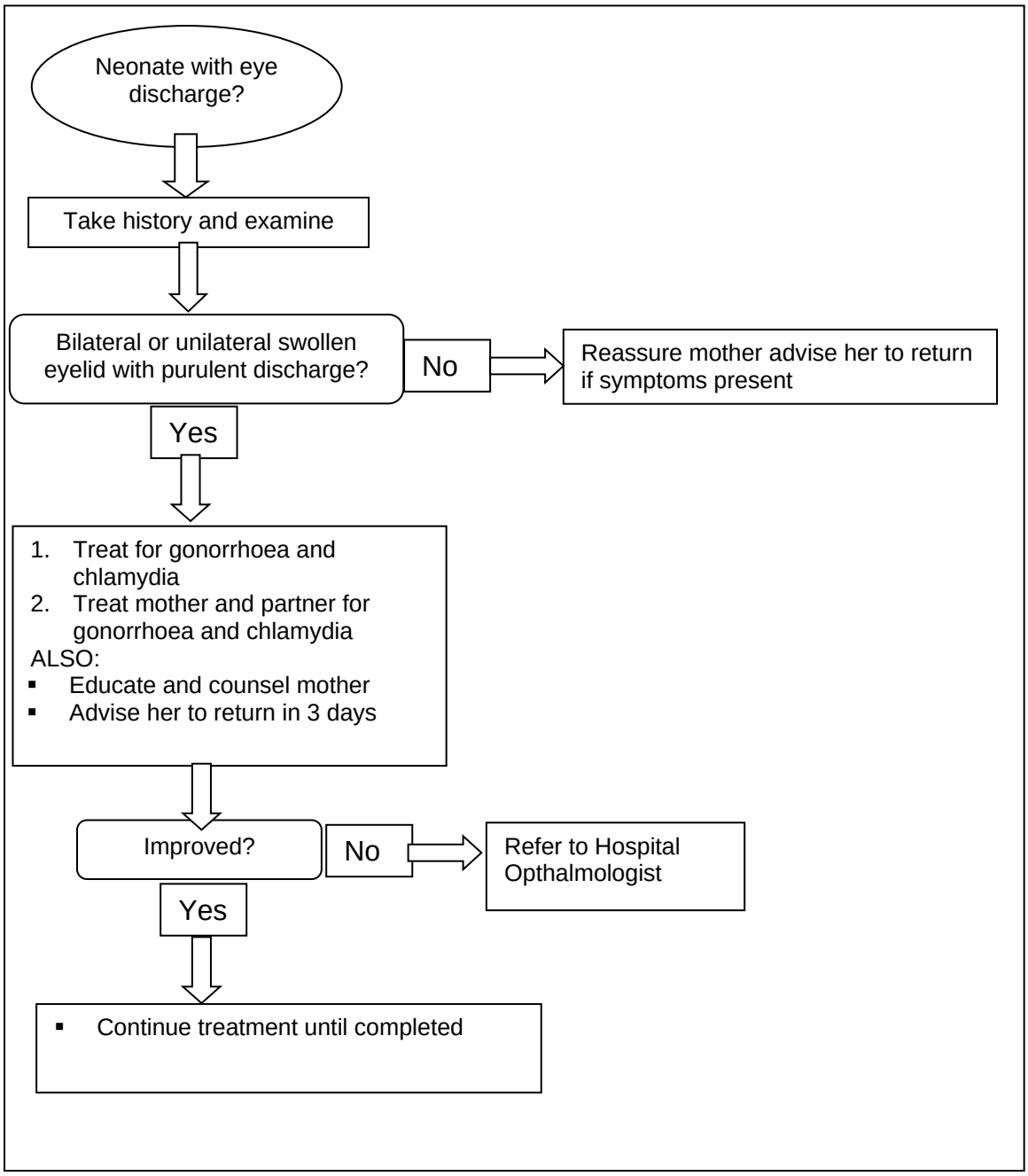
- Gonococcal conjunctivitis—neutrophils, Gram-negative intracellular diplococci on Gram stain
- Chlamydial conjunctivitis—neutrophils, lymphocytes, plasma cells on Gram stain; basophilic intracytoplasmic inclusions in epithelial cells on Giemsa stain
- Herpetic conjunctivitis—lymphocytes, plasma cells, multinucleate giant cells on Gram stain; eosinophilic intranuclear inclusions in epithelial cells on Pap test (low sensitivity)

b. Treatment

Treatment of opthalmia neonatorum must be based on the cause; therefore a careful history and physical examination are required, with particular attention to maternal and infant risk factors. Because the clinical manifestations and possible complications of gonorrhoea and chlamydia are similar and therefore difficult to differentiate, in settings where it is impossible to tell the difference, treatment should cover both. Other organisms, such as HSV, may also be implicated; specific therapy is therefore required.

Syndromic treatment is indicated in situations of diagnostic uncertainty and where resources are limited; see figure 14 for details.

Figure15. Syndromic management options for opthalmia neonatorum



c. Management

Table 79. Management plan for newborns with opthalmia neonatorum

Treatment steps
• Perform an eye swab and send it for Gram stain culture and sensitivity testing • Perform serology for infant: HIV DNA PCR (if available), HTLV 1 or 2, VDRL, HBV, HCV • Perform serology for mother: HIV, HTLV 1or 2, VDRL, HBV • Examine mother for STIs, examining endocervix and performing a high vaginal swab for Gram stain culture and sensitivity testing • Refer mother's partner/s for examination and treatment • Consult with paediatrician for full work up if pneumonia or disseminated disease are possibilities • Consider providing topical erythromycin ointment prior to laboratory results (but topical antibiotic therapy alone is inadequate and unnecessary if systemic antibiotics are being used) • Provide treatment regimen as per protocols
Treatment regimens
With gonorrhoea and chlamydia: • Erythromycin base or ethylsuccinate: 50 mg/kg/day orally divided into 4 doses daily for 14 days[a,b]; PLUS • Ceftriaxone: 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg Chemical conjunctivitis: • Treatment is not necessary • Lubrication with artificial tear preparations may ease mild discomfort Suspected neonatal herpetic conjunctivitis: • Acyclovir to reduce the chance of systemic infection: 60 mg/kg/day IV TID for 14–21 days • Infants with neonatal HSV keratitis should receive a topical ophthalmic drug, most commonly 1% trifluridine drops or 3% vidarabine ointment
Follow-up
• Modify treatment regimen based on culture results • See patient daily until treatment response is confirmed • Continue treatment as per protocol on discharge • Avoid eye patch use
[a] *An association between oral erythromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants <6 weeks of age who were treated with this drug. Infants treated with erythromycin should be followed for signs and symptoms of IHPS.* [b] *Data on use of other macrolides (e.g., azithromycin, clarithromycin) for the treatment of neonatal chlamydia infection are limited..*

i. Prophylaxis

Topical therapy is indicated for prophylaxis against opthalmia neonatorum. The recommended regimen provides coverage against gonorrhoea and chlamydia. Topical tetracycline and silver nitrate reduce the incidence of chlamydial ophthalmia neonatorum but do not eliminate nasopharyngeal colonization or pneumonia. Such treatments may not fully treat disseminated disease, so systemic treatment is required for gonococcal, chlamydial, and herpetic ophthalmia neonatorum.

Table 80. Treatment for opthalmia neonatorum

Recommended regimens
• Topical 0.5% erythromycin: 1 cm ribbon placed in the lower conjunctival sac apply to both eyes stat[a]; OR • Topical 1% tetracycline: 1 cm ribbon placed in the lower conjunctival sac apply to both eyes stat[a]; OR • 2 drops of 1% silver nitrate in both eyes
[a] *After 1 minute, any excess ointment should be wiped gently from the eyelids and surrounding skin with a sterile cotton. To prevent potential cross contamination a separate ampule or tube of antibiotic ointment should be used for each eye and discarded after use.*

d. Prevention

Preventing opthalmia neonatorum is essential to reducing STI complications in newborns. Although the rates of gonorrhoea have been decreasing, the rates of chlamydia have risen, making it the most common STI. However, due to the close association of the two bacterial species, optimal prevention means providing treatment for both. Some of the recommendations for preventing chlamydia-related opthalmia neonatorum have been aligned with gonococcal prevention. Measures to improve gonococcal prevention include the following:

- Prophylaxis to prevent opthalmia neonatorum due to gonorrhoea should be provided to all infants. **(A1)**
- The recommended prophylactic agents are noted above. **(A1)**
- Prophylaxis should be given as soon as possible after birth; however, delaying treatment up to an hour probably does not impair its efficacy. **(B3)**
- A check system should be established to ensure that all infants are treated. **(A3)**
- Infants born by caesarian section should also receive prophylaxis because infections have been reported following this type of delivery—however, the actual risk is unknown. **(B3)**
- Pregnant women should be screened for gonorrhoea and chlamydia during pregnancy and subsequently treated, if necessary. **(A3)**
- Infants born to women with gonorrhoea that was discovered during labour or delivery should be given a single dose of ceftriaxone (25–50 mg/kg) or cefotaxime (100 mg/kg) in addition to topical prophylaxis. Optical prophylaxis in newborns does not prevent oropharyngeal colonization by *N. gonorrhoeae*. Infants with established gonorrhoea require additional investigation and therapy. **(A2)**

As recommended above, prophylaxis with 1% silver nitrate ophthalmic drops, 0.5% erythromycin ophthalmic ointment, or 1% tetracycline ointment all have comparable efficacy in preventing chlamydial opthalmia neonatorum. However, they do not protect against nasopharyngeal colonization or pneumonia. Therefore, systemic treatment with erythromycin is recommended for infants with this infection.

Further, in light of the growing incidence of chlamydia and the strong correlation between chlamydia and gonorrhoea, the ideal strategy for preventing opthalmia neonatorum in the OECS is to continue offering prenatal screening and treatment of infected mothers, as well as providing neonatal prophylaxis and follow-up care.

13. Human Papilloma Virus

HPV is a small, slow growing DNA virus belonging to the papovavirus group. There are more than 50 types of HPVs, causing conditions ranging from benign to oncogenic. About 90% of genital warts are caused by HPV types 6 and 11—both of which are benign. HPV types 6 and 9 have been associated with conjunctival, nasal, oral and laryngeal warts. Clinically, genital warts are often asymptomatic, though depending on the size and anatomic location, they may produce symptoms such as pain or puritis. The morphology often varies, but they are usually flat, papular, or pedunculated growths on the genital mucosa. Most genital warts are painless and do not lead to serious complications, unless they cause vaginal obstruction in pregnant women or laryngeal papillomatosis in infants. Laryngeal papillomatosis, though uncommon, is an important clinical situation that must be considered in babies that have progressive hoarseness and stridor. In HIV-infected patients, genital warts may grow rapidly and are often difficult to control.

Unlike the benign type HPVs, the oncogenic ones cause dysplasia in the epithelial cell lining of the site of inoculation (e.g., cervix, anus, vulva, throat) leading to the development of abnormal cells lines and eventually cancer. HPV types 16, 18, 33, and 53are the leading causes of cancer among women in developing countries. In men, new research suggests that, due to oral sex, oropharngeal cancer is on the rise, as are rates of ano-rectal cancer in HIV-infected men, despite HAART.

a. Diagnostic Process

i. Diagnosis

Genital warts are usually diagnosed via visual inspection and can be confirmed by biopsy if:

- Diagnosis is uncertain
- Lesions do not respond to standard therapy
- Symptoms worsen during therapy
- Lesions are atypical
- The patient has compromised immunity
- Warts are pigmented, indurated, fixed, bleeding, or ulcerated

ii. Screening

The recommended schedule for routine cervical cancer screening is:

- 16–20 years: HPV screening and Pap test for women with multiple partners every year
- 21–29 years: Pap test every 2 years
- 30 and over: Pap test every >3 years

Every STI clinic should have the following protocol for conducting Pap test screening:

- Women who do not have a recent (within 12 months) clinically recorded normal Pap test.
- Women who do not have another provider for screening.

When performing a pelvic examination, the clinician should:

- Enquire about the results of the patient’s most recent Pap test.
- Explain the purpose of the Pap test.

- Convey the importance of having regularly scheduled Pap tests between the ages of 21–65.

Women should receive a copy of their Pap test results.

STI clinics that offer routine cervical cancer screening should ensure that, where required, follow-up care and referral for further investigation and treatment are provided. If it is not possible to offer a Pap test to a patient who needs one, she should be given a list of providers and referral clinics and helped to made arrangements to that end.

As for special populations who should be screened:
- Women who have received the HPV vaccine should be screened in the same manner as unvaccinated women.
- Pregnant women should be screened with the same frequency as non-pregnant women.
- HIV-infected women with a CD4 count <200 cells/mm^3 or AIDS should be screened twice a year, as women with AIDS have an increased risk for cervical dysplasia and cancer.

Due to the increased incidence of anal cancer in HIV-infected men, it is important to consider screening men for that disease annually using anoscopy and digital rectal exams. Pap testing men who engage in anal sex may also be appropriate. Also, because of the increased incidence of HPV-induced oral cancers in men, oral HPV testing should be considered.

All screening tests must be processed by certified labs that have either conventional or liquid-based cytologic tests (e.g., Pap tests). The results reporting system should be based on the following Bethesda terminology:
- Atypical squamous cells (ASC)
- ASC of undetermined significance (ASC-US)
- ASC—cannot exclude high-grade squamous intraepithelial lesion (HSIL)
- Low-grade squamous intraepithelial lesion (LSIL)
- HSIL

1. Visual Inspection with Ascetic Acid (VIA)

VIA is another viable method for cervical cancer screening. It is best used for women in their 30s and 40s who may have precancerous and cancerous lesions and who have certain risk factors, including high parity, oral contraceptive use, smoking, and HIV infection. Screening women once every 3 years still gives a 90% detection rate and therefore is quite effective given the 10–15 year latency period of cervical cancer.

Procedure
The procedure for VIA is very simple and involves applying a cotton swab dipped in 5% trichloroacetic acid (the same strength found in typical vinegar) to the cervix, coating it. The clinican should look for acetowhite changes on the cervix, focusing on the squamocolumnar junction. Whether the patient needs referral depends on the following criteria:

If lesion is VIA negative:

- Normal squamocolumnar junction: Advise patient to return for another VIA within 1–3 years, unless high risk (uses hormonal contraceptives, is a smoker, has high parity, is HIV-infected), in which case she should return in 1 year.

If lesion is VIA positive:
- Lesion extends beyond squamocolumnar junction to transformation zone but <70% of cervix and within limits of probe: Treat with cryotherapy.
- Lesion is >70% and 2mm beyond limits of probe: Refer for colposcopy and biopsy.

If lesion is cancerous (ulcerative, bleeds easily, fungating mass):
- Refer immediately to gynaecologist for surgery (total abdominal hysterectomy plus chemotherapy/radiation, based on clinical staging.

Given the low cost of this technique, it is a good option to use in low resource settings and high risk populations who may not return for follow-up or do not have the money to pay for Pap tests. The results are immediately available and have a sensitivity rate of 56–96% and specificity of 44–97%.

b. Prevention and Treatment

Many clinicians are increasingly using HPV vaccines, which not only offer protection from genital cancers but also from oral and throat cancers. The vaccines available in the OECS region are:
- Cervarix bivalent vaccine, which contains HPV types 16 and 18 and protects against 70% of cervical cancers.
- Gardasil quadrivalent vaccine, which contains HPV types 6, 11, 16, and 18 and protects against 90% of cervical cancers (due to additional type 6 and 11 protection).

Both Gardisil and Cevarix have been approved for use in girls and boys ages 11–12 years and can be administered to those as young as 9. Girls and women ages 13–26 who have not started or completed the vaccine series should also receive it; it works best if they have not started sexual activity. Gardisil can be used in boys to prevent genital warts and works best if they have not yet started sexual activity.

Both vaccines are administered as a three-dose series of IM injections over a 6 month period.

Table 81. HPV vaccination timetable

Dose	Time
First dose	X
Second dose	1–2 months after X
Third dose	6 months after X

Women who have received the HPV vaccine should continue getting routine cervical cancer screening because 30% of cervical cancers are caused by HPV types other than 16 or 18.

i. Management of Pap Test Results

Pap tests provide a wide variety of information—they can detect infections, inflammation, or precancerous lesions, ranging from bacterial vaginosis and candida to inflammatory changes and a concomitant STI. Pap tests should be repeated after 6 months if inflammatory changes are observed and then regularly, according to age-specific testing recommendations.

Patients with significant risk factors and abnormal changes noted on Pap results (e.g., ASC-US high grade histological changes CIN 2 and above) should be referred to a gynaecologist for colposcopy and further management.

CIN (cervical intraepithelial neoplasia) identifies how much of the lining of the cervix is invaded by abnormal cells.
CIN Classifications
CIN I: Mild dysplasia; abnormal cells can be found in 1/3 of the lining of the cervix
CIN II: Moderate dysplasia; abnormal cells can be found in 2/3 of the lining of the cervix
CIN III: Severe dysplasia; abnormal cells can be found in more than 2/3 of the lining of the cervix and up to the full thickness of the lining

Men who have abnormal changes on anal Pap tests must be immediately referred for treatment; this is especially true for HIV-infected men, who have a higher risk of anal cancer.

ii. Treatment

For patients with inflammatory effects, antimicrobials are recommended.

Table 82. Treatment of inflammatory Pap test

Condition	Recommendation
Inflammatory effect	• Metronidazole: 500 mg PO BD for 1 week & • Consider fluconazaole: 150 mg PO stat; OR • Clotrimazole pessaries: 1 pv nocte for 1 week
Concomitant conditions	Treat or refer accordingly

The treatment of genital warts can be long and painstaking. Careful follow-up is needed to ensure adequate therapy is being provided. The following table provides a complete list of treatment options.

Table 83. Treatment of genital warts

Disease	Recommended regimen(s) and dose/route		Alternative regimens[a]
	Patient-applied	Provider-administered	
External genital warts	• Podofilox 0.5% solution or gel: Apply 2 x daily for 3 days followed by 4 days of no treatment, repeating cycle up to 4 x (total volume of podofilox should not exceed 0.5 ml per day); OR • Imiquimod 5% cream; OR • Sinecatechins 15% ointment	• Cryotherapy with liquid nitrogen or cryoprobe; repeat applications every 1–2 weeks; OR • Podophyllin resin: 10–25% in a compound tincture of benzoin o External genital and perianal warts should be washed thoroughly 1–4 hours after the application of podophyllin o Podophyllin applied to warts on vaginal or anal epithelial surfaces should be allowed to dry before the speculum or anoscope is removed o Repeat treatment at weekly intervals; OR • Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80–90% followed by powdering of the treated areas with talc or sodium bicarbonate to remove unreacted acid; OR • Surgical removal either by tangential scissor excision, tangential shave excision, curettage or electrosurgery	Imiquimod, sinecatechins, podophylin, and podofilox should not be used in pregnancy
Cervical warts		Pap test: • Treatment of cervical warts should not be started until the results from a Pap test are known • For women who have exophytic cervical warts, a biopsy evaluation to exclude high grade squamous intraepithelial lesion must be performed before treatment is initiated • Management of exophytic warts should include consultation with a specialist	No TCA or podophyllin
Vaginal warts		• Cryotherapy with liquid nitrogen; OR • TCA or BCA 80% to 90% applied to warts o A small amount should be applied only to the wart and allowed to dry, at which time a white frosting develops o If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap preparations to remove unreacted acid o This treatment can be repeated weekly if necessary	• The use of the cryoprobe in the vagina is not recommended because of the risk of vaginal perforation and fistula formation • Podophyllin and TCA are not recommended for intravaginal use
Urethral meatus warts		• Cryotherapy with liquid nitrogen; OR • Podophylin 10–25% in compound	• The safety of podophylin during

		tincture of benzoin: The treatment area and adjacent normal skin must be dry before contact with podophylin; treatment can be repeated weekly, if necessary	pregnancy has not been established • Data is limited on the use of podofilox and imiquimod for treatment of distal meatal warts
Anal warts		• Cryotherapy with liquid nitrogen; OR • Apply TCA or BCA 80–90% to warts. o A small amount should be applied only to the wart and allowed to dry, at which time a white frosting develops o If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap preparations to remove unreacted acid o This treatment can be repeated weekly if necessary; OR • Surgical removal	

[a] *To be used if medical contra-indication to recommended regimen.*

Note: The removal of a lesion does not mean that the HPV infection has been cured—no treatment is completely satisfactory.

14. Hepatitis A

Hepatitis A, which is caused by infection with HAV, has an incubation period of 28 days. The infection produces a self-limiting disease that does not result in chronic infection or chronic liver disease. Symptoms are typical of an acute viral illness—fever, malaise, myalgia, lymphadenopathy, and jaundice. Ten to 15% of individuals with HAV experience a relapse of acute symptoms within 6 months.

The main mode of transmission is faecal-oral but it can also be transmitted through oral sexual practices. High-risk groups include MSM, injection drug users, and persons with chronic liver disease.

a. Diagnostic Process

i. Diagnosis

Hepatitis A cannot be diagnosed on clinical grounds alone; a positive serologic antibody test indicating the presence of IgM antibody to HAV is required.

b. Treatment

Treatment for acute hepatitis A is usually supportive. Patients who are acutely ill and have serious signs and complications of acute liver failure (e.g., jaundice, pale stools, dark urine) should be hospitalized. Medications that are metabolized by the liver must be used with caution in persons with hepatitis A as they may cause liver damage.

c. Prevention

Two products are available to prevent HAV infection—the hepatitis A vaccine and immunoglobulin.

- The vaccine is administered IM in a two-dose series at 6–12 months of age. It is recommended for all persons who are found to be antibody negative by HAV testing.
- Immunoglobin (IG) IM administered prophylactically before or within 2 weeks after exposure to HAV is >85% effective in preventing infection.

Condoms are not effective in preventing HAV because most transmission is faecal-oral.

15. Hepatitis B

Hepatitis B, which is caused by infection with HBV, has an incubation period ranging from 6 weeks to 6 months. It can be self-limiting or chronic. In adults, approximately half of newly acquired infections are symptomatic and around 1% result in acute liver failure and death. Symptoms range from mild (e.g., flulike symptoms) to severe (e.g., fever, jaundice, encephalopathy, abdominal pain, dark urine, pale stool).

The main route of transmission is through percutaneous, or mucous membrane exposure to blood or body fluids that contain blood infected with HBV. The risk of HBV transmission is close to 3% per contact exposure and so universal safety precautions must be followed in all health care institutions.

Unlike HAV, HBV has serious sequelae, including cirrhosis of the liver and hepatocellular carcinoma, which can lead to premature death. Many persons control the infection to become chronic carriers.

a. Diagnostic Process

i. Diagnosis

Hepatitis B—acute or chronic—must be diagnosed via serologic testing. A complete HBV antibody profile that includes the following analyses is ideal for diagnosis and management:

- IgM antibody to hepatitis B core antigen (IgM anti-HBc) is diagnostic of acute or recently acquired HBV infection (HBsAg is present in both acute and chronic infections).
- Antibody to HBsAg (anti-HBs) is produced after a resolved infection and is the only HBV antibody marker present after vaccination.
- HBsAg and total anti-HBc with a negative test for IgM anti-HBc indicates chronic HBV infection.
- Anti-HBc alone might indicate a false positive result or acute resolved or chronic infection.

b. Treatment

Because no specific therapy is available for persons with acute HBV infection, treatment is usually supportive. Persons with chronic infection should be referred to a physician experienced in the management of chronic liver disease. Therapeutic agents can help to achieve sustained suppression of HBV replication and remission of liver disease. Treatment is mainly based on interferons (pegylated interferon alfa-2a) and antivirals, such as NRTIs.

In the case of HIV-HBV co-infection, two NRTIs—TDF and FTC or 3TC—are used in combination with an NNRTI (preferably EFV) to manage both diseases. Drug management here requires careful supervision due to the risk of viral rebound if one of the drugs is withdrawn; such patients should be referred to a clinician experienced in managing HIV.

c. Prevention

Two products have been approved for preventing hepatitis B: the hepatitis B vaccine and hepatitis B immune globulin (HBIG). HBIG provides temporary (3–6 months) protection from HBV infection and is typically used as a PEP measure, either adjunct to vaccination in previously unvaccinated persons, or alone in persons who have not responded to the vaccine series administered both pre- and post-exposure. There are two monovalent vaccines available for use in adolescents and adults—Recombivax HB and Energix. Twinrix, a combination vaccine containing HAV and HBV, is available for use in adults.

The goal of vaccination is to prevent infection. The approved vaccination schedule options for adolescents and adults for Energix and Recombivax HB are as follows:

Table 84. HBV vaccination schedule

Option	Timeline
1	0, 1 month then 6 months
2	0, 1 month then 4 months
3	0, 2 months then 4 months

Infants born to mothers infected with HBV must be given HBIG after birth, followed by the complete routine childhood HBV immunization series. According to the WHO, it is safe for mothers to breastfeed their babies, though women with cracked nipples must proceed with caution.

Other prevention measures providers can take include:

- Advising patients to use condoms
- Referring partner(s) of index-case patients for HBV testing and follow-up care
- Following universal safety precautions for blood-borne infections
- Advising patients to avoid alcohol and drugs (especially injection drugs)
- Advising patients to eat a healthy diet and exercise

16. Hepatitis C

Hepatitis C, which is caused by HCV, can be highly contagious, with as much as 30% risk of exposure per contact event. The average time from exposure to antibody to HCV seroconversion is 8–9 weeks. Individuals with typical infections have mild symptoms or are asymptomatic. Chronic infection develops in 70–80% of HCV-infected persons, of which 60–70% develop evidence of active liver disease. HCV can lead to hepatocellular carcinoma.

HCV is not very common in the OECS. Its primary mode of transmission is injection drug use, though it can also be transmitted through blood transfusion, so blood donors should be carefully screened as a matter of course. Although HCV is not efficiently transmitted sexually, high-risk behaviours like unprotected sexual contact and injection drug use increase the likelihood of

transmission, particularly within vulnerable groups. For this reason, it is important to consider offering HCV testing to injection drug users who may be accessing care at STI treatment clinics, HIV testing and counselling facilities, or other public health settings where such services are available. Correctional facilities should also perform HCV testing.

a. Diagnostic Process

i. Diagnosis

Anti-HCV testing, which detects the presence of HCV antibodies, is recommended for routine screening of symptomatic persons based on their risk of exposure (e.g., injection drug use, percutaneous needlestick injury). Testing should include HCV antibody testing using EIA or enhanced chemiluminescence immunoassay, and, if recommended, supplemental antibody tests.

b. Treatment

Therapeutic agents can help to achieve sustained virological suppression of HCV and remission of liver disease. Combination therapy with pegylated interferon and ribavirin is the current treatment of choice for patients with chronic HCV infection. Though recent advances in the development of oral agents are promising, current treatment options are very expensive and of variable efficacy, depending on a variety of factors, including the strain (genotype) of HCV as well as patient co-morbidities. A specialist knowledgeable about HCV management should be consulted.

c. Prevention

No vaccine is available to prevent hepatitis C and prophylaxis with immunoglobin is not an effective PEP measure.

Prevention measures providers can take include:

- Advising patients to use condoms
- Referring partner(s) of index-case patients for HBV testing and follow-up care
- Following universal safety precautions for blood-borne infections
- Advising patients to avoid alcohol and drugs (especially injection drugs)

17. Human T-lymphotrophic Virus Infection

HTLV was the first retrovirus discovered. It belongs to the *Retroviridae* family in the genus *Deltaretrovirus* and is comprised of four strains (types 1, 2, 3 and 4); types 1 and 2 are dominant in the OECS. HTLV-1 and -2 are endemic to Japan as well as the Caribbean region, and affect 15–20 million people worldwide. The prevalence of HTLV in some Caribbean countries, such as Jamaica and Trinidad, has reached as high as 6% in the last decade.

HTLV-1 and -2 can be transmitted via sexual contact, breastmilk, childbirth, injection drug use, blood transfusions, and mucous membrane exposure.

HTLV-1 is the more clinically significant strain. Acute HTLV-1 infection is rare—most infections are latent and asymptomatic. Symptoms mimic a typical viral syndrome, with fever, headache, myalgia, and lymphadenopathy. Some individuals infected with HTLV-1 develop a rapidly fatal adult T-cell leukemia. Others experience neurological changes, including a

debilitative myelopathy (known as HTLV-1–associated myelopathy [HAM] or ‘tropical spastic paraparesis’ [Note: Subsequently refered to as ‘HAM’], which may lead to urinary or faecal incontinence, lower motor weakness, and erectile dysfunction. Still others develop uveitis, infective dermatitis, or other inflammatory disorders.

HTLV-2 is associated with milder neurologic disorders and chronic pulmonary infections.

Many HIV-infected patients are co-infected with HTLV-1. Their inflammatory response is more severe, leading to exacerbation in chronic co-morbid diseases, such as peripheral neuropathy, arthritis, and asthma. Patients with an HIV-HTLV co-infection may experience greater morbidity, leading to a reduced quality of life.

a. Diagnostic Procedure

i. Diagnosis

HTLV-1 and -2 infections are detected using ELISA, which then must be confirmed with Western blot, immunofluorescence assay, or PCR. PCR or EIA with virus-specific synthetic peptides is necessary to distinguish between HTLV-1 and HTLV-2. PCR is also necessary in infants who may have false-positive results because of circulating maternal anti-HTLV antibodies. It is also used to determine the HTLV viral load, which is helpful in determining disease progression in patients with HAM.

Due to the distinct possibility of co-infection, patients diagnosed with HTLV-1 or HTLV-2 should:

- Consider being tested for HIV.
- Have routine blood work performed, including: CBC with differential and peripheral blood smear, complete chemistry with calcium level, liver function tests, and LDH.
- Have the following laboratory testing: Viral hepatitis serology (A, B, C), RPR, purified protein derivative, *Strongyloides stercoralis* serology, and stool examination for ova and parasites.

The florid immunosuppression and inflammatory response induced by HTLV may predispose individuals to OIs. Therefore, screening for TB and *Strongyloides stercoralisi* is recommended. Clinicians should also consider the likelihood of other OIs, such as molluscum contagiousum and complications of *Staphylococcus* and *Streptococcal* infections like skin abscess and renal failure.

b. Treatment

No treatment intervention exists for acute or chronic HTLV infection. Patients should be managed within a chronic disease framework, with regular visits to their health care providers based on prevailing signs and symptoms. Visits should include a full physical examination, including thorough ophthalmological- and neurological examinations, as well as additional blood work, such as CBC with peripheral blood smear.

Treatment for complications like adult T-cell leukemia should be the same as in any other case. Treatment for HAM is currently limited to symptomatic therapy. Consultations with an

infectious disease specialist, a neurologist and an oncologist are advised depending on the HTLV-induced complications.

In patients co-infected with HIV and HTLV-1, a hyperimmune proliferative response and an abnormally high CD4 count may occur. This may lead to a false interpretation of the actual immune status of the individual, which has implications for starting HAART. In cases of this co-infection, it is better to use the CD4 percentage as a determination, as it gives a truer picture of the patient's immune status.

c. Prevention

Preventing HTLV-1 and -2 infections is the cornerstone of controlling their spread. Considerations should be given to both horizontal and vertical transmission. The main forms of prevention are as follows:

- Condom use
- Referral of index case partner(s) for testing and follow-up care
- Avoidance of breastfeeding
- Avoidance of injection drug use
- Screening of blood donors

Optimal screening for blood-borne diseases in STI patients requires a full serological panel, including HAV, HBV, HCV, VDRL, HTLV, and HIV. This approach is especially useful when managing an occupational-risk exposure because it establishes the serology statuses of both the source and exposed individual and allows for seroconversion monitoring in the exposed patient. It further provides the exposed individual an opportunity to review their risk behaviours and to update their immunization series based on the results of testing.

18. Molluscum Contagiosum

Molluscum contagiosum are lesions on the skin caused the poxvirus, which is an unclassified member of the *Poxviridae* family. These skin lesions characteristically consist of a single or—more often—multiple, rounded, dome-shaped, pink, waxy papules that are 2–5 mm (rarely up to 1.5 cm, in the case of a giant molluscus) in diameter. The papules are umbilicated and contain a caseous plug, which gives a central white core appearance. Lesions may be located anywhere on the body. Distribution is influenced by the mode of transmission, type of clothing worn, and climate. In children, they are usually found on the face, trunk, and extremities and in adults, on the groin and genitalia. In sexually active individuals, the lesions may be confined to the penis, pubis and inner thighs.

In children, the virus is most often transmitted through regular contact, whereas in adults, it is mostly sexually transmitted. Its appearance outside of the genital area in adults is unusual and may be a presenting sign of yet-to-be-diagnosed HIV infection.

Complications of molluscum contagiosum include skin irritation, inflammation, and secondary infections, such as *Staphylococcal* abscesses and a necrotizing cellulitis due to *Pseudomonas*. In HIV-infected patients, the lesions can be quite extensive and may produce some level of disfigurement. Lesions may also take a prolonged period of time to resolve, even with therapy.

a. Diagnostic Procedure

i. Diagnosis

- Molluscum contagiosum can be diagnosed on clinical grounds based on the distinct papular lesion with central umbilication.
- If diagnosis is uncertain, lesions may be biopsied. Characteristic intracytoplasmic inclusion bodies (molluscum bodies or Henderson-Paterson bodies) are seen on histologic examination.
- PCR can be used to detect the poxvirus in skin lesions.

b. Treatment

The treatment of molluscum contagiosum is dynamic and often depends on the age of the individual as well as the severity and distribution of the lesions. Treatment approaches include:

- Benign neglect: Molluscum contagiosum lesions often resolve spontaneously in healthy patients. For many, ignoring the lesions is a good option—this is best in treating children, to minimize their discomfort.
- HAART: HAART is the mainstay of treatment for patients with HIV infection and AIDS.

Table 85. Recommended combination therapy

Recommended regimen	Considerations in pregnancy
Prick lesion and apply phenol 5% to it	May be used
Prick lesion and apply TCA 80–90% solution	May be used
Cryotherapy	May be used
Curretage	May be used
Imiquimod 5% cream: Apply to the lesion 3 x week	Do not use

Patients treated for molluscum contagiosum should receive follow-up and repeat treatment may be necessary, depending on the resolution of the lesions. Combination therapy may be required in complicated cases (e.g., dual therapy with HAART, curettage in HIV-infected patients).

c. Prevention

For adults and adolescents, the following prevention advice is recommended:

- Abstain from sexual contact during symptomatic period
- Avoid autoinoculation of the lesion by manipulation (e.g., shaving)
- Practice good hygiene

It is important to communicate to patients that this condition is benign in healthy individuals and that prognosis is good.

ii. Ectoparasitic Infections

STI-related ectoparasitic infections are usually found in adults rather than children. The clinical presentation depends on the causative organism.

1. Scabies

Scabies is a common parasitic infection found globally; worldwide, 300 million cases occur annually.

Scabies is caused by the mite *Sarcoptes scabiei*, which burrows into the skin of the infected individual. Protease enzymes in the faecal matter induce a hypersensitivity reaction that causes puritis. Puritis occurs about 2–6 weeks after infestation, though subsequent infestation may produce sensitization and lead to puritis within 24 hours of infection. The mites produce burrows, papules, pustules, nodules, occasionally urticarial papules, and plaques, usually located between web space of fingers, flexor aspects of the wrists, axilla, antecubital area, abdomen, umbilicus, genitals, gluteal areas, and feet. In women, the nipples and areolae of the breasts often are affected. In men, red papules or nodules are typically found on the penile glans, shaft, and scrotum. Compared with adults, scabies in infants and young children tends to be more disseminated and, while the head and face usually are spared in adults, they may be affected in the very young.

Complications from scabies include secondary bacterial infections such as impetigo, furunculosis and cellulitis. Crusted scabies (e.g., Norwegian scabies) is an aggressive form of scabies that usually occurs in the debilitated and malnourished but can be particularly severe in PLHIV and those mistakenly treated with steroids.

a. Diagnostic Process

i. Diagnosis

Diagnosing the presence of *Sarcoptes scabiei* relies on the identification of mites, eggs, eggshell fragments, or mite pellets (scybala). This is best tested by placing a drop of mineral oil directly over the burrow on the skin and then superficially scraping it longitudinally and laterally with a scalpel blade. Failure to find mites under the microscope does not rule out the diagnosis. Final diagnosis is based on history, physical examination of/for burrows, and microscopic examination of mites, eggs, and scybala on mineral oil preparation.

b. Treatment

Treatment for scabies requires careful monitoring and a combination of therapies, with consideration to the index patient, their partners, and household contacts. Treatment of the index patients involves whole body treatment application at night followed by bathing with soap for optimal results. Sexual contacts and those who have had close personal or household contact with the patient within the preceding month should be examined and treated. Within the household, clothing and bedding should be cleaned thoroughly to kill the mites.

Because scabies outbreaks frequently occur in multi-resident settings, such as nursing homes, treatment should be given to all residents, all visitors, all workers, and their families, irrespective of whether they are itching.

Table 86. Treatment recommendations for scabies

Recommended regimen	Considerations in pregnancy
Benzyl benzoate 25% lotion applied on 2 consecutive nights by all household contacts; repeat in 1 week if indicated	May be used
Lindane 1% lotion applied 1 night; repeat in 1 week if indicated	Do not use
Permethrin cream 5% applied for 10 minutes then washed off	May be used
Ivermectin 200ug/kg PO stat; repeat in 2 weeks	Do not use
Crotamiton 10% (ointment or lotion) applied to the entire body from the neck down nightly for 2 nights; wash off thoroughly 24 hours after the second application	May be used
6% sulphur in petrolatum applied nightly for 3 nights	May be used
Piperonyl botoxide applied for 10 minutes then washed off	May be used

Sources: World Health Organization. Guidelines for the management of sexually transmitted infections. Geneva: WHO; 2003. Available from: http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf; and Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

2. Pediculosis Pubis

Pediculosis pubis (lice) is caused by the louse *Phthirus pubis*, which dates back to prehistoric times. Louse infestation remains a major problem throughout the world. Hundreds of millions of cases are reported annually worldwide, with an apparent increase over the past few decades.

There are three different types of lice: *Pediculosis capitis* (head lice), *Pediculosis corporis* (body lice), and *Pediculosis pubis* or *Pthirus pubis* (pubic lice, sometimes called 'crabs'). Lice spreads from person to person via close physical contact or through fomites (e.g., combs, clothes, hats, linens). Overcrowding encourages the spread of lice. The body louse is the vector of typhus, trench fever, and relapsing fever.

Pthirus pubis (pubic lice) is an STI. Pubic lice are white to gray and oval in shape, and have a smaller abdomen than both *Pediculosis capitis* and *Pediculosis corporis*. Their average life span is about 24 hours. Humans are the only reservoir for them and transmission occurs through intimate sexual and non-sexual contact. Infestation is usually found around the coarse hairs on the groin and perianal areas but it can also extend to the eyelashes, eyebrows, facial hair, axillary hair, and occasionally the periphery of the scalp.

The bite of the pubic louse produces an inflammatory reaction; symptoms include itching, scratching, erythema, and skin irritation that can be very disconcerting to the infected individual. After being bitten, small blue spots can appear on the skin resulting in hyperpigmentation. Extensive infestation can lead to systemic symptoms of fever, malaise, and secondary bacterial skin infection involving *Staphylococcal* and *Streptococcal* bacteria.

a. Diagnostic Process

i. Diagnosis

Diagnosis is based on a thorough history and physical examination, including a careful search for adult lice and eggs. It may be helpful to look in the hair for an area of scabs with nits. Nits attach to hair and are not loose and flaky. It might be necessary to examine nits or scabs with a microscope; placing cellulose tape over an infested area then putting the lice-stuck tape on a

microscopic slide is an easy way to prepare them for examination. A Woods lamp examination of the area considered to be infested is another way to determine the presence of pubic lice—they will show up yellow-green under fluorescence.

b. Syndromic Management

In a household infected with pubic lice, all used clothing and bedding must be washed in hot water (50°C) or dry cleaned, which will kill all stages of the mites. Mattresses should be vacuumed to prevent spread or reinfection.

Any sexual partners from within the last month should be treated. Both the index and partner can be retreated within one month if symptoms persist or there is no clinical improvement. Puritis, which is often worse at night, can be controlled with antihistamines like diphenhydramine. Persons who need to be alert on the job might use a non-sedating antihistamine like loratidine.

c. Treatment

Table 87. Recommended treatment for pubic lice

Recommended regimen	Consideration in pregnancy
• Permetherin 1% cream rinse daily for 3 days applied to affected areas and washed off after 10 minutes; may be repeated in 1 week; OR	• May be used
• Pyrethirins with piperonyl butoxide applied to the affected area and washed off after 10 minutes; OR	• May be used
• Lindane 1% shampoo; may repeat in 3–7 days	• Do not use
Alternative	**Consideration in pregnancy**
• Malathion 0.5% lotion applied for 8–12 hours then washed off; OR	• Do not use
• Ivermectin 250ug/kg orally, repeated in 2 weeks	• Do not use

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

Special considerations:

- Lindane can cause neurotoxicity. Instructions for use must be carefully followed to avoid toxicity. It is contra-indicated in children <2 years, pregnant or lactating women, and patients with extensive dermatitis.
- In patients with damaged or excoriated skin, consider dose modification to compensate for increased absorption of topical agents.
- Testing for other STIs—especially HIV—should be considered for persons presenting with lice infection.
- Notifying national authorities about cases of pubic lice is not necessary.

b. CONTACT TRACING

Contact tracing is a cornerstone in preventing the spread of HIV disease and other STIs. Contract tracing involves contacting the sex partners of those who have been diagnosed with an STI, notifying them of the condition, and asking them to come in for testing and examination. If the contact fits the criteria for treatment because of their level of risk, then they must be treated to reduce further disease transmission.

It is vital that both the index case and the partner receive follow-up, not only for surveillance but to ensure that disease transmission has been interrupted. When the partner of an infected patient has been identified, the management of their case is based on the index patient's diagnosis (syndromic or specific). The following treatment strategies can be chosen from:

- Offer immediate epidemiological treatment (treatment based solely on the diagnosis of the index patient) without any laboratory investigation.
- Offer immediate epidemiological treatment, but obtain specimens for subsequent laboratory confirmation.
- Delay treatment until the results of definitive laboratory tests are available.

Partner notification should be considered whenever an STI is diagnosed, irrespective of where care is provided. The form of notification can vary and the approach used may be based on the circumstances. Notification can be done by patient referral or provider referral. In patient referral, infected individuals are encouraged to bring their partners in for examination and treatment. In provider referral, the health authority contacts the partners and invites them to come in for STI testing and treatment. The health authority may give infected patients a certain amount of time within which to contact their partners; if the contacts do not come in for examination and treatment, the health authority may undertake the process of contact tracing, subject to public health law and regulations.

Success in contract tracing is based on a working and collaborative relationship; it should be voluntary and not coercive. Every step of the process must be carried out with sensitivity and appropriateness to the social and cultural norms, to avoid ethical and practical issues like domestic violence against both women and men. Additionally, the highest level of confidentiality must be maintained to ensure the privacy and rights of the individual contacts.

A contact tracing protocol can be helpful to guide STI programmes, which may consist of specific steps to ensure that contacts are found and tested. Using contact tracing allows programmes to provide in-depth counselling to persons who are engaging in high-risk behaviours and thus effect behaviour change. It also allows programmes' health care teams to educate participating contacts about STIs, HIV, and AIDS and to dispel any misconceptions they might have.

It is a basic tenet of STI- and HIV management that all contacts be traced as part of a broad based, comprehensive package to protect public health. In order to do so effectively, clinicians in provate practice should be involved as significant numbers on index patients and contacts are managed privately. These practitioners should play a pivotal role in controlling the spread of HIV and STIs as well. A key component of this collaboration is the recording and reporting of all

identified cases of STIs and HIV. Public health departments and private practitioners alike should operate under the same procedures as well as work from standardized reporting forms, which should be filled out and returned to the central epidemiology unit at the ministry of health. Both public and private practitioners should refer patients and their contacts for further management to the appropriate STI and HIV clinicians.

i. Protocol, Post-STI Diagnosis

The steps to be followed when a patient is diagnosed with any STI are described below.

1. Have all patients who are diagnosed with an STI make a full list of sexual contacts for the time period in question.
   - In the case of HIV disease, a minimum time span of 5 years and a maximum time span of 10 years must be investigated.
   - In the case of syphilis, the time span will depend on the stage of the disease:
     - Primary syphilis—at least 3–6 months
     - Secondary syphilis—at least 6–12 months
     - Tertiary syphilis—at least 5–10 years or longer
   - For other STIs, use the incubation period of the disease and the clinical history for which the patient is being seen (i.e., the length of time for which they have had the disease).

2. For each patient contact, obtain *at least* the folloing information, assuring patients that the information is kept in the strictest confidence:
   - Name, including 'pet' names and aliases
   - Age
   - Address, including details like 'close to a specific landmark' (e.g., church, bar) or colour of the house
   - Telephone numbers (home, work, cell)
   - Workplace and/or type of work done
   - Time frame in which the sexual contact occurred

For all contacts, write the information noted above (name, age, etc.) on the contact tracing form.

Allow patients a period of 6 weeks (but not to exceed 2 months) to voluntarily inform their contacts about their STI. If patients fail to inform their contacts after the specified period or if they indicate that they will not be able to inform their contacts, institute the procedure outlined in step 3. All contract tracing forms should be passed to the STI clinician at the end of every month; the clinician will pass these on to the appropriate regional contact tracer.

3. Follow these procedures in the contact tracers meetings:
   - Have the STI clinican distribute the contact tracing forms to the contact tracers who cover the specific regions in which the contacts live.
   - For each contact, discuss any possible problems that could arise in the search for them.
   - Strategize on how best to locate the contact and encourage them to attend the clinic.
   - Have each contact tracer report on their activities during the month under review, indicating:

    - How many contacts were traced?
    - How many contacts were located?
    - Any problems encountered in tracing so that new strategies may be employed if necessary.
    - How many cases were abandoned because they were unable to locate the contact?
- Based on the information supplied by the contact tracers, calculate:
    - The percentage of contacts traced.
    - The percentage of contacts traced who actually attended the clinic (this information can be found in clinic attendance registers).
    - The percentage of contacts traced who were found to have an STI (this information can be found in clinic attendance registers).
- Report all data derived from contact tracing activities to the clinical surveillance officer of the STI/HIV programme, who reports it to the national epidemiologist and the monitoring and evaluation coordinator of the National HIV/AIDS programme, if available.

Note: All contact tracing must be done in a strictly confidential and non-judgemental fashion. The contact tracer must not reveal to the contact the identity of the index patient who presented to the clinic.

c. SURVEILLANCE

Surveillance—the process by which behaviour is monitored for the purpose of influencing, managing, directing, or protecting the health of the individual and the public—is an important part of STI management. Surveillance is done at all levels of the health care system. Examining the various STI trends in the community enables clinicians to identify high-risk groups and also to employ programmatic interventions that aim to improve quality of life for patients and the public. Surveillance reports should be shared with all stakeholders so that they know what is going on in various regions of the country. Ideally, an annual surveillance report detailing the incidence and prevalence of various diseases around the country would be written by the epidemiology department of the ministry of health.

Data collection and reporting on observed trends are needed for clinical monitoring and programme performance evaluation. It is important that registers are established to keep records of key clinical and programme indicators, such as attendance and STIs diagnosed, and to capture demographic information, such as age and sex of patients. This information, when cross-tabulated, serves to answers questions like who is accessing care and which STIs are most affecting certain groups. Based on this data, targeted interventions can then be planned, organized, and implemented to more effectively control the spread of STIs. Further, data can be used to measure the success of programmes as well as to improve programme activities to better deliver services to the community.

Apart from programmatic monitoring, it is essential that clinical information be collected and reported for the purpose of treatment decision-making. Registers of drug sensitivities related to antimicrobial and antiviral medications used in care should be established, supplemented by research surveys and studies to ascertain drug resistance patterns, especially in the case of gonorrhoea, which can be difficult to treat due to emerging resistance. The information gleaned from such clinical evidence would strengthen microbiological surveillance and early warning systems for drug resistance, which, in turn, provide the basis for updating STI/HIV treatment and care guidelines.

4. APPENDICES

4.1 SUMMARY OF TREATMENT RECOMMENDATIONS FOR ADULTS AND ADOLESCENTS WITH SEXUALLY TRANSMITTED INFECTIONS

Disease	Recommended regimen(s) and dose/route	Alternative regimens (to be used if medical contra-indication to recommended regimen)
Chlamydia		
Uncomplicated genital/rectal/ pharyngeal infections[1]	• Azithromycin: 1 g PO single dose • Doxycycline[2]: 100 mg PO BID x 7 days	• Erythromycin base: 500 mg PO QID x 7 days; OR • Erythromycin ethylsuccinate: 800 mg PO QID x 7 days; OR • Ofloxacin[2]: 300 mg PO BID x 7 days; OR • Levofloxacin[2]: 500 mg PO QID x 7 days
Pregnant women[3]	• Azithromycin: 1 g PO single dose; OR • Amoxicillin: 500 mg PO TID x 7 days	• Erythromycin base: 500 mg PO QID x 7 days; OR • Erythromycin base: 250 mg PO QID x 14 days; OR • Erythromycin ethylsuccinate: 800 mg PO QID x 7 days; OR • Erythromycin ethylsuccinate: 400 mg PO QID x 14 days
Gonorrhoea		
Ceftriaxone is the preferred treatment for adult and adolescent patients with uncomplicated gonorrhoea infections. Cefixime may be used if ceftriaxone is not available, but is inferior in eradicating pharyngeal infection, which is usually asymptomatic. Fluoroquinolones are no longer recommended for treatment of gonococcal infections in the US because of high levels of resistance. Routine use of azithromycin to treat gonorrhoea is not recommended because of mounting concern about emerging resistance.		

Uncomplicated genital/rectal infections[1]	• Ceftriaxone[4]: 250 mg IM single dose; OR, if not available
	• Cefixime[4]: 400 mg PO single dose; OR
	• Single-dose injectable cephalosporin regimens
	• PLUS either:
	  • Azithromycin: 1 g PO single dose; OR
	  • Doxycycline: 100 mg BID for 7 days (regardless of results of chlamydia testing)
		• Cefpodoxime [4] 400 mg PO single dose
		• Spectinomycin[5] 2 g IM (not available)
		• Azithromycin[6] 2 g PO single dose

Pharyngeal infections	• Ceftriaxone[4]: 250 mg IM single dose
	• PLUS either:
	  ○ Azithromycin 1 g PO single dose; OR
	  ○ Doxycycline: 100 mg BID for 7 days
		• Azithromycin[6]: 2 g PO single dose

Disease	Recommended regimen(s) and dose/route	Alternative regimens (to be used if medical contra-indication to recommended regimen)

Pregnant women[3]	• Ceftriaxone[4]: 250 mg IM single dose; OR
	• Cefixime[4]: 400 mg PO single dose
	• Plus either:
	  ○ Azithromycin: 1 g PO single dose; OR
	  ○ Amoxicillin: 500 mg PO TID for 7 days
		• Cefpodoxime[4]: 400 mg PO single dose
		• Spectinomycin[5]: 2 g IM for women who cannot tolerate a cephalosporin
		• Azithromycin[6]: 2 g PO single dose

Trichomoniasis[7]		
Non-pregnant women	• Metronidazole: 2 g PO single dose; OR • Tinidazole[8]: 2 g PO single dose	• Metronidazole: 500 mg PO BID x 7 days
Pregnant women	• Metronidazole: 2 g PO single dose	• Metronidazole: 500 mg PO BID x 7 days
HIV-infected women	• Metronidazole: 500 mg PO BID x 7 days	• Metronidazole 2 g PO single dose
Bacterial vaginosis		
Non-pregnant women	• Metronidazole: 500 mg PO BID x 7 days; OR • Metronidazole gel: 0.75%, 1 full applicator (5 g) intravaginally QD x 5 days; OR • Clindamycin topical cream: 2%, 1 full applicator (5 g) intravaginally QD at bedtime x 7 days	• Tinidazole[8]: 2 g PO QD x 3 days; OR • Tinidazole[8]: 1 g PO QD x 5 days; OR • Clindamycin: 300 mg PO BID x 7 days; OR • Clindamycin topical ovules: 100 mg intravaginally once at bedtime for 3 days
Pregnant women	• Metronidazole: 500 mg PO BID x 7 days; OR • Metronidazole: 250 mg PO TID x 7 days; OR • Clindamycin: 300 mg BID x 7 days	
LGV	• Doxycycline[2]: 100 mg PO BID x 21 days	• Erythromycin base: 500 mg PO QID x 21 days; OR • Azithromycin: 1 g PO every week x 3 weeks
Anogenital herpes[9]		
First clinical episode of herpes	• Acyclovir: 400 mg PO TID x 7–10 days; OR • Acyclovir: 200 mg PO 5 x day x 7–10 days; OR • Famciclovir: 250 mg PO TID x 7–10 days; OR • Valacyclovir: 1 g PO BID x 7–10 days	• None
Established infection in the HIV-uninfected person • Suppressive therapy[10]	• Acyclovir: 400 mg PO BID; OR • Famciclovir: 250 mg PO BID; OR • Valacyclovir: 500 mg PO QD; OR • Valacyclovir: 1 g PO QD	• None
• Episodic therapy for recurrent	• Acyclovir: 400 mg PO TID x 5 days; OR	• None

Disease	Recommended regimen(s) and dose/route	Alternative regimens (to be used if medical contra-indication to recommended regimen)
episodes	• Acyclovir: 800 mg PO BID x 5 days; OR • Acyclovir: 800 mg PO TID x 2 days; OR • Famciclovir: 125 mg PO BID x 5 days; OR • Famciclovir: 1,000 mg PO BID x 1 day; OR • Famciclovir: 500 mg once, followed by 250 mg BID x 2 days; OR • Valacyclovir: 500 mg PO BID x 3 days; OR • Valacyclovir: 1 g PO QD x 5 days	
Established infection in the HIV-coinfected person[11] • Suppressive therapy [10]	• Acyclovir: 400–800 mg PO BID or TID; OR • Famciclovir: 500 mg PO BID; OR • Valacyclovir: 500 mg PO BID	• None
• Episodic therapy for recurrent episodes	• Acyclovir: 400 mg PO TID x 5–10 days; OR • Famciclovir: 500 mg PO BID x 5–10 days; OR • Valacyclovir: 1 g PO BID x 5–10 days	• None
Syphilis[12]		
Primary, secondary, and early latent	• Penicillin G benzathine: 2.4 million units IM single dose	• Doxycycline[13]: 100 mg PO BID x 14 days; OR • Tetracycline[13]: 500 mg PO QID x 14 days; OR • Ceftriaxone[13]: 1 g IM or IV QD x 8–10 days
Late latent and latent of unknown duration	• Penicillin G benzathine: 2.4 million units IM once weekly for 3 weeks	• Doxycycline[13]: 100 mg PO BID x 28 days; OR • Tetracycline[13] 500 mg PO QID x 28 days
Neurosyphilis[14]	• Aqueous crystalline penicillin G: 18–24 million units daily, administered as 3–4 million units IV every 4 hours x 10–14 days	• Procaine penicillin G: 2.4 million units IM QD x 10–14 days; PLUS probenecid: 500 mg PO QID x 10–14 days; OR • Ceftriaxone[13] 2 g IM or IV QD x 10–14 days
Pregnant women[15] • Primary, secondary, and early latent	• Penicillin G benzathine: 2.4 million units IM as a single dose	• None
• Late latent and latent of unknown duration	• Penicillin G benzathine: 2.4 million units IM weekly for 3 weeks	• None
• Neurosyphilis[14]	• Aqueous crystalline penicillin G: 18–24 million units daily, administered as 3–4 million units IV every 4 hours x 10–14 days	• Procaine penicillin G: 2.4 million units IM QD x 10–14 days; PLUS probenecid: 500 mg PO QID x 10–14 days
HIV co-infected	• Penicillin G benzathine: 2.4 million	• Doxycycline[13] 100 mg PO BID

Disease	Recommended regimen(s) and dose/route	Alternative regimens (to be used if medical contra-indication to recommended regimen)
• Primary, secondary, and early latent	units IM single dose	x 14 days; OR • Tetracycline[13]: 500 mg PO QID x 14 days
• Late latent and latent of unknown duration with normal CSF exam	• Penicillin G benzathine: 7.2 million units, administered as 3 doses of 2.4 million units IM each, at 1-week intervals	• Doxycycline[13]: 100 mg PO BID x 28 days
• Neurosyphilis[14]	• Aqueous crystalline penicillin G: 18–24 million units daily, administered as 3–4 million units IV every 4 hours x 10–14 days	• Procaine penicillin G: 2.4 million units IM QD x 10–14 days; PLUS probenecid: 500 mg PO QID x 10–14 days; OR • Ceftriaxone[13]: 2 g IM or IV QD x 10–14 days
Chancroid		
Primary	• Azithromycin: 1 g PO in a single dose OR • Ceftriaxone: 250 mg IM in a single dose OR • Ciprofloxacin: 500 mg PO 2 x a day for 3 days OR • Erythromycin base: 500 mg PO 3 x a day for 7 days	
Granuloma inguinale (donovanosis)		
Primary	• Doxycycline: 100 mg PO 2 x QD for at least 3 weeks and until all lesions have completely healed	• Azithromycin: 1 g PO 1 x QW for at least 3 weeks and until all lesions have completely healed • Ciprofloxacin: 750 mg PO 2 x QD for at least 3 weeks and until all lesions have completely healed • Erythromycin base: 500 mg PO QID for at least 3 weeks until all lesions have completely healed • Co-trimoxazole: 1 double strength (160 mg/800 mg) tablet PO 2 x QD for at least 3 weeks and until all lesions have completely healed

1. *Annual screening for women aged ≤25 years. All patients should be retested 3 months after treatment for chlamydia or gonorrhoea infections.*
2. *Contra-indicated for pregnant and nursing women.*
3. *Test-of-cure follow-up (preferably by NAAT) 3–4 weeks after completion of therapy is recommended in pregnancy.*
4. *For patients with cephalosporin allergy, anaphylaxis-type (IgE-mediated) penicillin allergy or other contra-indication: The CDC recommends considering desensitization; however, in the vast majority of cases, this may not be feasible. Judicious use of azithromycin is a practical option if spectinomycin is not available or not indicated.*
5. *Spectinomycin has not been manufactured since January 2006, and future availability is uncertain.*
6. *Use only if there are medical contra-indications to a cephalosporin and when spectinomycin is not available or not indicated. Test-of-cure is prudent in all cases because efficacy data are limited and because of mounting concern about emergent resistance].*
7. *For suspected drug-resistant trichomoniasis, rule out reinfection; see* Trichomonas Follow-up *in [Centers for Disease*

Disease	Recommended regimen(s) and dose/route	Alternative regimens (to be used if medical contra-indication to recommended regimen)

Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.] for other treatment options, and evaluate for metronidazole-resistant T. vaginalis. *For laboratory and clinical consultations, contact the CDC at 001-770-488-4115 or visit http://www.cdc.gov/std. The longer regimen of metronidazole is preferred in HIV-infected women, as it provides superior cure rates.*

8. *Safety in pregnancy has not been established; pregnancy category C.*
9. *Counselling about natural history, asymptomatic shedding, and sexual transmission is an essential component of herpes management.*
10. *The goal of suppressive therapy is to reduce recurrent symptomatic episodes and/or to reduce sexual transmission.*
11. *If HSV lesions persist or recur while receiving antiviral treatment, antiviral resistance should be suspected. A viral isolate should be obtained for sensitivity testing, and consultation with an infectious disease expert is recommended.*
12. *Penicillin G benzathine is the recommended treatment for syphilis not involving the CNS and is available in only 1 long-acting formulation (Bicillin L-A), which contains only penicillin G benzathine. Other combination products, such as [Bicillin C-R], contain both long- and short-acting penicillins and are not effective for treating syphilis.*
13. *Alternates should only be used for penicillin-allergic patients because efficacy of these therapies has not been established. Compliance with some of these regimens is difficult, and close follow-up is essential. If compliance or follow-up cannot be ensured, the patient should be desensitized and treated with penicillin G benzathine.*
14. *Some specialists recommend 2.4 million units of penicillin G benzathine every week for up to 3 weeks after completion of neurosyphilis treatment.*
15. *Patients allergic to penicillin should be treated with penicillin after desensitization.*
16. *Ciprofloxacin is contra-indicated in pregnancy.*

Readers should refer to: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR. 2010 Dec 17; 59(12). Available from: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf.

4.2 SUMMARY OF TREATMENT RECOMMENDATIONS FOR CHILDREN AND ADOLESCENTS WITH SEXUALLY TRANSMITTED INFECTIONS

Disease	Special conditions	Treatment recommendations
Bacterial vaginosis and trichomoniasis	None	Metronidazole: 15 mg/kg in 3 divided doses daily for 7–10 days
Chanchroid	None	• Ceftriaxone, as per dosage schedule for uncomplicated gonorrhoea; OR • Erythromycin, as per dosage schedule for chlamydia for 7 days
Chlamydia	Ophthalmia neonatorum and Pneumonia in neonates	Erythromycin: 50 mg/kg/day PO divided into four doses QD for 10–14 days
	Children who weigh <45 kg	• Erythromycin base or ethylsuccinate: 50 mg/kg/day PO divided into 4 doses QD for 14 days • Erythromycin's effectiveness is only 80% so a second treatment may be necessary
	Children who weigh ≥45 kg but who	Azithromycin 1 g orally in a single

Disease	Special conditions	Treatment recommendations
	are <8 years of age	dose
	Children ≥8 years of age	• Azithromycin 1 g orally in a single dose; OR • Doxycycline 100 mg orally twice a day for 7 days
Gonorrhoea	Opthalmia neonatorum caused by *N. gonorrhoeae*	Ceftriaxone 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg
	Opthalmia neonatorum caused by *N. gonorrhoeae*	Erythromycin: 0.5% ophthalmic ointment in each eye in a single application
	Prophylactic treatment for infants whose mothers have gonococcal infection Recommended regimen in the absence of signs of gonococcal infection	Ceftriaxone: 25–50 mg/kg IV or IM, not to exceed 125 mg in a single dose
	DGI (etc. arthritis); AND gonococcal scalp abscesses in newborns	• Ceftriaxone: 25–50 mg/kg/day IV or IM in a single dose for 7 days with a duration of 10–14 days, if meningitis is documented; OR • Cefotaxime: 25 mg/kg/IV or IM every 12 hours for 7 days, with a duration of 10–14 days, if meningitis is documented
Genital warts	None	As per adult therapy
HSV	None	Neonatal acyclovir: 20 mg/kg/Q8H IV for 21 days for disseminated and CNS disease, or for 14 days for disease of the skin and mucous membranes
LGV	None	Erythromycin, as per dosage schedule for chlamydia for 21 days
Mulloscum contagiosum	None	As per adult therapy
Pediculosis	None	As per adult therapy
Scabies	None	• As per adult therapy • Do not use Lindane under 2 years of age • Dilute benzyle benzoate to half strength for infants • 2.5% sulphur in white soft paraffin may be used for infants • Monosulfiram soap used daily for 1 week
Vulvo-vaginal candidiasis		Topical external creams as per adult therapy
Syphilis	Presumed congenital syphilis if mother was positive before delivery	• Aqueous crystalline penicillin G: 100,000–150,000 units/kg/day administered as 50,000 units/kg IV every 12 hours during the first 7 days of

Disease	Special conditions	Treatment recommendations
		life and every 8 hours thereafter for 10–14 days; OR • Procaine penicillin G: 50,000 units/kg IM daily in a single dose for 10–14 days • If more than one day of therapy is missed, the entire course should be restarted
	After the new born period and where it is determined that the child has congenital syphilis or has neurological involvement	Aqueous crystalline penicillin G: 200,000–300,000 units/kg IV or IM administered as 50,000 units/kg every 4–6 hours for 10–14 days
	Where the child is determined to have acquired syphilis the management is as for the stage of the disease	• Primary syphilis , Secondary syphilis and early latent syphilis benzathine penicillin G: 50,000 units/kg IM stat up to the adult dose of 2.4 mega units • Late latent or latent syphilis of unknown duration benzathine penicillin G: 50,000 units/kg up to the adult dose of 2.4 million units IM weekly for 3 weeks, to a total dose of 7.2 million units.

4.3 DRUG SAFETY DURING PREGNANCY AND BREASTFEEDING

Drug	Pregnancy consideration	Breastfeeding consideration
Azithromycin	Manufacturer advises use only if adequate alternatives not available (can be used)	Present in milk; manufacturer advises use only if no suitable alternative
Acyclovir	Not known to be harmful—manufacturer advises use only when potential benefit outweigh risk; limited absorption from topical acyclovir preparation	Significant amount in milk after systemic administration—not known to be harmful but manufacturer advises caution
Cefotaxime	Not known to be harmful	Present in milk in low concentration
Ceftriaxone	Not known to be harmful	Present in milk in low concentration
Ciprofloxacin	Avoid—athropathy in animal studies; safer alternatives available	Amount probably too small to be harmful but manufacturer advises avoid
Clindamycin	Not known to be harmful	Amount probably too small to be harmful but bloody diarrhoea reported in 1 infant
Clotrimazole cream	No known contra-indication	No known contra-indication
Penicillins • Co-amoxiclav (Augmentin) • Benzathine • Aqueous crystalline • Procaine	Not known to be harmful	Trace amounts in milk
Tetracycline Doxycycline	**Do not use** • Effects on skeletal development in animal studies • Dental discolouration; maternal hepatotoxicity with large parental doses	**Avoid** (although absorption and therefore discolouration of teeth in infant probably usually prevented by chelation with calcium in milk)
Erythromycin	Not known to be harmful	Only small amounts in milk not known to be harmful
Famciclovir	See aciclovir	Manufacturer advises avoid unless potential benefit outweigh risk-present in milk in animal studies
Fluconazole	Manufacturer advises avoid—multiple congenital abnormalities reported with long term high doses	Present in milk but probably too small to be harmful (avoid)
Gentamicin	• Auditory or vestibular nerve damage • Risk greatest with streptomycin • Probably very small with gentamicin and tobramycin, but avoid unless essential • If given, serum aminoglycoside concentration monitoring essential	• Poorly excreted into breastmilk • Data are not available with single daily dose regimens • Monitor infant for possible effects on the gastrointestinal flora, such as diarrhoea, candidiasis (e.g., thrush, diaper rash) or rarely, blood in the stool indicating possible antibiotic-associated colitis
Lindane	**Do not use** FDA Pregnancy Category C	Avoid breastfeeding

Drug	Pregnancy consideration	Breastfeeding consideration
Imiquimod	**Do not use** • FDA Category C • Animal studies have revealed fetal toxicity and teratogenicity	Manufacturer advises caution; no information available
Ivermectin	**Do not use** FDA Category C	• Limited data • Small amounts found in breastmilk • Use only if benefits outweigh the risks
Malathion	**Do not use** Pregnancy Category B	• Limited data • Undetermined use • Drug can be absorbed through the skin
Metronidazole	Manufacturer advises avoidance of high dose regimens	Significant amount in milk; manufacturer advises avoid in large single doses
Podophylin	Avoid	Avoid
Trichloroacetic acid (local)	Can be used	Can be used
Co-trimoxazole	Teratogenic risk (folate antagonist); manufacturer advises caution, especially during first trimester	Present in milk; short-term use not known to be harmful
Valaciclovir	See acyclovir	No information available; see aciclovir

Source: British National Formulary BNF 2007
Joint Formulary Committee (2007). British National Formulary. 54th edition. London: British Medical Association and Royal Pharmaceutical Society of Great Britain.

4.4 WHO CLINICAL STAGING FOR ADULTS AND ADOLESCENTS— PRESUMPTIVE AND DEFINITIVE CRITERIA FOR RECOGNIZING HIV/AIDS-RELATED CLINCIAL EVENTS

Clinical event	Presumptive diagnosis	Definitive diagnosis
Clinical stage 1		
Asymptomatic	No symptoms reported and no signs on examination	Not required
Persistent generalized lymphadenopathy	Swollen or enlarged lymph nodes >1 cm, in two or more non-contiguous sites, excluding inguinal nodes, in absence of known cause	Not required but can be confirmed by histology (germinal centre hyperplasia, lymph node structure preserved)
Clinical stage 2		
Moderate unexplained weight loss (<10% of presumed or measured body weight)	Reported weight loss but no obvious thinning of face or body	Confirmed by documented weight loss
Recurrent presumed bacterial Respiratory Tract Infection (RTI) (two or more in any 6-month period)	Symptom complex (e.g., unilateral face pain with nasal discharge [sinusitis], painful swollen eardrum [otitis media], cough with purulent sputum [bronchitis], sore throat [pharyngitis]; two or more documented occurrences of antibiotic-responsive RTI	Not required but may be confirmed by laboratory studies where available (e.g., culture of suitable body fluid)
HZV	• Painful rash of small fluid-filled blisters in distribution of a nerve supply, can be haemorrhagic on erythematous background, and does not cross midline • Current or in the last 2 years • Severe or frequently recurrent HZV is usually associated with more advanced HIV disease	Not required
Angular cheilitis	• Splits or cracks on lips at the angle of the mouth with depigmentation, usually responds to antifungal treatment but may recur • Common in nutritional deficiency (e.g., B vitamin)	Not required
Recurrent oral ulcerations occurring twice or more in 6 months	Aphthous ulceration, typically with a halo of inflammation and a yellow-grey pseudomembrane	Not required
Papular pruritic eruptions	• Papular pruritic vesicular lesions • Common in uninfected adults • Scabies and obvious insect bites should be excluded	Not required
Seborrhoeic dermatitis	• Itchy scaly skin condition, particularly affecting scalp, face, upper trunk and perineum	Not required

Clinical event	Presumptive diagnosis	Definitive diagnosis
	• Common in uninfected adults	
Fungal nail infections of fingers	• Fungal paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails • Common in uninfected adults • Proximal white subungual onchomycosis is uncommon without immunodeficiency	Not required, but confirmed by culture of nail scrapings
Clinical stage 3		
Severe unexplained weight loss (more than 10% of presumed or measured body weight)	Reported weight loss without trying and noticeable thinning of face, waist, and extremities	Documented loss of >10% of body weight
Unexplained chronic diarrhoea for longer than one month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than 1 month	Not required, but confirmed if three or more stools observed and documented as unformed, two or more stool tests reveal no pathogens on microscopy and culture, and no faecal leukocytes
Unexplained persistent fever (intermittent or constant and for longer than 1 month)	• Reports of fever or night sweats for more than 1 month, either intermittent or constant with reported lack of response to antibiotics or antimalarials • No other obvious foci of disease reported or found on examination • Malaria must be excluded in malarious areas	Not required, but confirmed if documented fever >37.5°C with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray (CXR), and no other obvious foci of disease
Oral candidiasis	Persistant creamy white-to-yellow soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudomembranous); or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form), and not responsive to local antifungal treatment	Not required
Oral hairy leukoplakia	Fine small linear patches on lateral borders of the tongue, generally bilaterally, which do not scrape off	Not required
Pulmonary TB (current or in last 2 years)	• Chronic (symptoms lasting 3 or more weeks) productive cough, haemoptysis, shortness of breath, weight loss, fever, night sweats, and fatigue, with no resolution of symptoms with standard broad-spectrum antibiotics, positive Ziehl-Nielsen stain • Response to standard anti-TB treatment in one month.	Not required but confirmed by positive sputum culture

Clinical event	Presumptive diagnosis	Definitive diagnosis
	• TB diagnosis and treatment should follow national or international guidelines • CD4 count should be used where possible to guide therapy; very low CD4 count may require urgent ART	
Severe presumed bacterial infection (e.g., pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia	Fever accompanied by specific symptoms or signs that localize infection and respond to antibiotics	Not required, but confirmed by bacteria isolated from appropriate clinical specimens
Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue	Not required
Unexplained anaemia (<8g/dl), neutropenia (<1,000/mm^3) or thrombocytopenia (<50,000/ mm^3) for more than 1 month	No presumptive clinical diagnosis	• Diagnosed on laboratory testing and not explained by other non-HIV conditions • Not responsive to standard therapy with haematinics, antimalarials, or anthelmintics as outlined in relevant national treatment guidelines, WHO guidelines, or other relevant guidelines
Clinical stage 4		
HIV wasting syndrome	Unexplained weight loss >10% of body weight and visible thinning of face, waist, and extremities, plus either unexplained chronic diarrhoea (lasting more than 1 month) or unexplained prolonged or intermittent fever for 1 month or more	• Confirmed by documented weight loss without trying, plus documented unformed stools negative for pathogens and negative modified Ziehl-Nielsen stain • Documented temperature of 37.5°C or more on occasions with no obvious foci of disease, negative blood culture, negative malaria slide, and normal or unchanged CXR
PCP	• Dry cough, progressive shortness of breath, especially on exertion, with cyanosis, tachypnoea and fever, responsive to high-dose co-trimoxazole with or without prednisolone • Bilateral crepitations on auscultation with or without reduced air entry; CXR may show typical bilateral interstitial infiltrate with bat wing appearance	Not required, but confirmed by microscopy of induced sputum or BAL, or histology of lung tissue
Recurrent severe or radiological bacterial pneumonia (two or more	• Two episodes of fever, wet cough, fast and difficult	Not required but confirmed by culture or antigen test from

Clinical event	Presumptive diagnosis	Definitive diagnosis
episodes within 1 year)	breathing and chest pain • Consolidation on clinical examination and CXR • Responsive to antibiotics	appropriate specimen
Chronic HSV infection (orolabial, genital or anorectal) of <1 month or visceral of any duration	Severe and progressive painful orolabial, genital, or anorectal lesions caused by recurrent HSV infection reported for more than 1 month, with history of previous episodes and possible evidence of scarring from previous episodes	• Not required for mucocutaneous HSV but required for visceral HSV • Suggestive symptoms of organ damage (e.g., bronchitis, pneumonitis, oesophagitis, colitis, encephalitis) supported by histology or culture
Oesophageal candidiasis	• Chest pain and dysphagia (difficulty swallowing), odynophagia (pain on swallowing food and fluids), or retrosternal pain worse on swallowing (food and fluids) with or without oral Candida • Responds to antifungal treatment	Not required, but confirmed by macroscopic appearance at endoscopy or bronchoscopy, microscopy or histology
Extrapulmonary/disseminated TB	• Systemic illness usually with prolonged fever, night sweats, weakness, and weight loss • Clinical features of organs involved (e.g., focal lymphadenopathy, cold abscess, sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis, lupus vulgaris) • CXR may reveal diffuse, uniformly distributed, small miliary shadows • Responsive to standard anti-TB treatment in 1 month	• Not required, but confirmed by AFB seen in microscopy of CSF, effusion, lymph node aspirate, urine, etc. • MTB isolated from blood culture or any appropriate specimen except sputum or BAL • Histology (e.g., pleural or pericardial biopsy) • CXR may show interstitial infiltrates • Lymphocytic CSF with typical abnormalities, no bacterial growth and negative CrAG
Kaposi's sarcoma	• Typical appearance in skin or oropharynx—persistent, initially flat patches with a pink or blood-bruise colour or skin lesions that usually develop into nodules • Can be confused clinically with bacillary angiomatosis, non-Hodgkin lymphoma, and cutaneous fungal or bacterial infections	Not required, but may be confirmed by typical red-purple lesions seen on bronchoscopy or endoscopy; dense masses in lymph nodes, viscera or lungs by palpation or radiology; or histology
CMV (retinitis or CMV infection of an organ other than liver, spleen, or lymph nodes)	• Retinitis only—CMV retinitis may be diagnosed by experienced clinicians • Progressive floaters in field of vision, light flashes, and scotoma • Typical eye lesions on serial fundoscopic examination—	• Definitive diagnosis required for other sites • Symptoms and signs of other organ involvement (e.g., pneumonitis, pancreatitis, colitis, cholecystitis) not responsive to co-trimoxazole or antibiotics • Histology

Clinical event	Presumptive diagnosis	Definitive diagnosis
	discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels • Associated with retinal vasculitis, haemorrhage and necrosis	• CSF PCR
CNS toxoplasmosis	• Fever, headache, focal neurological signs, convulsions • Rapid response (within 10 days) to high-dose co-trimoxazole, pyrimethamine and sulphadiazine, or clindamycin	• Not required, but confirmed by CT scan showing single/multiple lesions with mass effect/enhancing with contrast • If lumbar puncture performed, CSF nonspecific or normal • Resolution of findings after treatment if patient survives
Cryptococcal meningitis or other extrapulmonary *Cryptococcus* infection	• Meningitis is usually sub-acute—fever with increasing severe headache, meningism, confusion, and behavioural changes • Responds to antifungal therapy	Confirmed by CSF microscopy (India ink or Gram stain) or serum or CSF CrAG-positive or culture-positive
HIV encephalopathy	• Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection which might explain the findings • LP should be conducted to exclude other infectious causes	Recommended to confirm clinical features and exclude other causes including neurosyphilis: • Brain scan by means of CT or MRI, with lumbar puncture
Disseminated non-tuberculous mycobacteria infection	No presumptive diagnosis	• Non-specific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea • Severe anaemia and/or elevated alkaline phosphatase and/or (in case of diarrhoea) persisting AFB in the stool in spite of TB therapy • Plus: Culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung
PML	No presumptive diagnosis	• Progressive focal neurological signs without headache or fever, cortical blindness, cerebellar signs, dementia • Confirmed by consistent MRI or CT scan and biopsy • Viral PCR for Jacob Creutzfeldt

Clinical event	Presumptive diagnosis	Definitive diagnosis
		virus
Candidiasis of trachea, bronchi, lungs	No presumptive diagnosis	Confirmed by symptoms, clinical signs suggestive of organ involvement and/or macroscopic appearance at bronchoscopy; histology or cytology; or microscopy of specimen from tissue
Cryptosporidiosis (with diarrhoea lasting more than 1 month)	No presumptive diagnosis	Chronic diarrhoea, often profuse and watery; with weight loss; with or without abdominal pain, nausea, vomiting; confirmed by modified ZN microscopic examination of stool, observed to be unformed and organism visible
Isosporiasis	No presumptive diagnosis	• Watery diarrhoea, cramps and weight loss • Symptoms usually indistinguishable from those of cryptosporidiosis • Isosporiaisis responds to high-dose co-trimoxazole
Any disseminated mycosis (e.g., coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive diagnosis	• Non-specific clinical symptoms (e.g., skin rash, cough, shortness of breath, fever, anaemia, weight loss) • CXR: infiltrates or nodules • Confirmed by direct microscopy • Histology—usually granuloma formation • Isolation—antigen detection from affected tissue • Skin lesion culture or microscopy positive
Recurrent non-typhoidal salmonella septicaemia (two or more episodes in last year)	No presumptive diagnosis	Non-specific symptoms (e.g., fever, sweats, headaches, weight loss, diarrhoea, and anorexia); confirmed by blood culture
Lymphoma (cerebral or B cell non-Hodgkin)	No presumptive diagnosis	• Symptoms consistent with lymphoma (e.g., lymphadenopathy, splenomegaly, pancytopenia, testicular or lung mass lesions); not clinically responsive to antitoxoplasma or anti-TB treatment • CNS imaging—at least one lesion with mass effect on brain scan; histology
Invasive cervical carcinoma	No presumptive diagnosis	• Persistent vaginal discharge, postcoital or intermenstrual bleeding unresponsive to appropriate antibacterial or antifungal treatment; cervical lesions visualized.

Clinical event	Presumptive diagnosis	Definitive diagnosis
		• Histology • Cytology, but not carcinoma in situ
Visceral leishmaniasis	No presumptive diagnosis	• Suggestive symptoms—malaise, chronic fever, hepatosplenomegaly, pancytopenia • Amastigotes visualized or cultured from any appropriate clinical specimen.

Source: World Health Organization. Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance: African Region. Geneva: WHO; 2005. Available from: http://www.who.int/hiv/pub/guidelines/clinicalstaging.pdf.

4.5 DOSAGES AND FIXED-DOSE COMBINATIONS OF ANTIRETROVIRAL MEDICATIONS

Generic name	Dose
NRTIs	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Didanosine (ddI)	400 mg once daily (>60 kg) 250 mg once daily (≤60 kg)
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg twice daily
Stavudine (d4T)	30 mg twice daily
Zidovudine (AZT)	250-300 mg twice daily
Nucleotide reverse transcriptase inhibitors (NRTIs)	
Tenofovir (TDF)	300 mg once daily[a]
NNRTIs	
Efavirenz (EFV)	600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily[b]
PIs	
Atazanavir PLUS ritonavir (ATV/r)	300 mg PLUS 100 mg once daily
Darunavir PLUS ritonavir (DRV/r)	600 mg PLUS 100 mg twice daily
Fos-amprenavir PLUS ritonavir (FPV/r)	700 mg PLUS 100 mg twice daily
Indinavir PLUS ritonavir (IDV/r)	800 mg PLUS 100 mg twice daily
Lopinavir/ritonavir (LPV/r)	Fixed dose combination tablets (LPV 200 mg/RTV 50 mg) Two tablets (400 mg/100 mg) twice daily[c]
	Considerations for individuals on TB therapy: • In the presence of rifabutin, no dose adjustment required • In the presence of rifampicin, use RTV superboosting (LPV 400 mg PLUS RTV 400 mg twice daily) or LPV 800 mg PLUS RTV 200 MG twice daily, with close clinical and hepatic enzyme monitoring

[a] *TDF dosage adjustment for individual with altered creatinine clearance can be reconsidered (using Cockcroft-Gault formula). Creatinine clearance ≥50ml/min. 300 mg once daily. Creatinine clearance 30–49 ml/min. 300 mg every 48 hours. Creatinine clearance 10–29 ml/min (or dialysis). 300 mg once every 72–96 hours. Cockcroft-Gault formula: GFR = (140-age) x (wt in kg) x (0.85 if female)/(72 x Cr).*

[b] *In the presence of rifampicin, or when patients switch from EFC to NVP, no need for lead-in dose of NVP.*

[c] *LPV/r can be administered as 4 tablets once daily (i.e., LPV 800 mg PLUS RTV 200 mg once daily) in patients with less than three LPV resistance-associated mutations on genotypic testing. Once-daily dosing is not recommended in pregnant women or patients with more than three LPV resistance-associated mutations.*

Source: World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach, 2010 revision. Geneva: WHO; 2010. Available from: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf.

4.6 COMBINATION FIXED-DOSE COMBINATIONS OF ANTIRETROVIRAL MEDICATIONS

Component medications	Dosing
AZT + 3TC	One tablet bid
AZT + 3TC + NVP	One tablet bid
TDF + FTC	One tablet daily
TDF + FTC + EFV	One tablet daily
TDF + 3TC + EFV	One tablet daily

4.7 HAART REGIMEN OPTIONS AND ADJUSTMENTS FOR TB-INFECTED PATIENTS RECEIVING A RIFAMYCIN

HAART regimen	Potentially interacting ARV	ARV/rifamycin dosing recommendations			
		Rifabutin		Rifampicin	
		ARV dose	Rifabutin dose	ARV dose	Rifabutin dose
2 NRTI + EFV (preferred if possible)	EFV	600 mg QD	450 mg QD *OR* 600 mg 3 x a week	600 mg QD	600 mg QD
Triple NRTI	none	No change	300 mg QD	No change	600 mg QD
2 NRTI + NVP [a b c]	NVP	200 mg BID	300 mg QD	200 mg BID	600 mg QD
2 NRTI + LPV/r [b c]	LPV/r	400 mg/100 mg BID	150 mg every other day (QOD) *or* 3 x a week	400 mg/400 mg BID *OR* 800 mg/200 mg BID	600 mg QD
2 NRTI + SQV/r [b c]	SQV/r	400 mg/400 mg BID	150 mg QOD *OR* 3 x a week	400 mg/400 mg BID *OR* 1,000 mg/100 mg BID	600 mg QD
2 NRTI + ATV [b]	ATV	400 mg QD	150 mg QOD	Contra-indicated	Contra-indicated
2 NRTI + f-APV [b]	f-APV	1,400 mg BID	150 mg QD *OR* 300 mg 3 x a week	Contra-indicated	Contra-indicated
2 NRTI + IDV [b]	IDV	1,000–1,200 mg Q8H	150 mg QD	Contra-indicated	Contra-indicated
2 NRTI + NFV	NFV	1,250 mg BID	150 mg QD	Contra-indicated	Contra-indicated
2 NRTI + IDV/r [b c]	IDV/r	800 mg/100 mg BID *or* 800 mg/200 mg BID	150 mg QOD *OR* 3 x a week	Contra-indicated	Contra-indicated
2 NRTI + ATV/r [b c]	ATV/r	300 mg/100 mg QD	150 mg QOD *OR* 3 x a week	Contra-indicated	Contra-indicated
2 NRTI + f-APV/r [b c]	f-APV/r	700 mg/100 mg BID *or* 1,400 mg/200 mg QD	150 mg QOD *OR* 3 x a week	No data	No data

[a] Switching to an EFV-based or triple NRTI regimen is preferred in this scenario due to the high potential for liver toxicity when NVP is administered with a rifamycin, as well as uncertainty over appropriate dose adjustments of NVP and the rifamycins.
[b] Substituting back to the original regimens once rifampicin containing regimen is completed can be considered. Note that when switching back from EFV to NVP no lead-in dose is required.
[c] Careful clinical and laboratory monitoring (e.g. ALT) is advised when NVP or boosted PIs are administered concurrently with rifampicin.

4.8 DRUG INTERACTIONS BETWEEN ANTIRETROVIRAL MEDICATIONS AND OTHER DRUGS

ARV	NVP	EFV	LPV/r	NFV	SQV
Antimycobacterium					
Rifampicin	• ↓NVP level by 20–58% • Virologic consequences are uncertain; the potential of additive hepatotoxicity exists • Co-administration is recommended with careful monitoring	• ↓EFV level by 25%	• ↓LPV area under the curve (AUC) by 75% • Should not co-administer	• ↓NFV level by 82% • Should not co-administer	• ↓SQV level by 84% • Severe liver impairment with co-administer reported • Should not co-administer
Rifabutin	• Levels: NVP↓ 16%; no dose adjustment	• Levels: EFV unchanged • Rifabutin ↓ 35% • Dose: ↑ rifabutin dose to 450–600 mg • Once daily or 600 mg 3x/week • EFV: Standard	• Levels: Rifabutin AUC ↑ 3-fold • Decrease rifabutin dose to 150 mg once daily or 3 x a week • LPV/r: Standard	• Levels: NFV ↓ 82% • Should not be co-administered	• Levels: SQV↓40% • Contra-indicated unless SQV/RTV • Dose: Rifabutin 150 mg once dialy or 3 x a week
Clarithromycin	• None	• ↓clarithromycin by 39% • Monitor for efficacy or use alternative drugs	• ↑clarithromycin AUC by 75%, adjust clarithromycin dose if renal impairment	• No data	• Without RTV—↑clarithromycin level by 45% and ↑SQV level 177% • With RTV—can ↑clarithromycin level by 75% • No clarithromycin dose adjustment needed for unboosted SQV • For boosted SQV if renal impairment—no data

ARV	NVP	EFV	LPV/r	NFV	SQV
Antifungal					
Ketoconazole	• ↑ketoconazole level by 63% • ↑NVP level by 15–30% • Do not recommend co-administer	• No significant changes in ketoconazole or EFV levels	• ↑LPV AUC • ↑ketoconazole level 3-fold • Do not exceed 200 mg/day ketoconazole	• No dose adjustment necessary	• ↑SQV level 3-fold • No dose adjustment necessary if given unboosted • For RTV-boosted SQV—no data (RTV treatment dose can increase ketoconazole level 3-fold)
Fluconazole	• ↑NVP maximum concentration (Cmax), AUC, minimum concentration (Cmin) by 100% • No change in fluconazole level • Possible increase hepatotoxicity with co-administer requiring monitoring of NVP toxicity	• No data	• No data	• No data	• No data
Intraconazole	• No data	• No data	• ↑itraconazole level • Do not exceed 200 mg/day itraconazole	• No data, but potential for bi-directional inhibition • Monitor toxicities	• Bi-directional interaction has been observed • May need to decrease intraconazole dose • Consider monitoring SQV level, especially if given unboosted with RTV
Oral contraceptives					
Ethinyl estradiol	• ↓ethinyl estradiol by 20%	• ↑ethinyl estradiol by 37%	• ↓ethinyl estradiol level by 42%	• ↓levels of norethindrone by 18% and ethinyl	• No data for unboosted SQV • RTV treatment

ARV	NVP	EFV	LPV/r	NFV	SQV
	• Use alternative or additional birth control methods	• Use alternative or additional birth control methods	• Use alternative or additional methods	estradiol by 47%	dose—can ↓level of ethinyl estridiol by 41%
Anti-convulsants					
Carbamazepin, phenytoin	• Use with caution; one case report showed low EFV concentrations with phenytoin	• Unknown; use with caution	• Many possible interactions: carbamazepine ↑ levels when co-administered with RTV • Use with caution and monitor anti-convulsant levels • Phenytoin: ↓levels of LPV, RTV, and↓ levels of phenytoin when administered together • Avoid concomitant use or monitor LPV level	• Unknown, but may decrease NFV levels substantially • Monitor anti-convulsant levels and virological response	• Unknown, but may markedly ↓ SQV levels • Monitor anti-convulsant levels and consider obtaining SQV level
Opiod substitution treatment (OST)					
Methadone	• Levels: NVP unchanged; methadone ↓ significantly • Opiate withdrawal common when this combination is used • Increased methadone dose often necessary • Titrate methadone dose to effect	• Levels: methadone ↓ 60% • Opiate withdrawal common, increase methadone dose often necessary • Titrate methadone dose to effect	• Methadone AUC ↓ 53% • Opiate withdrawal may occur. • Monitor and titrate dose if needed • May require↑ methadone dose	• NFV may decrease methadone levels, but opiate withdrawal rarely occurs • Monitor and titrate dose if needed • May require↑ methadone dose	• Methadone AUC ↓ 20% • When co-administered with SQV/RTV 400/400 mg BID • No adjustment for this PI regimen, but monitor and titrate to methadone response as necessary
Buprenorphine	• Not studied	• Buprenorphine levels ↓ 50% but no withdrawals reported	• No significant interactions	• No significant interactions	• No significant interactions

ARV	NVP	EFV	LPV/r	NFV	SQV
		• No dose adjustment is recommended			
Lipid lowering agents					
Simvastatin, lovastatin	• No data	• ↓ simvastatin level by 58% • EFV level unchanged • Adjust simvastatin dose according to lipid response; not to exceed the maximum recommended dose	• Potential large ↑ statin level • Avoid concomitant use	• ↑ simvastatin AUC by 505% • Potential large ↑ lovastatin AUC • Avoid concomitant use	• Potential large ↑ statin level • Avoid concomitant use
Atorvastatin	• No data	• ↓atorvastatin AUC by 43% • EFV level unchanged • Adjust atorvastatin dose according to lipid response; not to exceed maximum recommended dose	• ↑atorvastatin AUC 5.88-fold • Use lowest possible starting dose with careful monitoring	• ↑atorvastatin AUC 74% • Use lowest possible starting dose with careful monitoring	• ↑ atorvastatin level by 450% when use as SQV/RTV • Use lowest possible starting dose with careful monitoring
Pravastatin	• No data	• No data	• ↑pravastatin AUC 33% • No dose adjustment needed	• No data	• ↓pravastatin level by 50% • No dose adjustment needed
Proton pump inhibitors					
All the PIs and EFV can ↑ levels of cisapride and non-sedating antihistamines (aztemizole, terfenedine), which can cause cardiac toxicity; co-administration is not recommended					

Note: Concomitant use of fluticasone with RTV can result in significantly elevated serum cortisol concentrations. Coadministration of fluticasone with RTV or any RTV-boosted PI regimen is not recommended unless the potential benefit outweighs the risk of systemic corticosteroid side effects.

Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: Department of Health and Human Services; 2013 [last update]. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

4.9 DRUGS THAT SHOULD NOT BE USED IN COMBINATION WITH PIS OR NNRTIS DUE TO DANGEROUS DRUG INTERACTIONS

Drug category[#]	Calcium channel blocker	Cardiac	Lipid-lowering agents	Anti-mycobacterial[‡]	Anti-histamine[∂]	Gastro-intestinal drugs[∂]	Neuroleptic	Psychotropic	Ergot alkaloids (vasoconstrictor)	Herbs	Other
PIs											
Indinavir (IDV)	(none)	(none)	simvastatin lovastatin	rifampicin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	ATV
Ritonavir (RTV)	bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	
Saquinavir (SQV)	(none)	(none)	simvastatin lovastatin	rifampicin[Δ] rifabutin[Δ] rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	

Drug category[#]	Calcium channel blocker	Cardiac	Lipid-lowering agents	Anti-mycobacterial[‡]	Anti-histamine[∂]	Gastro-intestinal drugs[∂]	Neuroleptic	Psychotropic	Ergot alkaloids (vasoconstrictor)	Herbs	Other
Nelfinavir (NFV)	(none)	(none)	simvastatin lovastatin	rifampicin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	
Amprenavir (APV)[*]	bepridil	(none)	simvastatin lovastatin	rifampicin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	
Lopinavir (LPV) + ritonavir	(none)	flecainide propafenone	simvastatin lovastatin	RIF[‖] rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	

Drug category[#]	Calcium channel blocker	Cardiac	Lipid-lowering agents	Anti-mycobacterial[‡]	Anti-histamine[∂]	Gastro-intestinal drugs[∂]	Neuroleptic	Psychotropic	Ergot alkaloids (vasoconstrictor)	Herbs	Other
Atazanavir (ATV)	bepridil	(none)	simvastatin lovastatin	rifampicin rifapentine	astemizole terfenadine	cisapride proton pump inhibitors	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	IDV irinotecan
NNRTIs											
Nevirapine (NVP)	(none)	(none)	(none)	rifampicin rifapentine[‡]	(none)	(none)	(none)	(none)	(none)	St. John's wort	
Delavirdine (DLV)	(none)	(none)	simvastatin lovastatin	rifampicin rifapentin[‡] rifabutin	astemizole terfenadine	cisapride H-2 blockers proton pump inhibitors	(none)	alprazolam midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	
Efavirenz (EFV)	(none)	(none)	(none)	rifapentine[‡]	astemizole terfenadine	cisapride	(none)	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	

[#]Certain listed drugs are contra-indicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with P450–3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur among patients.
[‡]HIV patients being treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended for this population.
[Δ] Rifampicin and rifabutin are contra-indicated unless SQV is combined with RTV.
[∫]In one small study, higher doses of RTV or LPV/r offset RIF-inducing activity of LPV. Of note, 28% of subjects discontinued due to increases in LFTs. The safety of this combination is still under evaluation; further studies are needed.
[Σ]Midazolam can be used with caution as a single dose and given in a monitored situation for procedural sedation.
[†]This is likely a class effect.
[∂]Astemizole and terfenadine are not marketed in the US. The manufacturer of cisapride has a limited-access protocol in place for patients meeting specific clinical eligibility criteria.
[*]Each 150 mg APV Agenerase® capsule has 109 international units (IU) of vitamin E and 1 mL of APV oral solution has 46 IU of vitamin E. At FDA approved doses, the daily amount of vitamin E in Agenerase® is a 58-fold increase over the federal government's reference daily intake for adults. Patients should be cautioned to avoid supplemental doses of vitamin E. Multivitamin products containing minimal amounts of vitamin E are likely acceptable.

Suggested alternatives:
Cerivastatin (no longer marketed in the US), simvastatin, lovastatin: Pravastatin and fluvastatin have the least potential for drug-drug interactions; atorvastatin should be used with caution, using the lowest possible starting dose and monitoring closely.
Rifabutin: Clarithromycin, azithromycin (MAC prophylaxis); clarithromycin, azithromycin, ethambutol (MAC treatment)
Astemizole, terfenadine (no longer marketed in the US): Desloratadine, loratadine, fexofenadine, cetirizine
Midazolam, triazolam: Temazepam, lorazepam

Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: Department of Health and Human Services; 2013 [last update]. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

4.10 SEVERITY GRADING OF SELECTED CLINICAL AND LABORATORY TOXICITIES

Sources: World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach, 2010 revision. Geneva: WHO; 2010. Available from: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf;

For abnormalities NOT found elsewhere on the table below, use the following scale to estimate grade of toxicity:

Grade 1 Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

Grade 2 Mild-to-moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.

Grade 3 Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization possible.

Grade 4 Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care.

Haematology	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Haemoglobin	8.0–9.4 g/dL **OR** 80–94 g/L **OR** 4.93–5.83 mmol/L	7.0–7.9 g/dL **OR** 70–79 g/L **OR** 4.31–4.92 mmol/L	6.5–6.9 g/dL **OR** 65–69 g/L **OR** 4.03–4.30 mmol/L	<6.5 g/dL **OR** <65 g/L **OR** <4.03 mmol/L
Absolute neutrophil count	1,000–1,500/mm^3 **OR** 1.0–1.5/G/L*	750–999/mm^3 **OR** 0.75–0.99/G/L*	500–749/mm^3 **OR** 0.5–0.749/G/L*	<500/mm^3 **OR** <0.5/G/L*
Platelets	75,000–99,000/mm^3 **OR** 75–99/G/L*	50,000–74,999/mm^3 **OR** 50–74.9/G/L*	20,000–49,999/mm^3 **OR** 20–49.9/G/L*	<20,000/mm^3 **OR** <20/G/L*
Chemistries	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
		Sodium		
Hyponatremia	130–135 meq/L **OR** 130–135 mmol/L	123–129 meq/L **OR** 123–129 mmol/L	116–122 meq/L **OR** 116–122 mmol/L	<116 meq/L **OR** <116 mmol/L
Hypernatremia	146–150 meq/L **OR** 146–150 mmol/L	151–157 meq/L **OR** 151–157 mmol/L	158–165 meq/L **OR** 158–165 mmol/L	>165 meq/L **OR** >165 mmol/L
		Potassium		
Hyperkalemia	5.6–6.0 meq/L **OR** 5.6–6.0 mmol/L	6.1–6.5 meq/L **OR** 6.1–6.5 mmol/L	6.6–7.0 meq/L **OR** 6.6–7.0 mmol/L	>7.0 meq/L **OR** >7.0 mmol/L
Hypokalemia	3.0–3.4 meq/L **OR** 3.0–3.4 mmol/L	2.5–2.9 meq/L **OR** 2.5–2.9 mmol/L	2.0–2.4 meq/L **OR** 2.0–2.4 mmol/L	<2.0 meq/L **OR** <2.0 mmol/L
		Bilirubin		
Hyperbilirubinemia	>1.0–1.5 x ULN	>1.5–2.5 x ULN	>2.5–5 x ULN	>5 x ULN
		Glucose		
Hypoglycemia	55–64 mg/dL **OR** 3.01–3.55 mmol/L	40–54 mg/dL **OR** 2.19–3.00 mmol/L	30–39 mg/dL **OR** 1.67–2.18 mmol/L	<30 mg/dL **OR** <1.67 mmol/L
Hyperglycemia (nonfasting and no prior diabetes)	116–160 mg/dL **OR** 6.44–8.90 mmol/L	161–250 mg/dL **OR** 8.91–13.88 mmol/L	251–500 mg/dL **OR** 13.89–27.76 mmol/L	>500 mg/dL **OR** >27.76 mmol/L

Triglycerides	----------	400–750 mg/dL **OR** 4.52–8.47 mmol/L	751–1,200 mg/dL **OR** 8.48–13.55 mmol/L	>1,200 mg/dL **OR** >13.55 mmol/L
Creatinine	>1.0–1.5 x ULN	>1.5–3.0 x ULN	>3.0–6.0 x ULN	>6.0 x ULN
Chemistries (continued)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Transaminases				
AST (SGOT)	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN	>10.0 x ULN
ALT (SGPT)	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN	>10.0 x ULN
GGT	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN	>10.0 x ULN
Alkaline phosphatase	1.25–2.5 x ULN	>2.5–5.0 x ULN	>5.0–10.0 x ULN	>10.0 x ULN
Pancreatic enzymes				
Amylase	>1.0–1.5 x ULN	>1.5–2.0 x ULN	>2.0–5.0 x ULN	>5.0 x ULN
Pancreatic amylase	>1.0–1.5 x ULN	>1.5–2.0 x ULN	>2.0–5.0 x ULN	>5.0 x ULN
Lipase	>1.0–1.5 x ULN	>1.5–2.0 x ULN	>2.0–5.0 x ULN	>5.0 x ULN
Lactate	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
Gastro-intestinal	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	Mild **OR** transient; reasonable intake maintained	Moderate discomfort **OR** intake decreased for <3 days	Severe discomfort **OR** minimal intake for ≥3 days	Hospitalization required
Vomiting	Mild **OR** transient; 2–3 episodes per day **OR** mild vomiting lasting <1 week	Moderate **OR** persistent; 4–5 episodes per day **OR** vomiting lasting ≥1 week	Severe vomiting of all food/fluids in 24 hours **OR** orthostatic hypotension **OR** IV Rx required	Hypotensive shock **OR** hospitalization for IV Rx required
Diarhoea	Mild **OR** transient; 3–4 loose stools per day **OR** mild diarrhoea lasting <1 week	Moderate **OR** persistent; 5–7 loose stools per day **OR** diarrhoea lasting ≥1 week	Bloody diarrhoea **OR** orthostatic hypotension **OR** >7 loose stools/day **OR** IV Rx required	Hypotensive shock **OR** hospitalization required
Respiratory	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Dyspnoea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring O_2 therapy
Urinalysis	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria				
Spot urine	1+	2–3+	4+	Nephrotic syndrome
24 hour urine	200 mg–1 g loss/day **OR** <0.3% **OR** <3 g/l	1–2 g loss/day **OR** 0.3 - 1.0% **OR** 3- 10 g/l	2–3.5 g loss/day **OR** >1.0% **OR** >10 g/l	Nephrotic syndrome **OR** >3.5 g loss/day
Gross haematuria	Microscopic only	Gross, no clots	Gross plus clots	Obstructive
Miscellaneous	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Fever (oral, >12 hours)	37.7–38.5ºC **OR** 100.0–101.5ºF	38.6–39.5ºC **OR** 101.6–102.9ºF	39.6–40.5ºC **OR** 103–105ºF	>40.5ºC **OR** >105ºF for ≥12 continuous hours
Headache	Mild; no Rx required	Moderate **OR** non-narcotic analgesia Rx	Severe **OR** responds to initial narcotic Rx	Intractable
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria angioedema	Anaphylaxis

Rash, hypersensitivity	Erythema, pruritus	Diffuse maculopapular rash **OR** dry desquamation	Vesiculation **OR** moist desquamation **OR** ulceration	**ANY ONE:** mucous membrane involvement, suspected Stevens-Johnson Syndrom/ Toxic Epidermal Necroysis (SJS/TEN), erythema multiforme, exfoliative dermatitis
Fatigue	Normal activity reduced <25%	Normal activity reduced 25–50%	Normal activity reduced >50%; cannot work	Unable to care for self

4.11 CO-TRIMOXAZOLE DESENSITIZATION AND SULFONAMIDE ALLERGY

Co-trimoxazole is the preferred antibiotic for prophylaxis and treatment of several common OIs. Most patients who report a non-severe allergic reaction to this drug or other sulfonamide-based drugs can be successfully 'desensitized', allowing them to take co-trimoxazole without adverse effects. However***, desensitization should not be attempted if the prior reaction included hepatitis, aseptic meningitis, or a severe hypersensitivity reaction (marked by high fever, severe rash, or mucosal involvement suggestive of Stevens-Johnson syndrome)***. An example desensitization protocol is presented in the table below.

Sample Co-trimoxazole Desensitization Protocol[40]

Use commercially available paediatric suspension (containing TMP 8 mg and SMX 40 mg per mL [40 mg/200 mg per 5 mL]), followed by double-strength tablets, as follows:

Days	Co-trimoxazole dosage	Volume or tablet
1–3	8 mg/40 mg	1 mL
4–6	16 mg/80 mg	2 mL
7–9	40 mg/200 mg	5 mL (or 1/2 single strength tablet)
9–12	80 mg/400 mg	1/2 double strength tablet (or 1 single-strength tablet)
13 and thereafter	160 mg/800 mg	1 double strength tablet
***Note**: These day ranges are approximate; patients can be advanced more quickly or more slowly depending on their reactions to the dosages.*		

In the event of mild reaction (e.g., mild morbilliform rash without fever, systemic symptoms, or mucosal involvement), the dose can be reduced to the last tolerated step or continued at the same dosage for an additional day, while simultaneously treating the rash or reaction. Antihistamines or antipyretics may be used to treat symptoms of mild reactions. If the reaction diminishes, the patient may advance to the next dosage (consider more gradual increase of dosages); if the reaction worsens or if systemic symptoms develop, co-trimoxazole should be discontinued.

In the event of severe reaction (e.g., hepatitis; aseptic meningitis; or a severe hypersensitivity reaction including high fever, severe rash, or mucosal involvement suggestive of Stevens-Johnson syndrome), the desensitization regimen should be discontinued and the patient should be treated appropriately for the reaction. The patient should never be re-challenged with co-trimoxazole.

[40] United States AIDS Education and Training Centers National Resource Center. Sulfa desensitization. In guide for HIV/AIDS clinical care. Washington, DC: Health Resources and Services Administration; 2012. Available from: http://www.aidsetc.org/aidsetc?page=cg-1002_sulfa_densisitization.

4.12 RECOMMENDATION STRENGTH AND EVIDENCE QUALITY CLASSIFICATIONS

The following is the classification system used throughout this document to determine the strength of clinical recommendations and the quality of the evidence on which the recommendations were based.

Category	Definition
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Insufficient evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Grade	**Definition**
1	Evidence from at least one properly randomized, controlled trial
2	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies, preferably from more than one centre, from multiple time series, or from dramatic results in uncontrolled experiments
3	Evidence from opinions or respected authorities on the basis of clinical experience, descriptive studies or reports of expert committees

Source: Canadian Paediatric Society Infectious Diseases and Immunization Committee. Recommendations for the prevention of neonatal ophthalmia. Paediatr Child Health. 2002 Sep; 7(7): 480–483.

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