National HIV Treatment Guidelines

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CLINICAL MANAGEMENT GUIDELINES FOR HIV/AIDS

National TB, HIV/AIDS & other STIs Programme

Ministry of Health

Belize

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List of Acronyms

3TC	lamivudine
AB	antibody
ABC	abacavir
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	antenatal clinic
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AZT	zidovudine (also known as ZDV)
BID	twice daily
BMI	body mass index
bPI	boosted protease inhibitor
CD4	cell T-lymphocyte bearing CD4 receptor
CEM	cohort event monitoring
CMV	cytomegalovirus
CNS	central nervous system
CXR	chest X-ray
d4T	stavudine
DBS	dried blood spot
ddI	didanosine
DNA	deoxyribonucleic acid
DRV	darunavir
EC	enteric-coated
EFV	efavirenz
EIA	enzyme immunoassay
ETV	etravirine
EPTB	extrapulmonary tuberculosis
FBC	full blood count
FDC	fixed-dose combination
FPV	fos-amprenavir
FTC	emtricitabine
GI	gastrointestinal
GNP+	Global Network of People Living with HIV
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hb	haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus

HIVDR	HIV drug resistance
HIVRNA	human immunodeficiency virus ribonucleic acid
HSV	herpes simplex virus
ICW	International Community of Women Living with HIV/AIDS
IDV	indinavir
INH	isoniazid
IRIS	immune reconstitution inflammatory syndrome
ITPC	International Treatment Preparedness coalition
LPV	lopinavir
LPV/r	lopinavir/ritonavir
PMTCT	Prevention of mother-to-child transmission (of HIV)
NAM	nucleoside/nucleotide analogue mutation
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OBR	optimized background regimen
OI	opportunistic infection
OST	opioid substitution treatment
PCP	*Pneumocystis jiroveci* pneumonia
PEPFAR	President's Emergency Plan for AIDS Relief
PETRA	Perinatal Transmission Study
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
PHIV	people with HIV
PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother-to-child transmission (of HIV)
/r	low-dose ritonavir
RAL	raltegravir
RBV	ribavirin
RCT	randomized clinical trial
RNA	ribonucleic acid
RT	reverse transcriptase
RTI	reverse transcriptase inhibitor
RTV	ritonavir
Sd-NVP	single-dose nevirapine
SJS	Stevens-Johnson syndrome
SQV	saquinavir
STI	structured treatment interruption
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TEN	toxic epidermal necrolysis
TLC	total lymphocyte count

VL	viral load
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
WBC	white blood cell count
WHO	World Health Organization

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Foreword

My friends,

Thanks to the integrated efforts of all involved in our national response, the HIV epidemic in Belize seems to have reached a plateau. Indeed, for three years in a row Belize has shown a decrease in the total number of new HIV infections. This is a huge achievement and my congratulations are extended to all involved.

The updating of these new Clinical Guidelines in 2012 was much needed in light of the overwhelming new evidence in the care and treatment of persons with HIV/AIDS.

The key objective of this manual is to standardize and provide the core basics of the clinical management of a person with HIV requiring ARV therapy and thus improve their overall clinical condition.

It reflects substantial changes in the treatment of patients with HIV infection and AIDS since the first edition was published in 2003.

Recommendations made here reflect current evidence based medicine and is in line with international published guidelines within the context of our Belizean reality.

In gaining a national consensus on the guidelines, our team consulted widely with clinicians who are practicing in Belize and who know the reality of the HIV epidemic within out population.

The guidelines once again reflect my government's commitment to free anti-retroviral therapy to those meeting medical criteria as well as the gradual scaling up in care and treatment that the Ministry of Health has initiated.

It is intended that this will be implemented immediately across the country.

The field of public health is dynamic and constantly evolving and our response must be no less dynamic. Our care providers across the country continue to work every day to bring help to their fellow Belizeans. We thank them for their hard work and commitment. The new guidelines will provide another tool to help in the ongoing challenge of an effective national response to the HIV epidemic in Belize.

With thanks,

Hon. Pablo Marin,
Minister of Health

Introduction

In 2003, the Ministry of Health initiated the implementation of care and treatment for persons with HIV. This initiative, has from the onset, included the free provision of antiretrovirals for everyone who meets the medical criteria. Care and treatment for pediatric patients is mostly provided by the Karl Heusner Memorial Hospital , via its Pediatric Department, and Hand in Hand Ministries located in Belize City. There are currently, thirteen sites providing anti-retroviral therapy for both adults and adolescents in the country. However, because The National Clinical Management guidelines have not been revised since their development in 2003, the clinical management has been largely guided by the Caribbean Guidelines for the Care and Treatment of Persons with HIV Infection (2007). The 2007 guidelines were developed by the CAREC/PAHO and Caribbean HIV/AIDS Regional Training Network (CHART). Both sets of guidelines focus mainly on adult and adolescent populations. In effect, there is a lack of current standardized national guidelines for the clinical management of HIV/AIDS in the pediatric, adolescent, and adult populations, notwithstanding the updated management being reflected on the ground.

The Ministry of Health recognizes the need for revising the national guidelines. Therefore, The Clinical Management Guidelines of HIV/AIDS are being updated with financial support fromthe Global Fund Project Round 9, “Accelerating the pace, reaching marginalized populations with critical services”. The Pan American Health Organization Caribbean HIV Office (PHCO) has also played a vital role in the revision of these guidelines, through its indispensable technical support. Embedded in this revised set of guidelines is a comprehensive approach to the clinical management of persons with HIV infection, including the guidance for the management of HIV in pediatric populations. The guidelines detail when to start ART, what to start, adherence and preparation for beginning treatment, the monitoring of patients to identify treatment failure, what ARVs to switch to (second line regimens), treatment for OIs including TB and hepatitis co-infections, and HIV co-morbidities, as well as a note on salvage treatment.

The effective implementation of the new guidelines will require the availability of timely and appropriate laboratory support for CD4, viral load tests, and the monitoring of HIV Drug Resistance (HIV-DR) in treatment sites. Monitoring will be conducted through the

implementation of HIV Drug resistance early warning indicators (HIV-DR EWIs). Viral load tests are not yet available in the country. Nonetheless, it should be noted that the absence of laboratory results should not prevent the initiation of antiretrovirals where there is enough clinical criteria to start ARV therapy.

Objectives of the Guidelines

The objective of this document is to provide a standardized guidance for the care and treatment of adults, adolescents, and children infected with HIV.

Methodology for Revising and Updating the Clinical Guidelines for HIV

In order to revise and update the clinical guidelines for HIV/AIDS, the Ministry of Health, Belize, requested the technical support of PAHO/WHO. This technical support entailed the revision of the document based on current evidence and various established international guidelines. The International guidelines considered included: WHO (2010), European AIDS Clinical Society Guidelines (2011), US Department of Health and Human Services (DHHS) Guidelines (2011), The British HIV Association Guidelines, and the Caribbean Care and Treatment Guidelines (2007).

In an effort to obtain information regarding the current situation of the country, so as to effectively update the guidelines, the Ministry of Health's National HIV/AIDS Program organized a one day consultation with doctors, and other key health care providers. Key elements for the guidelines were proposed and revised. It was decided that training for health care providers in the care and treatment sites would be conducted for all health care providers. In addition, based on the information collected from the consultation, a small group was assigned to formally update the document. Upon its completion, the first draft of the document was shared with the Care and Treatment Sub-Committee of the National AIDS Commission and other health care providers, and then sent to the office of the Director of Health Services for a final approval.

Key Areas Updated in the Guidelines

The updated guidelines for the clinical management of HIV includes information for the care and treatment of adults, adolescents and pediatric populations with HIV. Updates to the various sections of the guidelines include:

- Comprehensive Care
- Preparation for Beginning Treatment
- Adherence to Antiretrovirals
- When to Start
- What to Start
- Monitoring of Patients
- Management of TB/HIV Co-infection
- Treatment Failure and when to Switch ARVs
- Second Line Regimens
- Salvage Regimen
- Co-infections and Opportunistic Infections
- HIV and Non-infectious Co-morbidities

Guidelines for PMTCT are available in a separate document (last revised in 2009), which was specifically developed for the management of HIV during pregnancy, childbirth and post-partum. Included, are recommendations for the management of HIV-exposed infants.

Audit Standards

These guidelines have been developed to ensure that quality care and treatment is provided to all persons accessing HIV care and treatment. Audit standards are provided below based on the guidance provided in the document.

- All patients identified with HIV infection should be referred to HIV care and treatment services.

- During their first visit to the HIV care and treatment center, a complete history, physical examination and blood collected for baseline investigation, must be conducted on all patients as per table 1.
- All patients should have adherence counseling at least twice per year.
- Patients in follow-up care should receive a CD4 test at least twice per year.
- All patients with HIV (including those on ART) should have a complete physical examination and pertinent clinical/laboratory investigations as indicated in Table 2.

Comprehensive Care for HIV

The use of ART in the treatment of PHIV has resulted in the reduction of mortality and morbidity rates among persons infected with HIV. As a result, HIV should now be considered a chronic disease. The comprehensive care of PHIVs which is a critical factor in the provision of necessary psychosocial support, works in tandem with the provision of ART. Although, not all PHIVs will require ART at the time of diagnosis, it is imperative that as many PHIVs as possible enter care. This is so as to prevent them from becoming ill with their first opportunistic infection (OI), or developing advanced immuno-suppression (CD4 cell count <200 cells/mm^3), which places them at a higher risk of developing opportunistic diseases. It is fundamental that there be an earlier HIV diagnosis, early enrollment into care with regular CD4 count monitoring to determine eligibility for ART, and the initiation of ART as soon as required.

HIV Testing and Counseling

The strategies critical in identifying people who need to enter HIV care are expanded HIV testing and counseling, provider-initiated testing and counseling (PITC) and voluntary counseling and testing (VCT). In the VCT approach, clients request a test after recognizing they are at risk, however, attendance at at any health facility will now offer patients an opportunity to integrate discussion of HIV and HIV testing, into routine medical care. Medical care is supplied through PITC. This approach ensures greater access to HIV testing and counseling, and early diagnosis and referral into HIV care and treatment services. HIV testing and counseling strategies should be promoted in all the health services.

Risk Reduction Interventions

Care during the pre-ART period provides a setting for interventions to prevent the further transmission of HIV. This setting produces the identification of behavioural risk factors in persons with HIV, and the opportunity to discuss intervention strategies that reduce risk and HIV transmission to others. In this setting, positive prevention strategies discussed include the consistency of condom use, benefits in reducing the number of sexual partners, and education for further behavioural changes. In addition, risk reduction counseling, and psycho-social support services for high riskHIV negative persons should be available at all times.

Sexual and Reproductive Health

Early care facilitates the identification of clinical risk factors such as sexually transmitted infections (STIs), and provides the opportunity to give treatment and counseling to prevent other illnesses. Comprehensive care is an opportunity to provide STI services. These services should include a correct diagnosis by syndrome which, where possible, should be confirmed by a laboratory test. In addition, comprehensive care enables the provision of effective treatment at the first encounter, the notification and treatment of partners, the reduction of further risk behaviour, and the prevention of transmission through education, and the provision of condoms. Routine laboratory screening should include a serological test for syphilis, especially in pregnant women. Further interventions, should include those to reduce unplanned pregnancies and mother-to-child transmission of HIV. HIV pregnant women should be referred to family planning and all persons with HIV should have access to sexual and reproductive health services.

Nutritional Counseling

HIV infection is often associated with poor nutrition. This is due to many factors, including increased energy needs, decreased appetite, and environmental factors such as lack of resources and inaccessibility of foods. In addition, symptoms of HIV or opportunistic infections also lead to difficulty in swallowing and malabsorption. Proper nutrition is therefore important for PHIV. Patients with HIV should have access to nutritional education, nutritional assessment and where necessary, nutritional counseling and the provision of nutritional support.

Mental Health

Cognitive and neurological disorders are common among PHIV, especially those with drug dependence or advanced HIVdisease. Untreated mental conditions not only reduce the quality of life for HIV-affected individuals and households; they are also strongly associated with non-adherence to treatment regimens. Health-care providers must be able to recognize mental illnesses such as depression, substance and alcohol dependence/abuse. Patients who fit this diagnosis must be referred in a timely manner to the psychosocial services which include group counseling, disclosure support, caregiver support and, when indicated, medication for those conditions.

Treatment Preparedness

Treatment preparedness should be used to provide supportive counseling and education about the patient's condition. This preparation maximizes long-term retention in care, and prepares the patient for the eventual requirement of ART. Major factors contributing to good adherence to ART include a low pill count, and adequate education about the use of ART and its implications. Studies suggest that treatment readiness is associated with improved adherence once ART has been initiated. Enrollment into care before the time of initiation of ART provides an opportunity for PHIV to learn, understand, and prepare for successful lifelong ART. ART may be deferred until the patient has a full understanding of ART and adherence.

TB/HIV Co-Infection

Among people with HIV, TB is the most frequent life-threatening opportunistic infection and is a leading cause of death. Comprehensive care provides a setting for implementation of the WHO three I's strategy:

- isoniazid preventive treatment (IPT) where indicated,
- intensified case finding (ICF) for active TB,
- and TB infection control (IC)

These are key public health strategies to decrease the impact of TB among individuals and the community. Information about TB should be provided to all people with HIV. Patient education should include information about the risk of acquiring TB, strategies for reducing exposure, clinical manifestations of TB disease, and the risk of transmitting TB to others. The successful

implementation of the three Is initiative is imperative for Belize given the documented increased of HIV and TB co-infection rates over the last couple of years. In addition, all patients with TB should be tested for HIV to identify TB/HIV co-infections, for early management of TB/HIV as per guidelines.

Co-trimoxazole prophylaxis (CPT)

CPT is recommended for all symptomatic individuals (WHO clinical stages 2, 3 or 4) including pregnant women, and for individuals with a CD4 cell count of <350 cells/mm^3. The main targets for co-trimoxazole prophylaxis are *Pneumocystis jiroveci* pneumonia and toxoplasmosis infection. Data from an observational analysis in the DART trial showed that the use of co-trimoxazole prophylaxis reduced mortality by 50% in severely immune-suppressed HIV-infected adults initiating ART with the benefits of this treatment continuing for at least 72 weeks. Co-trimoxazole prophylaxis has also been shown to reduce malaria incidence in these patients.

Early initiation of ART

Enrollment into pre-ART care is critical for the early and successful initiation of ART. It maximizes treatment response and minimizes treatment complications such as immune reconstitution inflammatory syndrome (IRIS). Pre-ART care provides the opportunity for regular screening (see Table 1) for CD4 and viral loads which results in the timely identification of when to initiate treatment. Where pre-ART care is not provided to patients, they are more likely to present with advanced HIV disease and thus have a delayed initiation of ART. This results in higher mortality rates during the first year of ART (3–26%), with most deaths occurring in the first few months.

ART as Prevention

Studies have demonstrated the benefits of ART for the prevention of HIV transmission. There is evidence that individuals on fully suppressive ART who are adherent to the therapy, are less likely to transmit HIV to others. Conversely, those with unrecognized HIV infection contribute significantly to onward sexual transmission. At the individual level, ART reduces viral load and infectiousness, making it a prevention method.

Assessment of HIV-infected Patients at Initial and Subsequent Visits

Initial visit

- Complete medical history
- Physical examination, including height, weight, BMI, blood pressure, waist circumference
- Assessment of social and psychological condition: provision of support and counseling as needed
- Consideration of HBV vaccination (depending on serology results) and pneumococcal vaccination
- History of vaccination, travel and country of origin

Annually

- Physical examination
- Evaluation of social and psychological support
- Healthy lifestyle changes (nutrition, drug use)

Table 1: Screening/Laboratory Testing (PRE-ART)

Tests	Initial	6 Months	Annually
Confirmation of HIV positive antibody status	X		
Physical examination, including height, weight, BMI, blood pressure, waist circumference	X	X	X
CD4 count and % (optional: CD8 count and %)	X	X	X
HIV RNA (viral load)	X		X
Complete blood count	X	X	X
AST, ALT, Alk phosphatase, calcium, phosphate, creatinine clearance	X		X
Antibody tests for Hepatitis B, C and syphilis	X		X (if previously negative)
Fasting blood glucose and lipids to include total LDL & HDL cholesterol and triglycerides	X		X
Complete urinalysis	X		X
Cardiovascular risk assessment	X		X
Sexually Transmitted Infection (STI) screening (including anal swab)	X		X
PSA	X		
Cervical Pap smear	X	X	X
PPD - Negative PPD does not exclude active or latent tuberculosis.	X		X

Adopted from the European guidelines for HIV/AIDS 2011

Table 2: Screening/Laboratory Monitoring (on ART)

Tests	Treatment Initiation	6 months	Annually
CD4 count and % (optional: CD8 count and %)	X	X	X
HIV RNA (viral load)	X		X
Complete blood count	X	X	X
AST, ALT, Alk phosphatase, calcium, phosphate, creatinine clearance	X	X	X
Antibody tests for Hepatitis B, C and syphilis	X		X (if previously negative)
Fasting blood glucose and lipids to include total LDL & HDL cholesterol and triglycerides	X	X	X
Complete urinalysis	X		X
Cardiovascular risk assessment (according to ART)	X		X
Sexually Transmitted Infection (STI) screening (including anal swab)	X		X
Cervical Pap smear			X
PPD - Negative PPD does not exclude active or latent tuberculosis.			X

Adopted from the European Guidelines for HIV/AIDS 2011

Considerations in Laboratory Monitoring on ART

- For NNRTI-containing regimens, symptom-directed laboratory monitoring of liver enzymes is recommended. Symptom-directed monitoring means ordering tests only when the care provider recognizes signs and symptoms of potential ART-related toxicity. For

women initiating NVP with a CD4 count of 250−350 cells/mm^3, if feasible, it is recommended (but not required) to monitor hepatic enzymes at weeks 2, 4 and 12 after initiation.

- For AZT-containing regimens, haemoglobin (Hb) measurement is recommended before the initiation of AZT and then as indicated by signs/symptoms. Patients receiving AZT-containing regimens and with low body weight and/or low CD4 cell counts are at greater risk of anemia. These patients should have routine Hb monitoring 1 month after initiating AZT and then at least once every 3 months. AZT should not be given if Hb is <7 g/dl.
- For TDF-containing regimens, creatinine clearance calculation is recommended before initiation and every 6 months after that. The inability to perform creatinine clearance is not a barrier to TDF use. Creatinine clearance monitoring is recommended in those with underlying renal disease, of older age groups, and with low body weight or other renal risk factors such as diabetes or hypertension. There is evidence that individuals taking TDF and a PI/r may experience greater median decline in creatinine clearance than those taking TDF and an NNRTI-based regimen. Creatinine clearance should be monitored more closely when TDF is used with a PI/r.
- For individuals with HIV/HBV or HIV/HCV co-infection, it is recommended to monitor hepatic enzymes at weeks 4 and 12 following ART initiation, if feasible.

Table 3: Monitoring ART in those at higher risk of adverse events

ARV drug	Major toxicity	High-risk situations*
d4T	Lipodystrophy Neuropathy Lactic acidosis	Age > 40 years CD4 count of < 200 cells/mm^3 BMI > 25 (or body weight > 75 kg) Concomitant use with INH or ddI
AZT	Anemia Neutropaenia	CD4 count of < 200 cells/mm^3 BMI < 18.5 (or body weight <50 kg) Anemia at baseline
TDF	Renal dysfunction	Underlying renal disease Age > 40 years BMI < 18.5 (or body weight < 50 kg) Diabetes mellitus Hypertension Concomitant use of a PI or nephrotoxic drugs
EFV	Teratogenicity	1st trimester of pregnancy (do not use EFV)
	Psychiatric illness	Depression or psychiatric disease (previous or at baseline)
NVP	Hepatotoxicity	HCV and HBV co-infection

Readiness to Initiate ART and Adherence Counseling

Assessing and Supporting Patients' Readiness to Start ART

The goal is to facilitate decision making and the start of ART in patients who are eligible to begin therapy according to national guidelines. Matters for consideration to begin a patient on ART have to be judged clinically and must include identifying barriers to adherence. If a patient presents late or very late, i.e CD4 <200, the initiation of ART should not be delayed; the clinician should try to identify the most important adherence barriers which may be present, and support the patient in the preparation for prompt initiation of ART. Possible barriers to adherence include personal factors as well as systemic factors. Personal factors include depression, harmful alcohol or recreational drug use, cognitive problems, low literacy, health beliefs, cultural and

social backgrounds, lack of social support and disclosure. Systemic factors include continuity of drug supply and access to care and treatment services.

Patients presenting in the clinic may be at different stages of readiness to begin treatment. These stages are Pre-contemplation, Contemplation and Preparation. [Transtheoretic model; Prochaska JO. Am Psychol 47:1102- 1114, 1992]

Assessment and Support for Patients on ART

Assessment of adherence should be performed at every visit in order to identify and correct any potential barriers. A trusting and non-judgmental relationship between the clinician or health care provider and the patient is critical in this regard. Studies have found that clinicians do not reliably predict their patients' levels of adherence; more accurate methods of assessing adherence include patient recollection of missed doses and pharmacy refill records. Key strategies that may be useful in promoting adherence in patients who have recently initiated therapy include:

- establishing trust
- closely monitoring adherence at routine visits
- providing access between visits for questions or problems
- involving patient's social network to provide ongoing adherence support
- adding adherence assessment and reinforcement to job descriptions of support team members, such as nurses, pharmacists, case managers, and clinicians' assistants

Table 4: Assessment of Patients' Readiness to start ART and Continued Adherence

Before initiating ART:	
Potential adherence barriers	**Depression** **Harmful alcohol or recreational drug use** **Cognitive problems** **Low Literacy** **Health Beliefs** **Social and Cultural Background** **Social Supports and Disclosure** **Continuity of ART supply** **Access to HIV care and treatment services**

Useful questions assess patients' readiness and to identify some adherence barriers

I would like to talk about HIV medication. <wait> What do you think about it?

Assess Depression:

- **During the past month, have you often been bothered by feeling down, depressed or hopeless?**
- **During the past month, have you often been bothered by little interest or pleasure in doing things?"**
- **Is this something with which you would like help?**

If answers are positive, then sensitivity is 96%, specificity 89% (Arroll B et al. BMJ 327:1144-1146. 2003) as an indication of depression.

Alcohol and Recreational Drug Use

- **Have you thought about cutting down (Alcohol or recreational drug)?**
- **Have you ever become annoyed when people talk to you about your drinking?**
- **Have you ever felt guilty about your drinking?**
- **Do you ever have a drink first thing in the morning (Eye opener)?**

An affirmative answer to more than two CAGE questions means a sensitivity and specificity for problematic alcohol use of more than 90% (Kitchens JM. JAMA 272(22): 1782-1787. 1994). Ask similar questions for recreational drug use.

Cognitive Problems

- **Do you feel that you are having problems concentrating in your daily life?**
- **Do you feel slow in your thinking?**
- **Do you feel that you are having problems with your memory?**
- **Have relatives or friends expressed that they feel you are having problems with your memory or difficulty concentrating?**

Recognize, discuss and reduce problems wherever possible

Remember to set the agenda before every interview	Use open ended questions whenever possible	Use the WEMS-technique[1]
	Pre-contemplation:	***Support***:
	"I don't need it, I feel good" **"I don't want to think about it"**	**1. Show respect for patient's attitude** **2. Try to understand health and therapy beliefs** **3. Establish trust** **4. Provide individualized short information** 5. **Schedule the next appointment**
	NO	
Restage Again	***Contemplation:***	***Support***:
	"I am weighing things up and feel torn about what to do with it"	**1. Allow ambivalence** **2. Support to weigh pros and cons together with patient** **3. Assess information needs and support information seeking** 4. **Schedule the next appointment**
	NO	
	Preparation:	***Support:***
	"I want to start, I think the drugs will	**1. Reinforce decision**

	allow me to live a normal life"	**2. Make shared decision on most convenient regimen** **3. Educate: adherence, resistance, side effects** **4. Discuss integration into daily life** **5. Develop an adherence plan together** **6. Assess self-efficacy** **7. Ask: Do you think you can manage to take ART consistently once you have started?** **Use Visual Analogue Scale 0-10** **0 ----------5---------- 10**
Restage Again	YES	
Provide Supports for Adherence		**1. Consider skills training: Medication-taking training** **2. Directly Observed Therapy with educational support** **3. Use aids: pillboxes, cell phone alarm** **4. Peer and family support where appropriate**
Start and maintain Adherence		**Screen: for adherence problems in each meeting** **Suggested adherence questions:** **"In the past 4 weeks, how often have you missed a dose of your HIV medication: every day, more than once a week, once a week, once every 2 weeks, once a month, never?"** **"Have you missed more than one dose in a row?"** (Glass TR et al. Antiviral Therapy 13(1):77-85. 2008). Adapted from: J. Fehr, D. Nicca, F. Raffi, R. Spirig, W.

	Langewitz, D. Haerry, M. Battegay, NEAT, 2008. Support: 1. **Discuss side effects** 2. **Educate about surrogate makers (CD4 and viral load)/ Discuss integration of drug taking schedule** 3. **Empower: Give positive feedback**

[1]Wems-technique:waiting, (>3sec), echoing, mirroring, Summarizing
[2] VAS 0-10: Visual Analogue Scale; Range 1-10 ie, 1-I will not manage , 10- I will manage
Adapted from the EACS Guidelines 2011

Adherence and HIV Resistance to Antiretroviral Therapy

Treatment failure often occurs because a patient's strain of HIV has developed resistance to one or more of his/her antiretroviral medications. The way in which HIV develops resistance to ARVs is similar to the way in which 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, leading to treatment failure.

Resistance to antiretroviral medications most commonly develops in the setting of suboptimal adherence, but can occur even in patients who maintain very high levels of adherence to their medications. For example, a patient with poorly controlled diarrhoea may not fully absorb his or her medications, leading to sub-therapeutic drug levels in the blood, which could lead to the development of resistance.

The importance of adherence for those initiating HAART cannot be over emphasized. Studies suggest that adherence is especially critical in the first few months of ARV therapy, when the HIV viral load is expected to decline rapidly. Suboptimal adherence can rapidly lead to the development of drug resistance, ultimately resulting in regimen failure as well as the loss of antiretroviral options for second line and salvage regimens. To prevent the occurrence of resistance, patients must be educated and supported to take antiretrovirals as prescribed and this begins with the assessment of patient readiness and preparation for treatment. In addition, systemic factors must be addressed, for example, ensuring drug supply continuity through the efficient procurement and drug supply mechanisms.

When to start?

Box 1: Recommendations on when to start antiretroviral treatment

1. It is recommended to treat all patients with CD4 counts of ≤350 cells/mm^3 irrespective of the WHO clinical stage.

(Strong recommendation, moderate quality of evidence)

2. It is recommended to treat all patients with WHO clinical stage 3 and 4 irrespective of CD4 count.

(Strong recommendation, low quality of evidence)

In making these recommendations, the National HIV/AIDS Programme places high value on avoiding death, disease progression and the likely risk of HIV transmission over and above cost and feasibility.

**Special consideration for the initiation of ART for those patients with a CD4 count under500 should be made on an individual basis.*

The evidence used by WHO in formulating recommendations on when to start ART comes from a systematic review: *Optimal time of initiation of antiretroviral therapy for asymptomatic, HIV-infected, treatment-naive adults.* The review included randomized controlled clinical trials (RCTs) and cohort studies, in which ART initiation was stratified according to CD4 cell count.

Starting ART at CD4 levels higher than 200 or 250 cells/mm^3 reduces mortality rates in asymptomatic, ART-naive, HIV-infected people.

Table 5: Criteria for ART Initiation in specific populations

Target population	Clinical condition	Recommendation
Asymptomatic individuals (including pregnant women)	WHO clinical stage 1	Start ART if CD4 ≤ 350
Symptomatic individuals (including pregnant women)	WHO clinical stage 2	Start ART if CD4 ≤350
	WHO clinical stage 3 or 4	Start ART irrespective of CD4 cell count
TB and hepatitis B co-infections	Active TB disease	Start ART irrespective of CD4 cell count
	HBV infection requiring treatment*	Start ART irrespective of CD4 cell count

*The current standard definition of chronic active hepatitis in industrialized countries is mainly based on histological parameters obtained by liver biopsy, a procedure not usually available in Belize. A global definition of chronic active hepatitis for resource-limited settings based on clinical and moresimple laboratory parameters is under discussion.

Clinical Assessment

Clinical staging is intended for use where HIV infection has been confirmed by HIV antibody testing. It is used to guide decisions on when to start cotrimoxazole prophylaxis and when to start ART. Annex 1 (*WHO clinical staging of HIV disease in adults and adolescents*) and Annex 2 (*Criteria for HIV-related clinical events in adults and adolescents*) provide details of specific staging conditions and the criteria for recognizing them. For individuals with advanced HIV disease (WHO clinical stage 3 or 4), ART should be initiated irrespective of the CD4 cell count. Both stages 3 and 4 are independently predictive of HIV-related mortality. A CD4 test will assist in identifying the need to begin ART in patients at WHO clinical stages 1 and 2.

Immunological Assessment

A CD4 cell count performed at entry into care or prior to ART initiation will guide the decision on when to start ART and serves as the baseline CD4 value. ART should be commenced in individuals with a CD4 count of ≤350 cells/mm^3. Absolute CD4 cell counts fluctuate within

individuals and with inter-current illnesses. If feasible, CD4 testing should be repeated if a major management decision rests on the value, rather than using a single value. Serial CD4 measurements are more informative than individual values because they reflect trends over time. The total lymphocyte count (TLC) is no longer recommended to guide treatment decisions in adults and adolescents.

Virological Assessment

Plasma viral load (HIV-RNA) measurement is not required before the initiation of ART. However, expanded access to viral load testing is needed to improve the accuracy of diagnosing treatment failure. Earlier detection of virological failure allows both targeted adherence interventions, and better preservation of the efficacy of second-line regimens.

What to start?

Box 2: Recommendations of what ART regimens to start in ART-naïve patients

Start one of the following regimens in ART-naive individuals eligible for treatment.

- **AZT + 3TC + EFV**
- **AZT + 3TC + NVP**
- **TDF + FTC + EFV**
- **TDF + FTC + NVP**

In making these recommendations, we are placing a high value on avoiding the disfiguring, unpleasant, and potentially life-threatening toxicity of d4T, in addition to the selection of regimens suitable for use in most patient groups, treatment durability, and the benefits of using fixed-dose combinations. This is in line with WHO recommendations. The available information suggests that abacavir (ABC) and didanosine (ddI) have serious constraints for use in first-line regimens (toxicities and cost) and the WHO panel focused on comparisons between AZT, TDF

and d4T-based regimens. Specific notes regarding the 4 different combinations (**now labelled as 1st line therapy**) are highlighted below.

Table 6: Preferred first-line ART in treatment-naive adults and adolescents

Target population	Preferred options	Comments
Adults and adolescents	AZT or TDF + 3TC or FTC + EFV or NVP	These are the recommended first line treatment options for Belize Use fixed-dose combinations wherever possible
Pregnant women	AZT + 3TC + NVP or LPV/r	LPV/r for women having a CD4 count > 400 as an option In HIV women with prior exposure to PMTCT regimens, see ART recommendations in Table 11
HIV/TB co-infection	AZT or TDF + 3TC or FTC + EFV	Initiate ART as soon as possible (within the first 8 weeks) after starting TB treatment NVP is an acceptable option if EFV cannot be used
HIV/HBV co-infection	TDF + 3TC or FTC + EFV or NVP	Consider HBsAg screening before starting ART, especially when TDF is not the preferred first-line NRTI. Use of two ARVs with anti-HBV activity required

The choice between NVP and EFV

NVP and EFV have comparable clinical efficacy when administered in combination regimens. However, differences in toxicity profiles and the potential for interaction with other treatments should be considered when selecting either of the two. NVP is associated with a higher incidence of rash, Stevens-Johnson syndrome, and hepatotoxicity when compared to EFV. The simultaneous initiation of NVP and other new drugs that can also cause rash (e.g. co-trimoxazole) should be avoided where possible. In the case of severe hepatic or skin reactions, NVP should be permanently discontinued and not restarted. NVP is the preferred NNRTI for women in the fertile age groups, and where possible, the exposure during the first trimester of pregnancy should be minimized. While there are conflicting data regarding an increased risk of hepatic toxicity in women with CD4 counts between 250 and 350 cells/mm^3, the WHO panel

found that there was limited evidence for concern but still urged caution in the use of NVP in women with CD4 counts of >250 cells/mm^3 or in those with unknown CD4 cell counts. Close clinical monitoring and laboratory monitoring during the first 12 weeks of therapy is recommended when NVP is initiated in women with a CD4 cell count of 250−350 cells/mm^3.

EFV can be used once daily and is generally well tolerated. Its primary toxicities are related to the central nervous system (CNS) and possible, but not proven, teratogenicity and rash, if received during the first trimester of pregnancy (but not in the second and third trimesters). Rash is generally mild and self-resolving and usually does not require the discontinuation of therapy. The CNS symptoms are common. While they typically resolve after 2−4 weeks, they can persist for months, resulting in discontinuation of the drug. EFV should be avoided in patients with a history of severe psychiatric illness, when there is a potential for pregnancy (unless effective contraception can be assured) and during the first trimester of pregnancy. EFV is the NNRTI of choice in individuals with TB/HIV co-infection who are receiving rifampicin-based TB therapy.
There are clinical situations when individuals need to replace EFV with NVP. The most common scenarios are when patients temporarily change from NVP to EFV because they need to take rifampicin-containing TB treatment, and subsequently switch back to NVP on completion of TB treatment, and individuals with persistent EFV CNS intolerance. In this case, EFV can be stopped and full-dose NVP (200 mg twice daily) can be started immediately. There is no need for lead-in NVP dosing.

AZT + 3TC + EFV Option

In recommending this as a preferred first-line regimen, the WHO group places high value on the utility of EFV in the treatment of HIV/TB co-infection. EFV is preferred in individuals taking rifampicin-containing TB treatment. EFV is not approved in children less than 3 years of age (and there are insufficient data on appropriate dosing for that age group). Single-dose NVP for the prevention of mother-to-child transmission (PMTCT) may compromise response to EFV because of cross-resistance. This prior exposure must be documented. EFV is associated with CNS adverse events which are common. Potentially troublesome AZT toxicities, such as proximal myopathy, gastrointestinal intolerance, skin hyperpigmentation and lipodystrophy, are not uncommon.

AZT + 3TC + NVP Option

In recommending this as a preferred first-line regimen, the WHO panel places high value on it as the preferred option in pregnancy. It is widely available and there is extensive experience in its use. It is applicable to both pediatric and adult populations and a preferred option in pregnancy. There is large programmatic experience with its use. Triple FDC formulations are available for adults and children. Rifampicin and NVP drug-drug interactions are such that the combination should not be used unless no alternative is available. The NVP lead-in dose adds complexity to this particular regimen.

TDF + FTC + EFV Option

In recommending this as a preferred regimen, the WHO panel places high value on the simplicity of use and low toxicity levels. A triple FDC is available with low pill-burden (one pill once daily) which is well accepted by PHIV and having a lower pill burden enhances adherence. Two drugs in the regimen are active against HBV, no lead-in dosing is required, and the combination can be used in patients receiving rifampicin-containing TB treatment. TDF use should be accompanied by renal screening and monitoring. TDF is not approved in children and adolescents and there are limited data on the safety of TDF in pregnancy. An alternative non-EFV-containing regimen is required in the context of the first trimester of pregnancy or for women seeking to become pregnant.

TDF + FTC + NVP option

In recommending this as a preferred first-line regimen, an added value is present as this is also the treatment of HIV/HBV co-infection. Two drugs in the regimen are active against HBV. This is a relatively low pill burden and the potential for a once-daily regimen is present. There is limited programmatic experience with this combination and there have been reports of higher rates of virological failure when compared to TDF + 3TC or FTC + EFV.

Stavudine (D4T)

In resource-limited settings, d4T continues to play a critical role in the scaling up of ART. Cumulative exposure to d4T has the potential to cause disfiguring, painful, and life-threatening side-effects, such as lipodystrophy, peripheral neuropathy, and lactic acidosis. Studies have identified several risk factors associated with d4T-related adverse events. Peripheral neuropathy

was significantly associated with older patients (over 35 or 40 years). Lipodystrophy and hyperlactataemia were significantly associated with BMI >25 and the female gender. Transition to newer treatment regimens is encouraged but patients who are doing well on d4T should remain on it. The number of patients on d4T in Belize has not increased and there is a clinically good response of those patients to this treatment option. As such, patients on d4T will remain on that regimen for now, however, no new patients initiating ART will not be started on regimens containing d4T.

NRTIs Not To be Used Together

Certain dual NRTI backbone combinations should not be used in three-drug therapy. These are d4T + AZT (proven antagonism), d4T + ddI (overlapping toxicities) and 3TC + FTC (interchangeable, but should not be used together). The combinations of TDF + 3TC + ABC and TDF + 3TC + ddI select for the K65R mutation and are associated with high incidences of early virological failure. The combinations of TDF + ddI + any NNRTI are also associated with high rates of early virological failure and should be avoided.

When to Switch ART?

Box 3: Criteria for identification of treatment failure

1. Where available, use viral load (VL) to confirm treatment failure.

(Strong recommendation, low quality of evidence)

2. Where routinely available, use VL every 6 months to detect viral replication.

(Conditional recommendation, low quality of evidence)

3. A persistent VL of > 5000 copies/ml confirms treatment failure.

(Conditional recommendation, low quality of evidence)

4. When VL is not available, use immunological criteria to confirm clinical failure.

(Strong recommendation, moderate quality of evidence)

In making these recommendations, the WHO panel was concerned by the limitations of clinical and immunological monitoring for diagnosing treatment failure, and placed high value on avoiding premature or unnecessary switching to expensive second-line ART. The WHO panel also valued the need to optimize the use of virological monitoring to ensure adherence. ART switching has occurred at lower than expected rates and the limited use of virological monitoring has been identified as an important factor. Viral load monitoring optimizes the use of expensive second-line drugs. The same rationale applies when third-line or salvage drugs are available. Clinical and immunological monitoring is insufficient to promote a timely switch and viral load monitoring is recommended. The initial and on-going cost of viral load monitoring may be significant and a cost saving strategy is the use of viral load to confirm clinical-immunological switch (targeted approach) compared to the routine use of VL monitoring every six months. Quality assurance programmes should be in place at laboratories providing viral loads. Attention to mechanisms for adequate specimen transportation from clinic to laboratory should also be in place. Belize will utilize the cost saving targeted approach to viral load testing as outlined in Figure 1.

Clinical considerations

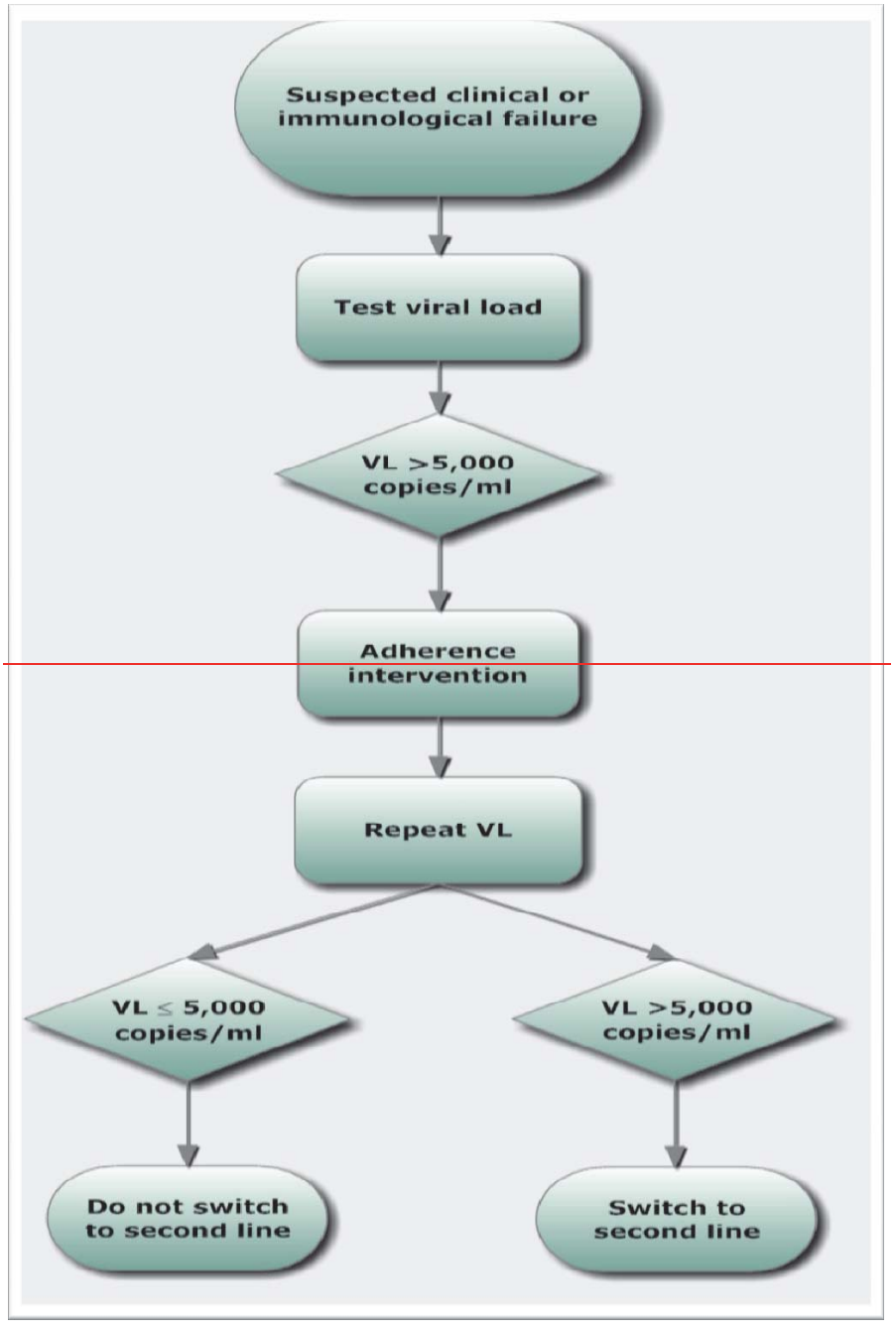
Definitions for ART failure remain basically unchanged except that the VL threshold for failure has changed from 10,000 copies/ml in 2006 (WHO recommendations) to 5,000 copies/ml in the 2010 WHO guidelines. An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed.

Table 7: ART Switching Criteria

Failure	Definition	Comments
Clinical failure	New or recurrent WHO stage 4 condition	Condition must be differentiated from immune reconstitution inflammatory syndrome (IRIS). Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections), may be an indication of treatment failure
Immunological failure	Fall of CD4 count to baseline (or below) OR 50% fall from on-treatment peak value OR persistent CD4 levels below 100 cells/mm^3	Without concomitant infection to cause transient CD4 cell decrease
Virological failure	Plasma viral load above 5,000 copies/ml	The optimal viral load threshold for defining virological failure has not been determined. Values of > 5,000 copies/ml are associated with clinical progression and a decline in the CD4 cell count

Adopted from WHO Guidelines 2010

Figure 1: Targeted viral load strategy for failure and switching



Second-line Regimens

Box 4: Recommendations for second line regimens

1. A boosted protease inhibitor (bPI) plus two nucleoside analogues (NRTIs) are recommended for second-line ART.

(Strong recommendation, moderate quality of evidence)

2. ATV/r and LPV/r are the recommended bPIs for second-line ART. In Belize LPV/r will be used as the second line option.

(Strong recommendation, moderate quality of evidence)

3. 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.

(Strong recommendation, moderate quality of evidence)

Laboratory assays have been developed to estimate the patterns of resistance that have developed in a given patient's strain of HIV. These assays have demonstrated clinical efficacy in aiding the design of second line treatment regimens following treatment failure. Hence, a resistance assay is recommended in the setting of treatment failure. Unfortunately, these assays are very expensive and are not widely available in the Caribbean, including Belize. 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.

Table 8: Preferred second-line ART options

Target population		Preferred options	Comments
Adults and adolescents (including pregnant women)	**If AZT used in first-line therapy**	TDF + FTC + LPV/r	NRTI sequencing based on availability of FDCs and potential for retained antiviral activity, considering early and late switch scenarios LPV/r is available as heat-stable FDCs or co-package formulations
	If TDF used in first-line therapy	AZT + 3TC + 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 bPIs, permitting standard bPI dosing
	If rifabutin not available	Same NRTI backbones as recommended for adults and adolescents plus LPV/r with superboosted dosing of RTV (LPV/r 400 mg/100 mg twice daily or LPV/r 800 mg/200 mg twice daily)	Rifampicin significantly reduces the levels of bPIs, limiting the effective options. Use of extra doses of ritonavir with selected bPIs (LPV) can overcome this effect but with increased rates of toxicity
Hepatitis B co-infection		TDF + FTC + LPV/r	In case of ART 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

Selection of Second-line NRTIs

The rationale for the selection of the NRTIs in second-line therapy is to choose the most logical combination depending on what was used in the first-line regimen. Residual activity of first-line NRTIs (with the possible exception of 3TC and FTC) is more likely if the earlier failure is detected and switching is implemented. Conversely, any new NRTIs may be compromised in the second-line regimen if there is late detection of failure and late switching. The recommended

NRTI sequencing is based on likely resistance mutations and the potential for retained antiviral activity.

If AZT + 3TC are used in the first-line regimen with sensitive monitoring and early switching, the NRTIs most likely to show activity are TDF and ddI. In the scenario of insensitive monitoring and late switching, TDF and ddI activity are less likely. If TDF + 3TC are used in first-line therapy, with early or late switching, the NRTIs with remaining activity are AZT and d4T (both very likely). Retained activity of 3TC is likely in the early switching scenario and less likely in the case of late switching. ABC and ddI are no longer recommended as preferred options in second-line regimens for adults. The panel concluded that there was no specific advantage in using ABC or ddI and their use added complexity and cost, but new data will be generated from ongoing trials.

Maintaining 3TC In the Second-line Regimen

One RCT conducted to examine this issue found no significant difference in the reduction of HIV-RNA in individuals who maintained 3TC in their second-line regimen, compared to those who did not. One observational study reported similar virological response among individuals with the M184V mutation (indicating resistance to 3TC and FTC) who subsequently took 3TC- or FTC-containing regimen compared to those who took a 3TC- or FTC-sparing regimen.

NRTIs for HIV/HBV Co-infection

Individuals with HIV/HBV co-infection who require treatment for their HBV infection and in whose case TDF + FTC failed in the first-line regimen, should continue NRTIs in the second-line regimen, irrespective of the selected second-line regimen, which should be AZT + TDF + FTC + bPI. This is necessary for anti-HBV activity and to reduce the risk of hepatic flares.

Selection of Boosted Protease Inhibitor

High value has been placed on using more simple second-line regimens and the availability of heat-stable formulations, and fixed-dose combinations. The recommended bPIs are equivalent in terms of efficacy. In studies of populations with PI resistance, there is growing support for the use of once-daily bPI regimens in which the ritonavir component is only 100 mg per day. Such regimens have fewer gastrointestinal side-effects and less metabolic toxicity than regimens that use ritonavir boosting at a dose of 200 mg per day. Generic heat-stable LPV/r is on the market

and can be procured in Belize. Alternative bPIs (SQV, IDV, FPV and DRV) are not available, as FDCs and are more expensive than the preferred option being given here. IDV has a high risk of toxicity and high pill burden and FPV is expensive.

Third-line Regimens

Box 5: Recommendations for third line regimens

1. National programmes will develop policies for third-line therapy, taking into consideration funding, sustainability and the provision of equitable access to ART.

(Conditional recommendation, low quality of evidence)

2. Third-line regimens should include new drugs likely to have anti-HIV activity, such as integrase inhibitors and second-generation NNRTIs and PIs.

(Conditional recommendation, low quality of evidence)

3. Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen.

(Conditional recommendation, very low quality of evidence)

Literature review of relevant studies provide limited evidence to guide third-line strategies in resource-limited settings as there are few studies of these newer agents in these settings. Data from RCTs, predominantly in developed countries, are available for boosted darunavir (DRV/r), etravirine and raltegravir. Taken together, these data support the efficacy of these agents in highly ART-experienced patients. The provision of third line regimens should not affect the provision of first-line and second-line ART. Therapy with newer agents is associated with a reduction in clinical progression and immunological deterioration. DRV/r has a higher genetic barrier to resistance compared to early-generation PIs and is active against multidrug-resistant HIV isolates. While high-level resistance to ETV following NVP or EFV failure appears uncommon, low-level resistance is common. For the Belize scenario, it was decided that 3rd line or salvage therapy would be provided on an individual basis, and would be upon the convening

of a special group to advise on the particular case. This select committee would then advise the National Programme on what specific ARVs would be procured for the case. The specific recommendations would take into account the historical use of ARVs and would be based on current evidence based medicine.

Table 9: Toxicities of third-line ARVs

Darunavir (DRV)	**Skin rash (10%) — DRV has a sulfonamide moiety; Stevens-Johnson syndrome and erythremamultiforme have been reported** **Hepatotoxicity** **Diarrhoea, nausea** **Headache** **Hyperlipidaemia** **Transaminase elevation** **Hyperglycaemia** **Fat maldistribution** **Possible increased bleeding episodes in patients with haemophilia**
Ritonavir (RTV) (as pharmacokinetic booster)	**GI intolerance, nausea, vomiting, diarrhoea** **Paresthesias — circumoral and extremities** **Hyperlipidaemia (especially hypertriglyceridaemia)** **Hepatitis** **Asthenia** **Taste perversion** **Hyperglycaemia** **Fat maldistribution** **Possible increased bleeding episodes in patients with haemophilia**
Raltegravir (RAL)	**Nausea** **Headache** **Diarrhoea** **Pyrexia** **CPK elevation**
Etravirine (ETV)	**Rash (2 % discontinuation because of rash during clinical trials)** **Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure** **Nausea**

HIV/Tuberculosis Co-infection

ART has been reported to reduce TB rates by up to 90% at the individual level, approximately 60% at the population level, and TB recurrence rates by 50%. Modelling suggests that the initiation of ART for all those with HIV/TB co- infection, if accompanied by high levels of coverage and ART adherence, reduces the number of TB cases, TB mortality rates and TB transmission at the population level.

Latent TB in HIV Co-Infected Patients

People with HIV that have latent TB infection can be protected from developing TB disease if they receive a daily dose of isoniazid for at least six months. Isoniazid preventative therapy (IPT) is an economical, relatively simple and highly effective measure that must be taken wherever TB and HIV coexist. Studies suggest that IPT can reduce the incidence of TB disease by at least 40 percent among people with HIV who test positive for TB on skin tests, and may decrease the burden of TB in the community at large. Programs providing care for persons with HIV should provide screening for active TB, treating those co-infected with TB and HIV, and providing preventive therapy to those who do not have the active disease but who are at risk.

- Test all HIV infected persons without a history of a positive PPD test; repeat annually.
- Positive PPD is considered: 5 mm induration at 48 to 72 hours.

Suggested Eligibility Criteria for IPT in HIV-Positive Persons:

PHIVs should be educated about the benefits of IPT as well as the side effects and risks. IPT should be offered to persons with HIV once active TB has been excluded if any of the following apply:

- Exposure to an infectious TB case
- Living in an area with a prevalence of latent TB infection estimated to be >30%, health care workers, prisoners, miners or other identified groups at high risk of acquiring or transmitting TB

- Mantoux tuberculin skin test result is ≥ 5 mm induration or (interferon gamma release assay test is positive) indicating latent TB infection
- Confirmed history of positive PPD without treatment or high risk exposure:
- Repeat PPD at 12 weeks and discontinue prophylaxis if negative at that time.

Screening for TB Should be Thorough to Ensure None of the Following Apply:

- Currently ill (new or worsening cough or sputum production, haemoptysis, night sweats, fever or measured weight loss of > 5%)
- Abnormal chest X-ray (even if TB has not been confirmed)
- History of alcohol use (daily alcohol use)
- Presence of jaundice or active hepatitis (acute or chronic)
- History of prior allergy or INH tolerance

Monthly Monitoring

Patients receiving IPT should be evaluated at least monthly to check three important issues:

1. Signs and symptoms of TB: If symptoms of tuberculosis should develop while taking IPT, isoniazid should be stopped immediately and patient referred for evaluation.
2. Side effects attributable to IPT may include liver toxicity, and peripheral neuropathy.
3. Adherence: Interruptions in therapy should be followed by counseling and an attempt should be made to understand and remove barriers to adherence.

Dosage of Isoniazid

The adult dose of isoniazid is 5 mg/kg (maximum 300 mg) daily for 6-9 months, self-administered or administered under the supervision of a treatment supporter. That is, INH 300 mg/day + pyridoxine 50 mg/day for a period of 9 months. The use of isoniazid with stavudine (d4T may increase the risk of peripheral neuropathy). To prevent peripheral neuropathy, administer pyridoxine 25-50 mg daily along with the isoniazid. For children, the isoniazid dose is 10 mg/kg body weight.

Box 6: ART regimens in the HIV-TB Co-infected Patient

1. Start ART in all HIV-infected individuals with active TB, irrespective of the CD4 cell count.

(Strong recommendation, low quality of evidence)

2. Start TB treatment first, followed as soon as possible by ART (and within the first eight weeks).

(Strong recommendation, moderate quality of evidence)

3. Use efavirenz (EFV) as the preferred NNRTI in patients starting ART while on TB treatment.

(Strong recommendation, high quality of evidence)

There is a reduction of early mortality from HIV/TB co-infection and the potential for reduction of TB transmission when all individuals with HIV are started earlier on ART. This results in improved morbidity/mortality, reduction of TB recurrence, and improved management of TB for co-infected HIV/TB patients. Recent studies have provided sufficient evidence to conclude that the early initiation of antiretrovirals for patients with low CD4 levels decrease the mortality associated with TB, thereby improving treatment outcomes. It is recommended that ART be initiated as soon as TB therapy is tolerated. Ideally, this may be as early as 2 weeks and not later than 8 weeks. There is limited data on the initiation of ART in patients with TB and CD4 counts of > 350 cells/mm^3.

Table 10: Suggested timing of HAART initiation in TB/HIV according to CD4

CD4 level	When to start
< 100	As soon as possible
100----350	As soon as possible, but can wait for a period of 2-8 wks after TB treatment due to drug-drug interactions, adherence, toxicity, and initial pill burden
>350	At physician's discretion

EFV is specifically recommended because of less interaction with rifampicin as compared to NVP. For HIV/TB coinfected individuals who are unable to tolerate EFV, an NVP-based regimen or a triple NNRTI (AZT + 3TC + ABC or AZT + 3TC + TDF) are alternative options. In the presence of rifampicin, no lead-in dose of NVP is required. Similarly, if patients temporarily change from NVP to EFV because they need to take rifampicin-containing TB therapy, and subsequently switch back to NVP on completion of TB treatment, no lead-in dosing of NVP is required.

Anti- Tuberculosis Drugs and Antiretrovirals Drug Interactions:

- NRTIs: No significant interaction with rifampicin and rifabutin
- NNRTIs: Efavirenz and rifampicin; EFV 800mg qd if > 60kg, 600mg qd< 60kg. Note: dosage modification may be necessary for EFV after 2 weeks. EFV standard dose and rifabutin 450mg daily.
- PIs: Rifampicin not recommended. Ideally use Rifabutin = 150mg 3 times per week with LPV/r at standard dose

Rifabutin

Drug interactions between rifampicin and boosted protease inhibitors (bPIs) prohibit the concomitant use of standard therapies for both HIV and TB. Rifampicin induces the cytochrome P450 enzyme system, lowering standard-dose bPI plasma concentrations by 75–90%. All bPIs (at standard doses) are contraindicated with rifampicin. LPV/r or SQV/r may be used with an adjusted, super boosted dose of RTV (LPV/r 400 mg/100 mg BID or SQV/r 400 mg/400 mg BID) or doubling the LPV/r daily dose (LPV/r 800 mg/200 mg BID) but this is associated with high levels of toxicity, and requires close clinical and laboratory monitoring. The recommendation to use LPV/r 800/200 mg BID is based on low-quality evidence and is associated with a similar level of toxicity to LPV/r 400 mg/100 mg BID. However, this option may be more feasible in RLS, as LPV/r is widely available but RTV as a sole formulation is not.

There is no comparable recommendation for ATV/r, a WHO-preferred bPI. Unlike rifampicin, rifabutin has minimal effect on bPI plasma concentrations. Studies report comparable safety and efficacy of rifabutin and rifampicin. However, evidence from RCTs comes largely from HIV-uninfected individuals, and data on the use of rifabutin with ART are limited to first-generation,

usually unboosted, PIs. The recommended dose of rifabutin in the presence of a bPI is 150 mg three times per week. However, it should be noted that this dose has been reported to result in inadequate rifabutin levels and acquired rifabutin resistance. The most common adverse events associated with rifabutin are: neutropenia, leucopenia, elevations of hepatic enzymes, rash, upper gastrointestinal complaints, and rarely uveitis. This involves a 6 month regime of first line antituberculars (see "Belize National TB Guidelines" for detailed information). Treatment for New Cases: 2 Months HRZE / 4 months HR and Retreatment: 2HRZES / 1HRZE / HRE

Table 11: Doses of first-line anti-tuberculosis drugs in adults and children

Drug	Recommended dose in mg/kg bodyweight (range)	
	Daily	**Three times weekly**
isoniazid (InH, H)	children: 10 (10-15)[a],max.300 mg/day adults: 5(4-6), max.300 mg/day	Children & adults: 10 (8-12),max.900 mg/dose
rifampicin (rIf, r)	children: 15 (10-20)[a,b],max. 600 mg/day adults: 10 (8-12), max. 600mg/day	Children & adults: 10 (8-12),max.600 mg/dose
pyrazinamide (PZa, Z)	children: 35 (30-40)[a], max. 2000 mg/day adults: 25 (20-30), max.2000 mg/day	Children & adults: 35 (30-40), max.3000 mg/dose
ethambutol(eMb, e)	children: 20 (15-25)[c], max.1000 mg/day adults: 15 (15-20), max.1600 mg/day	Children & adults: 30 (25-35), max. 2400 mg/dose
streptomycin[d] (SM,S)	Children & adults: 15 (12-18), max.1000 mg/day	Children & adults: 15 (12-18)

Anti-Tuberculosis Drug Regimens

a Daily dose recommendations for children as determined following review of existing pharmacokinetic studies and in consultation with pediatric pharmacology and TB experts www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf

b RIF dosages at the higher ranges may be preferable for children under 10 kilograms, and children with HIV infection or malnutrition

c The recommended daily dose of E is higher in children than in adults, because the pharmacokinetics are different (peak serum E concentrations are lower in children than in adults receiving the same mg/kg dose)

d Streptomycin should be avoided when possible in children because the injections are painful and irreversible auditory nerve damage may occur. The use of streptomycin in children is mainly reserved for the first 2 months treatment of TB meningitis. Streptomycin should also be avoided in patients with renal failure

because of increased risk of nephrotoxicity and ototoxicity. If streptomycin must be used, decrease frequency to two or three times per week, and monitor serum levels of the drug. Some sources recommend reduction of streptomycin dose to 10 mg/kg/day(max. 750mg/day) in patients > 59years of age. Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily (WHO Model Formulary 2008.www.who.int/selection_medicines/list/en/)

Adopted from the Caribbean Guidelines for the Prevention, Treatment, Care and Control of Tuberculosis and TB/HIV. PAHO

Hepatitis/HIV Co-Infection

Box 7: Recommendations for Hepatitis B/HIVco-infection

1. Start ART in all HIV/HBVco-infected individuals who require treatment for their HBV infection, (chronic active hepatitis), irrespective of the CD4 cell count or the WHO clinical stage.

(Strong recommendation, low quality of evidence)

2. Start TDF and FTC containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.

(Strong recommendation, moderate quality of evidence)

3. HIV infected patients should be tested for HBV to identify patients with HIV/HBV co-infection.

Observational data demonstrates that individuals with HIV/HBV co-infection have a three to six-fold increased risk of developing chronic HBV infection, an increased risk of fibrosis and cirrhosis and a 17-fold increased risk of death compared to HBV-infected individuals without HIV infection. Similarly, observational data supports a reduction in liver-related disease with earlier and HBV-active combination ART. ART should be started in all HBV co-infected patients who need treatment for their hepatitis B infection.

On the question of what ART to start in HIV/HBV co-infection, there is data from one RCT supporting the use of at least two agents with activity against HBV (TDF + FTC) in terms of improved HBV viral load response, and reduced development of HBV drug resistance.

HIV and Hepatitis C

Hepatitis C (HCV) co-infection is significantly associated with increased risk of death and advanced liver disease in HIV-positive individuals. HIV infection accelerates HCV-related disease progression and mortality. However, the reciprocal effect of HCV on the rate of HIV disease progression remains difficult to quantify because of the heterogeneity of study results. Laboratory capacity and treatment with ribavirin for HCV is not available in Belize. In anticipation that HCV testing may become available, it is to be noted that the initiation of ART in HIV/HCV co-infected people should follow the same principles and recommendations as in HIV-mono-infected individuals. However, patients should be closely monitored because of the increased risk of drug toxicities and drug interactions between some ARVs and anti-HCV drugs.

HIV and Chronic Liver Disease

All classes of ARV agents have been associated with liver toxicity, therefore, extra caution is warranted in prescribing HAART for patients with chronic liver disease. NVP and RTV have been associated with the highest risk of liver toxicity and should be avoided if other options exist, even though the risk of liver toxicity using low doses of RTV to boost another PI is not clear.

HIV and Other Infections

Opportunistic Infections

Prophylaxis against opportunistic infection (OI) is treatment given to HIV-infected individuals to prevent either a first episode of an OI (primary prophylaxis) or the recurrence of infection (secondary prophylaxis). Prophylaxis is recommended to prevent three important OIs: *Pneumocystis jiroveci* pneumonia (PCP), tuberculosis (TB), and toxoplasmosis. Prophylaxis is also recommended to prevent tuberculosis (TB) in patients with latent *Mycobacterium tuberculosis* infection (see section on TB/HIV co-infection).

Table 12: Prophylaxis of opportunistic infection

Pathogen	Indication	First choice
Pneumocystis pneumonia (PCP)	CD4 count <200 cells/μL or oropharyngeal candidiasis CD4 <14% or history of AIDS-defining illness CD4 count >200 but <250 cells/μL if monitoring CD4 count every 1–3 months is not possible	Trimethoprim-sulfamethoxazole (TMP-SMX), 1 DS PO daily; or 1 SS daily (TMP-SMX) 1 DS PO tiw
Toxoplasma gondii encephalitis	Toxoplasma IgG positive patients with CD4 count <100 cells/μL Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have toxoplasma serology retested if CD4 count decline to <100 cells/μL Prophylaxis should be initiated if seroconversion occurred	TMP-SMX, 1 DS PO daily **or** TMP-SMX 1 DS PO tiw ; or TMP-SMX 1 SS PO daily

Table 13: Treatment and Management of Opportunistic Infection

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance
Pneumocystis jiroveci pneumonia (PCP)	Preferred treatment for moderate to severe PCP Trimethoprim-sulfamethoxazole (TMP-SMX): 15–20 mg TMP and 75–100 mg SMX]/kg/day IV administered q6h or q8h, may switch to PO after clinical improvement Duration of therapy: 21 days Preferred treatment for mild to moderate PCP Same daily dose of TMP-SMX as above, administered PO in 3 divided doses; or TMP-SMX (160 mg/800 mg or DS) 2 tablets Duration of therapy: 21 days Preferred secondary prophylaxis TMP-SMX (160 mg/800 mg or DS) tablet PO daily; or TMP-SMX (80 mg/400 mg or SS) tablet PO daily
Toxoplasma gondii encephalitis (TE)	Preferred therapy Pyrimethamine 200 mg PO x 1, then 50 mg (<60 kg) to 75 mg (≥60 kg) PO daily plus sulfadiazine 1,000 mg (<60 kg) to 1,500 mg (≥60 kg) PO q6h plus leucovorin 10–25 mg PO daily (can increase 50 mg) Duration for acute therapy :At least 6 weeks; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks TMP-SMX (5 mg/kg TMP and 25 mg/kg SMX) IV or PO bid; or Preferred chronic maintenance therapy Pyrimethamine 25–50 mg PO daily plus sulfadiazine 2,000–4,000 mg PO daily (in two to four divided doses) plus leucovorin 10–25 mg PO daily
Treponema pallidum infection (syphilis)	Preferred therapy early stage (primary, secondary & early latent syphilis) Benzathine penicillin G 2.4 million units IM or 1 dose Preferred therapy late-latent disease (>1 year or of unknown duration, CSF examination ruled out neurosyphilis) Benzathine penicillin G 2.4 million units IM weekly for 3 doses Preferred therapy late-stage (tertiary – cardiovascular or gummatous disease) Rule out neurosyphilis before therapy with 3 doses of benzathine penicillin and obtain infectious diseases consultation to guide management Preferred therapy 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

	+/- benzathine penicillin G 2.4 million units IM weekly for 3 doses after completion of IV therapy
Candidiasis (mucosal)	Preferred therapy oropharyngeal candidiasis: initial episodes (7–14 day treatment) Fluconazole 100 mg PO daily; or Clotrimazole troches 10 mg PO 5 times daily; or Nystatin suspension 4–6 mL qid or 1–2 flavored pastilles 4–5 times daily Miconazole mucoadhesive tablet PO daily Preferred therapy esophageal candidiasis (14–21 days) Fluconazole 100 mg (up to 400 mg) PO or IV daily Itraconazole oral solution 200 mg PO daily Preferred therapy uncomplicated vulvovaginal candidiasis Oral fluconazole 150 mg for 1 dose Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days Preferred therapy fluconazole-refractory oropharyngeal candidiasis or esophageal candidiasis Itraconazole oral solution ≥200 mg PO daily Posaconazole oral solution 400 mg PO bid Preferred therapy complicated (severe or recurrent) vulvovaginal candidiasis Fluconazole 150 mg q72h x 2-3 doses Topical antifungal 7 days
Cryptococcal meningitis	Preferred induction therapy Amphotericin B deoxycholate 0.7 mg/kg IV daily plus flucytosine 100 mg/kg PO daily in 4 divided doses for at least 2 weeks; or Lipid formulation amphotericin B 4–6 mg/kg IV daily (consider for persons on therapy who have renal dysfunction or high likelihood of renal failure) plus flucytosine 100 mg/kg PO daily in 4 divided doses for at least 2 weeks Preferred consolidation therapy (after at least 2 weeks of successful induction – defined as significant clinical improvement & negative CSF culture) Fluconazole 400 mg PO daily for 8 weeks Preferred maintenance therapy Fluconazole 200 mg PO daily life long or until CD4+ count ≥200 cells/μL for >6 months as a result of ART

Histoplasma capsulatum infections	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 daily *Maintenance therapy* Itraconazole 200 mg PO tid for 3 days, then bid Preferred therapy for less severe disseminated disease *Induction and maintenance therapy* Itraconazole 200 mg PO tid for 3 days, then 200 mg PO bid Duration of therapy: at least 12 months Preferred therapy for meningitis *Induction therapy* (4–6 weeks) Liposomal amphotericin B 5 mg/kg/day *Maintenance therapy* Itraconazole 200 mg PO bid-tid for ≥1 year and until resolution of abnormal CSF findings Preferred therapy for long term suppression therapy In patients with severe disseminated or CNS infection and in patients who relapse despite appropriate therapy Itraconazole 200 mg PO daily
Cytomegalovirus (CMV) disease	Preferred therapy for CMV retinitis *For immediate sight-threatening lesions* Ganciclovir intraocular implant + valganciclovir 900 mg PO (bid for 14–21 days, then once daily) One dose of intravitrealganciclovir may be administered immediately after diagnosis until ganciclovir implant can be placed *For small peripheral lesions* Valganciclovir 900 mg PO bid for 14–21 days, then 900 mg PO daily Preferred chronic maintenance therapy (secondary prophylaxis) for CMV retinitis Valganciclovir 900 mg PO daily; or Ganciclovir implant (may be replaced every 6–8 months if CD4 count remains <100 cells/μL) + valganciclovir 900 mg PO daily until immune recovery Preferred therapy for CMV esophagitis or colitis Ganciclovir IV or foscarnet IV for 21–28 days or until resolution of signs and symptoms Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption Maintenance therapy is usually not necessary, but should be considered after relapses

	Preferred therapy CMV pneumonitis Treatment should be considered in patients with histologic evidence of CMV pneumonitis and who do not respond to treatment of other pathogens. The role of maintenance therapy has not been established Preferred therapy CMV neurological disease *Treatment should be initiated promptly* Combination of ganciclovir IV + foscarnet IV to stabilize disease and maximize response, continue until symptomatic improvement Maintenance therapy (with valganciclovir PO + IV foscarnet) should be continued for life unless evidence of immune recovery is evident
Herpes simplex virus (HSV) disease	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 Duration of therapy: Orolabial HSV: 5–10 days; Genital HSV: 5–14 days Preferred therapy for severe mucocutaneous HSV infections Initial therapy acyclovir 5 mg/kg IV q8h After lesions begin to regress, change to PO therapy as above 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 Preferred therapy for HSV encephalitis Acyclovir 10 mg/kg IV q8h for 21 days Suppressive therapy (For patients with frequent or severe recurrences of genital herpes) Valacyclovir 500 mg PO bid Famciclovir 500 mg PO bid Acyclovir 400 mg PO bid
Varicella zoster virus (VZV) disease	Varicella (chickenpox) *Uncomplicated cases* Acyclovir (20 mg/kg body weight up to a maximum of 800 mg PO 5x daily), valacyclovir 1,000 mg PO tid, or famciclovir 500 mg PO tid x 5–7 days *Severe or complicated cases* Acyclovir 10–15 mg/kg IV q8h x 7–10 days May switch to oral acyclovir, famciclovir, or valacyclovir after defervescence if no evidence of visceral involvement is evident Herpes zoster (shingles) *Acute localized dermatomal*

	Valacyclovir 1g tid or famciclovir 500 mg tid, or acyclovir 800 mg PO 5x daily x 7–10 days, 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 Switch to oral therapy (valacyclovir 1,000 mg tid or famciclovir 500 mg tid, or acyclovir 800 mg PO 5x daily) after clinical improvement is evident, to complete a 10–14 day course <u>Progressive outer retinal necrosis (PORN)</u> 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 Optimization of ART <u>Acute retinal necrosis (ARN)</u> Acyclovir 10 mg/kg IV q8h x 10–14 days, followed by valacyclovir 1,000 mg PO tid x 6 weeks
Human papillomavirus disease	Treatment of condyloma acuminata (genital warts) <u>Patient-applied therapy</u> 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; or Imiquimod 5% cream – apply to lesion at bedtime and remove in the morning on 3 non-consecutive nights weekly for up to 16 weeks. Each treatment should be washed with soap and water 6–10 hours after application.
Leishmaniasis, cutaneous	<u>Preferred therapy for acute infection</u> Liposomal amphotericin B 2–4 mg/kg IV daily for 10 days or interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg; or Sodium stibogluconate 2mg/kg IV or IM daily for 3–4 weeks

Adapted from US DHHS Guidelines for prophylaxis and management of opportunistic infections in adults and adolescents

Initiating ART in Acute Opportunistic Infections

In patients with opportunistic conditions for which there is no effective therapy, (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy) but for which ART may improve outcomes by improving immune responses, the benefits of ART outweigh any increased risk, and therefore treatment should be started as soon as possible. In the setting of opportunistic infections, such as cryptococcal meningitis or non-tuberculous mycobacterial infections, for which immediate therapy may increase the risk of immune reconstitution

inflammatory syndrome (IRIS), a short delay may be warranted before initiating ART. In the setting of other opportunistic infections, such as *Pneumocystis jiroveci* pneumonia (PCP), early initiation of ART is associated with increased survival, and therapy should not be delayed. In patients who have active tuberculosis, initiating ART within the first 2-8 weeks of treatment for tuberculosis has been shown to confer a significant survival advantage.

Immune Reconstitution Inflammatory Syndrome (IRIS)

For most patients, initiating ART improves immune responses to a wide range of opportunistic pathogens. However, a small percentage of patients develop inflammatory disease in response to specific opportunistic pathogens within a few weeks or months after initiating therapy. This exuberant inflammatory response has been called the immune reconstitution inflammatory syndrome (IRIS), also known as immune reconstitution syndrome (IRS) or immune reconstitution disease (IRD). The term IRIS is used to describe two distinct entities:

- An exacerbation of a partially or successfully treated opportunistic infection (OI), referred to as paradoxical IRIS
- A previously undiagnosed (subclinical) OI, referred to as unmasking IRIS

IRIS may occur in response to many pathogens, including *Mycobacterium tuberculosis*, *Mycobacterium avium* complex (MAC), cytomegalovirus (CMV), *Cryptococcus, Pneumocystis, Toxoplasma,* hepatitis B, and varicella-zoster virus. Many of the IRIS cases described in the medical literature occurred within a few months after initiating ART, and in the context of a rapid and marked rise in CD4 cell count from very low pre-treatment levels (often <50-100 cells/μL).

IRIS can also occur in the absence of ART, as has been reported during tuberculosis (TB) treatment. The specific mechanisms involved in the pathogenesis of IRIS are not well understood and may vary from one infection to another. However, experts believe that IRIS is caused by an enhanced immune response to disease-specific antigens, which leads to an overproduction of inflammatory mediators.

IRIS may be difficult to identify in clinical practice because the clinical presentation is nonspecific, and currently, there are no laboratory markers to identify the syndrome. To make the diagnosis of IRIS, the following must be excluded:

- Presence of a new OI or concomitant illness
- Failure of treatment for HIV infection (e.g., owing to poor adherence or drug resistance)
- Failure of treatment for a known OI (e.g., owing to drug resistance, inadequate treatment, or poor adherence)

The severity of IRIS varies widely, from mild to life-threatening. Treatment varies according to the specific pathogen and clinical situation, but typically includes continuing ART, if possible, treating the OI as indicated, and adding anti-inflammatory therapy as needed. Efforts should be made to diagnose as accurately as possible the pathogen(s) responsible, e.g. by aspirating and culturing lymphadenopathy. Key elements favouring the diagnosis of IRIS include:

- Low pre-treatment CD4 count
- 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

Management of the Patient with Suspected IRIS

1. Consider other possible aetiologies:

- Persistent active infection, e.g. OI treatment failure
- Adverse drug reaction(s)

2. Continue HAART

3. Attempt to diagnose the infection or condition responsible for IRIS

- Aspirate and culture any easily accessible abscesses or lymphadenopathy
- Obtain bacterial, mycobacterial, and (if available) fungal cultures

4. Initiate pathogen-specific therapy, if not already in place

- Development of IRIS does not require re-initiation of antimicrobial therapy, or change in maintenance therapy for the infection, if the patient is already on appropriate therapy
- Initiation of empiric therapy is reasonable for highly suspected conditions when the diagnosis is not immediately apparent

5. Provide anti-inflammatory therapy

- NSAIDs for mild-moderate cases (e.g. Ibuprofen, Naproxen, Diclofenac)
- Corticosteroids for moderate-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

HIV and Other Infectious Co-morbidities

Patients with HIV and Other Sexually Transmitted Infections (STIs)

Co-morbid STIs are commonly encountered in persons infected with HIV. Prompt diagnosis and treatment of STIs reduces the risk of HIV transmission to others. Recent data suggest that treatment of chronic herpes simplex virus (HSV) infections reduces the risk of HSV transmission, may reduce the risk of HIV transmission, and the level of HIV viraemia in patients not on HAART. (see Belize National Guidelines for the Management of Sexually Transmitted Infections)

Patients with HIV and Malaria

HIV infection appears to increase both the susceptibility to and the severity of malaria infection. Most of our understanding of the interaction between malaria and HIV is based on studies performed in Africa, primarily involving infection with *P. falciparum.* International literature suggest that HIV-infected patients appear to be more susceptible to acquiring malaria infection, particularly if they are pregnant. Both the prevalence of malaria parasitaemia and the incidence of clinical attacks of malaria are greater in patients with HIV-induced immunosuppression. Furthermore, the risks of severe malaria and malaria-related deaths appear to be significantly increased in HIV-infected patients of all ages who live in regions where malaria transmission is unstable. The influence of malaria on HIV infection is not fully characterized. However, malaria infection appears to increase the HIV viral load, which could result in an increased rate of HIV disease progression, as well as an increased risk of HIV transmission to others.

Appropriate treatment for malaria infection depends on several factors: the severity of infection, the responsible *Plasmodium* species (bearing in mind that mixed infections may occur), the pregnancy status of the patient, local antimalarial drug-resistance patterns, national drug policy and availability, and the likelihood of interactions or overlapping toxicities involving antimalarials and other medications the patient may be taking, including ARV agents and other medications used in the management of AIDS and its complications. The differential diagnoses of fever and anemia are broad in the HIV-infected patients. In order to avoid the unnecessary prescription (with resultant risks of toxicity and resistance) of antimalarials, it is important to ALWAYS HAVE laboratory confirmation of malaria infection prior to treatment, (other than prophylaxis in pregnancy) and to discourage patients from self-treatment with antimalarials.

Non-infectious Co-morbidities

Non-infectious co-morbidities include metabolic conditions in lipid abnormalities, insulin resistance and diabetes, cardiovascular, renal, hepatic, neoplastic, neuropsychiatric, anemia, and bone pathologies as well as depression. These co-morbidities are becoming increasingly important for HIV-infected persons as a consequence of increased life expectancy resulting from effective ART. Additionally, several demonstrated and proposed HIV-associated risk factors may contribute to their development including immune activation, inflammation and coagulation associated with (uncontrolled) replication of HIV, co-infections (e.g. HCV), ART itself and persistent immunodeficiency.

Health care professionals involved with the care of HIV-infected persons who are not familiar with the use of ART, should consult HIV specialists or experienced clinicians, before introducing or modifying any type of treatment that HIV-infected patients with these comorbidities receive. Conversely, HIV physicians who are not specialists in non-infectious co-morbidities, should seek expert advice where appropriate in the prevention and management of these conditions. Preventing or managing these diseases in HIV often involves multiple medications, which increases the risk of suboptimal adherence and may compromise the

continued benefit of ART. Additionally, the possibility of drug-drug interactions with ART should be carefully considered prior to introducing any treatment.

Metabolic Conditions, HIV and ART

A number of metabolic disturbances have been identified in HIV-infected patients on HAART. Patients who have initiated treatment for HIV infection should be monitored carefully for development of these complications, and managed appropriately as outlined below. The exact aetiology of these complications is not clearly understood, and may reflect a multifactorial process involving ART medications, HIV itself, and host factors.

Lactic Acidosis and Hepatic Steatosis

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

Clinically, this syndrome can range from asymptomatic hyperlactataemia to fatal lactic acidosis, often associated with hepatic steatosis. Development of this disorder appears to depend on the duration of NRTI exposure and on the specific ARVs used. Stavudine (d4T) appears to be most commonly associated with lactic acidosis, followed by ddI and AZT, followed by 3TC and ABC. TDF appears to carry a low risk of mitochondrial toxicity as well.

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

Lactic acidosis is treated with supportive care and discontinuation of ARVs until the syndrome resolves. Case reports have suggested that supplementation with high doses of vitamins involved in oxidative phosphorylation, such as riboflavin or L-carnitine, may hasten the recovery process. Following resolution of the syndrome, HAART should be re-initiated cautiously and in consultation with an HIV expert. NRTIs such as d4T and ddI that are strongly associated with mitochondrial toxicity should be avoided.

Lipohypertrophy, Lipodystrophy and Lipoatrophy

Abnormalities of body-fat distribution are a recognized complication of HIV infection and of ART, and are a common concern for patients. These abnormalities include central fat accumulation (lipohypertrophy) and subcutaneous fat wasting (lipoatrophy). These morphologic changes are often referred to as lipodystrophy, although that term fails to distinguish between the two phenomena. Abnormalities in fat distribution and body shape have been noted in up to 40-50% of patients treated with ART, but the incidence may be much lower with the use of newer, less lipotoxic, antiretroviral (ARV) medications and with earlier initiation of ART.

Lipohypertrophy and lipoatrophy are associated with other metabolic abnormalities such as, dyslipidemia and insulin resistance, and visceral fat accumulation is a risk factor for cardiovascular disease. Lipodystrophy refers to changes in body habitus associated with HIV infection and antiretroviral therapy. Lipoatrophy is typically apparent in the face and extremities; it has been associated with advanced HIV and NRTIs, especially d4T. Central fat deposits in the viscera, breasts, and dorsocervical fat pad (buffalo hump) have also been described, though the pathophysiology of lipohypertrophy remains unclear.

Routine screening for other metabolic abnormalities associated with the use of ARVs, such as dyslipidemias and impaired glucose metabolism (check fasting lipids and random or fasting blood sugar) should be part of the routine clinical monitoring of patients on ART. The optimal management of lipodystrophy is not known at this time. Lipoatrophy appears to improve, albeit very slowly, in patients who remove d4T from their ARV regimens and substitute NRTIs that have less potential for mitochondrial toxicity. Similar medication switch strategies have failed to consistently demonstrate a clinical benefit for patients with lipohypertrophy, even though improvements have been documented following dietary and exercise modifications. Cosmetic

plastic surgery options exist but are expensive and not widely available; furthermore, data regarding long-term outcomes are lacking.

Dyslipidemia

In the absence of ART, HIV infection can lead to dyslipidaemia, including lower HDL levels. HAART has been associated with elevated total cholesterol, LDL, and triglycerides. PIs (with the exception of ATV) have been most strongly associated with lipid abnormalities, though dyslipidaemia has also been documented in patients on NNRTI-based regimens as well as in regimens that include d4T. Recent data suggest that these abnormalities can lead to accelerated atherosclerosis and cardiovascular complications among HIV-infected persons. In general, patients with HIV/HAART-associated dyslipidaemia should be managed in a similar fashion as 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; atorvastation may also be used at reduced doses.

Insulin Resistance and Diabetes

Diabetes is a substantial risk factor for coronary artery disease, stroke, and peripheral vascular disease, as well as for a number of other conditions including retinopathy and kidney disease. Patients taking antiretroviral (ARV) medications, especially certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs), appear to have an increased risk of hyperglycemia and diabetes mellitus. In particular, the ARVs indinavir and stavudine have been shown to induce insulin resistance in short-term studies of healthy HIV-uninfected volunteers, but other ARVs can also affect glucose homeostasis. The etiology of insulin resistance and hyperglycemia in HIV-infected patients probably is multifactorial, with varying contributions from traditional risk factors (e.g., obesity, family history), comorbid conditions (e.g., hepatitis C virus infection), and ARV-related factors (e.g., direct effects of PIs, cumulative exposure to NRTIs, hepatic steatosis, and fat redistribution). Symptoms of hyperglycaemia have been reported as early as sixty days following initiation of PIs. EFV has also been associated with insulin resistance.

Disorders of glucose metabolism may present as the following:

- **Insulin resistance:** a state in which higher concentrations of insulin are required to exert normal effects; blood glucose levels may be normal but fasting insulin levels may be high because of compensatory insulin secretion by the pancreas
- **Impaired glucose tolerance:** glucose 140-199 mg/dL 2 hours after a 75 g oral glucose load
- **Impaired fasting glucose:** glucose 100-125 mg/dL after an 8-hour fast

Diabetes mellitus: any of the following three criteria may be used (results must be confirmed by retesting on a subsequent occasion): (a)Fasting glucose ≥126 mg/dL, (b) 2-hour glucose level ≥200 mg/dL during glucose tolerance testing, (c) Random glucose values ≥200 mg/dL in the presence of symptoms of hyperglycemia.

Patients with no History of Diabetes

These patients should be advised about the warning signs of hyperglycemia (polydipsia, polyuria, and polyphagia) and the need for healthy eating habits and routine exercise to maintain an ideal body weight. Routine fasting blood glucose measurements should be done every three to four months for patients with no previous history of diabetes that are receiving PIs or EFV. Closer monitoring of glucose levels should be performed for pregnant women receiving PIs. Patients should be counselled to recognize 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 supplementing the HAART regimen with oral hypoglycaemic agents or insulin.

Patients with HIV and Diabetes Mellitus

Many PIs, as well as the NNRTI EFV, have been associated with insulin resistance. Patients who have preexisting diabetes should be monitored closely when starting ART especially with PIs. Some experts would consider avoiding PIs for these patients, if other options are feasible. Ideally, PIs with favorable metabolic profiles (e.g., atazanavir) if available, may be preferred for such patients. The diabetic regimen may need to be intensified. Significant drug-drug interactions between ARVs and diabetic agents have not been described. The use of metformin

with NRTI-containing ARV regimens may in theory increase the risk of lactic acidosis, but this has not been clearly documented in clinical practice.

Neuropsychiatric Disorders

Significant drug-drug interactions exist between many ARVs and medications used to treat seizure disorders, bipolar affective disorder, and anxiety disorders. While some agents can be combined safely, as long as the dosage is adjusted appropriately, the use of certain agents in combination should be avoided altogether. Given its potential for neuropsychiatric side effects, EFV should be used with caution in patients with a history of an affective disorder. Patients identified with neuropsychiatric problems should be referred to a psychiatrist or to adequate mental services.

Sickle Cell Disease

Infection with encapsulated organisms is more common in Sickle Cell Disease (SCD) patients with functional asplenia. HIV co-infection also appears to increase susceptibility to these infections, especially in children. Prophylactic antibiotics, pneumococcal vaccine, and early identification and treatment of serious bacterial infections are therefore critical. The use of hydroxyurea (HU) in SCD is well established, and its suitability for treatment of HIV disease has been investigated. However, data from controlled clinical trials have revealed high rates of toxicity (e.g. pancreatitis, neuropathy, hepatotoxicity, and cytopaenias) and blunted CD4 cell count responses in patients receiving HU with antiretroviral therapy (ART). Current guidelines therefore suggest, that HU should generally not be offered as adjunctive therapy for HIV infection. Unfortunately, no data exists from controlled clinical trials involving patients with SCD who receive HU with ART. Clinicians considering the use of HU for HIV-infected patients with SCD should be aware of the potential additional toxicity of this agent when administered with NRTIs. Therapy is largely symptomatic for the sickle cell crisis. Standard interventions include rehydration, analgesics, and oxygen therapy. The presence of HIV infection in a patient suffering from a sickle cell crisis does not alter this general approach.

Anemia

Anemia is a common consequence of HIV disease, and some antiretroviral (ARV) agents, especially zidovudine (AZT). Therefore:

- Patients should be screened for anemia prior to initiation of ART
- The design of ARV regimens for patients at risk for anemia should take into account the potential of individual agents to induce or exacerbate anemia
- Monitoring of haemoglobin levels is warranted after initiation of therapy, especially for patients with SCD or other risk factors for anemia
- ARV-induced anemia typically improves once the offending agent is discontinued. Thus, appropriate modification of a patient's ARV regimen is advisable in the case of anemia that is attributable to one or more of the prescribed ARV agents.

HIV and Coronary Disease

The incidence of myocardial infarction or hospitalization for coronary heart disease (CHD) is increased two- to threefold in HIV-infected individuals, compared with age-matched controls without HIV infection. This increased risk of ischemic events is likely attributable to a higher prevalence of certain CHD risk factors that are independent of HIV status, such as smoking, as well as HIV infection and antiretroviral (ARV) medications. These various factors may interact in ways that are complex and incompletely understood. Among the traditional CHD risk factors, dyslipidemia is common among persons with HIV infection. Insulin resistance and diabetes also appear to be more prevalent in HIV-infected patients. A number of studies suggest that inflammation and immune activation as a result of uncontrolled HIV infection is also likely to contribute to atherosclerosis. Studies have suggested that initiation of ART leads to improvement of endothelial dysfunction (an early marker of atherosclerosis that is predictive of future CHD events) and leads to improvement in the markers of inflammation and immune activation. Earlier initiation of ART could reduce CHD risk. On the other hand, patients on ART, with virologic suppression, appear to have higher levels of various physiologic markers of cardiovascular risk than HIV-uninfected persons, perhaps owing to persistent immune activation.

Additionally, exposure to ARVs has been linked to risk of myocardial infarction in large cohort studies such as the D:A:D study. In particular, the risk has been associated with use of ARV regimens that are based on protease inhibitors (PIs), rather than non-nucleoside reverse transcriptase inhibitors (NNRTIs). The risk is attributable in part to adverse changes in lipid profiles, but there appears to be additional risk associated with PIs that is not accounted for by changes in lipids; this remains poorly understood. Among the nucleoside reverse transcriptase

inhibitors (NRTIs), abacavir and didanosine have been associated in some studies with increased risk of myocardial infarction. Clinicians should ask all patients about history of CHD and CHD risk factors, and should work closely with patients to reduce their risks of CHD events.

- For patients who smoke, smoking cessation is the single most important intervention to reduce risk of CHD events
- Manage dyslipidemia and hypertension by lifestyle intervention (e.g., sodium restriction, exercise, weight loss) and pharmacologic therapy as indicated
- Optimize glycemic control in patients with diabetes mellitus
- Encourage weight loss in overweight and obese patients, with referral to a dietitian as appropriate.
- Encourage exercise, ideally 30 minutes at moderate intensity 5-6 times per week, and a healthy diet that is low in saturated fats.
- Consider aspirin 81 mg once daily for primary prevention of CHD in patients at moderate to high risk who do not have contraindications to aspirin use.

HIV and Renal Disease

The prevalence of renal complications among patients with HIV infection has increased as more patients are living longer because of effective ART and opportunistic infection prophylaxis. More widespread access to, and earlier initiation of ART has decreased the incidence of HIV-associated nephropathy (HIV-AN). However, other causes of renal disease persist, and in some cases are increasing in prevalence. These may be infections and other conditions related to HIV infection, other comorbidities (e.g., hypertension, diabetes), or medication adverse effects, including those caused by some antiretroviral (ARV) medications.

Risk factors for renal disease in HIV-infected patients include the following:

- CD4 count <200 cells/μL
- HIV viremia, particularly RNA levels >4,000 copies/mL
- African descent
- Family history of kidney disease
- Use of nephrotoxins (including medications)

- Comorbidities
- Diabetes mellitus
- Hypertension
- Hepatitis C

Renal disease in HIV-infected individuals can occur as a primary disease, as a secondary disease in the setting of other systemic illnesses, or as an adverse effect of medications. Compared with seronegative individuals, HIV-infected patients are at a four-fold higher risk of developing diabetes mellitus and a threefold higher risk of developing hypertension, both of which are associated with renal disease. ART should be given to HIV-infected individuals with renal disease, according to usual criteria for ART initiation; however, some ARVs must be avoided and some should be given at modified dosages according to the degree of renal dysfunction. For patients with HIVAN, ART is the primary treatment.

HIV and Bone Metabolism:

HIV infected patients have 100 fold elevated risk of osteonecrosis compared with the general population. Osteopenia and osteoporosis are highly prevalent among patients with HIV infection. The cause is believed to be multifactorial in origin. In addition to the classical risk factors (low BMI, nicotine consumption, alcohol, steroids, hypogonadism, vitamin D deficiency) which are more frequent in patients with HIV, both ART and HIV infection affect bone metabolism. Loss of bone mineral density is associated with increased rates of bone fractures in persons with HIV, especially fractures of the spine, hips and wrists. Prophylaxis and treatment of bone loss should follow the recommendations for the general population.

HIV and the Elderly

The incidence and prevalence of HIV in the elderly population is increasing. There are several reasons why they are at risk of HIV infection. These are:

- Few HIV prevention campaigns target the elderly.
- Older people may not consider themselves at risk of HIV infection and would not seek an HIV test

- Health care providers may not consider the diagnosis in older patients, not deeming them at risk for HIV, and therefore not performing an HIV test when faced with symptoms suggestive of HIV disease.
- The introduction and usage of potency drugs has extended the sex lives of many elderly males. As a result, many older people lead sexually active lives. They may be involved in more than one sexual relationship including sex with sex workers, possibly without always using a condom. Older women may be especially at risk because age-related vaginal thinning and dryness can cause tears in the vaginal wall. Physicians need to ask their older patients about sexual activity and explain the importance of safe sex.
- The stigma of HIV may be perceived to be greater in the elderly population leading them to hide their diagnosis or avoid HIV testing.

Older patients have a weaker immune system than younger patients. Age has been shown to accelerate the progression of HIV to AIDS. Making a diagnosis of HIV to identify the disease, and referring the patient to HIV care and treatment, optimises prognosis. Patients treated with HAART have a significantly increased risk of other medical co-morbidities such as cardiovascular disease, dyslipidaemia and osteoporosis. In addition, HAART side effects and drug interactions are more common in the elderly population. Because of the delay in diagnosis, older patients may have higher viral load and lower CD4+ counts at the time of enrollment, and may never achieve the same CD4+ counts as younger patients. CD4+ cell reconstitution is significantly slower than in younger patients despite a better virologic response. However, older patients achieve lower viral loads than the under-50 group, possibly due to better adherence to treatment.

Side effects and toxicities of ARVs are more frequent in older patients who have more co-morbidities, and a higher chance of pharmacological interactions with concurrent medications. In addition, the rate of new co-morbidities (such as neuropathy, cardiovascular and metabolic disorders) is higher in older patients. This may be due to a combination of naturally occurring age-related events, and the toxic effects of anti-retrovirals 'acting synergistically with senescence. For example, coronary artery disease has been correlated with protease inhibitor-induced metabolic disturbances, and systemic hypertension may be related to atherosclerosis induced by HAART.

Special Considerations in the Elderly

- Promote HIV prevention, safe sex and discuss HIV risks with older patients; offer HIV tests to timely identify HIV infection in the elderly.
- An HIV test must be considered for older clients with symptoms and signs of HIV disease and co-morbid conditions that indicate an increased risk for HIV infection. If not done as yet, elderly patients who have chronic hepatitis B virus (HBV) or recent history of STDs should have HIV screening performed. 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 tuberculosis, recurrent herpes simplex (HSV) infections, gastrointestinal parasitosis, mucocutaneous candida, and fungal infections or molluscum contagiosum, may also 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 anemia, leukopenia (especially lymphopenia), thrombocytopenia, and elevated total protein, in the absence of other diagnoses, can also suggest HIV infection.
- Baseline investigations before initiating ART in the elderly must include screening for metabolic conditions including diabetes, cardiovascular disease, nephropathy dyslipidaemias, osteoporosis and other preexisting conditions. It is likely that the care provided will include management of other co-morbid conditions commonly associated with aging such as hypertension, diabetes, and hyperlipidemia.
- Attention must be paid to the ART regimen utilized to prevent worsening of the co-morbidity and drug interactions with medications utilized for existing conditions.
- Careful laboratory monitoring is important to identify any emerging co-morbidities and exacerbation of existing conditions.

HIV and Adolescents

Adolescence is defined as the period during which juveniles between 10 to 19 years of age undergo stages of physical, psychological and sexual maturation. These stages have implications for the provision of appropriate treatment and care for HIV-infected adolescents. An increasing number of HIV-infected adolescents are long-term survivors of HIV infection acquired perinatally, or in infancy through blood products. Such adolescents are usually heavily ART experienced. They may harbour resistant viruses and have a unique clinical course that differs from that of adolescents infected later in life.

Considerations and Challenges for Providing HIV Care and Treatment to Adolescents

Dosing

Based on the choice of ART regimen, the dosages for adolescents are based on sexual maturity rating (i.e. Tanner staging, Annex H):

- Adolescents in Tanner stage I, II, or III should be started on the pediatric schedule and monitored with particular care because they are undergoing hormonal changes associated with the growth spurt.
- Adolescents in Tanner stage IV or V are considered to be adults and therefore, the same recommendations and special considerations apply as for adults.

Antiretroviral Regimen

- EFV should not be used in adolescent girls who are at risk of becoming pregnant (i.e. are sexually active and not using adequate contraception) or those in the first trimester of pregnancy.
- Symptomatic NVP-associated hepatotoxicity or serious rash, while uncommon, is more frequent in females than in males, and is more likely to be seen in ARV-naive females with higher absolute CD4 cell counts (>250 cells/mm3). NVP should therefore be used with caution in adolescent girls with absolute CD4 counts greater than 250 cells/mm3. If used in such adolescent girls, careful monitoring, including liver enzymes, is needed during the first 12 weeks of therapy.

Adherence for Adolescents

Adherence to long-term therapy is particularly difficult among adolescents. In addition to providing routine adherence assessment and support, health-care providers should consider issues which are particularly relevant to adolescents and which may impair optimal adherence to ART. These include, the possible perception by adolescents of being immortal, their desire for independence, lack of disclosure of HIV status and stigma. The parents of adolescents who have become infected as infants or young children may find it hard to share the diagnosis of HIVwith their children. This is due to fear of stigma or blame from their children. However, without this knowledge, it is impossible for adolescents to progress completely through the transition process into adult care. Sharing this diagnosis with peers is difficult for adolescents who are aware of their HIV status.

HIV-infected adolescents are especially vulnerable to specific adherence problems based on their psychosocial and cognitive development. Comprehensive systems of care are required to serve the medical and psychosocial needs, and to cope with the challenges in adhering to medical regimens which may include:

- denial and fear of their HIV infection
- misinformation
- distrust of the medical establishment
- fear and lack of belief in the effectiveness of medications
- low self-esteem
- unstructured and chaotic lifestyles
- mood disorders and other mental illness
- lack of familial and social support
- absence of or inconsistent access to care
- disclosure of HIV status if this has not been done by their parents
- developmental delay
- the transition from pediatrics to adult care, including the choice of appropriate ART regimens

- physical and psychological changes associated with adolescence that have implications for the provision of appropriate HIV treatment and care.

In selecting treatment regimens for adolescents, clinicians must balance the goal of prescribing a maximally potent ART regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., beepers, timers, and pill boxes) that are stylish and inconspicuous. It is important to make medication adherence user friendly and as least stigmatizing as possible for the older child or adolescent.

Transitioning from Pediatric HIV Care

Given that HIV is a lifelong infection that requires treatment through several stages of growth and development, HIV care programs and providers need flexibility to appropriately transition care for HIV-infected children, adolescents, and young adults. Transitioning from pediatric HIV care to providing care for adolescents in clinics that cater for adults requires management and support by parents, guardians and health professionals.

In many instances adolescents are not aware of the health care systems and must be provided with an orientation. Adolescents require a more "teen-centered" and multidisciplinary approach which includes access to sexual and reproductive health, substance abuse treatment, mental health, treatment education, and adherence counseling services ideally in one clinic setting. In transitioning the care of emerging young adults, considerations of areas such as medical insurance, independence, autonomy, decisional capacity, confidentiality, and consent must be taken into account.

To maximize the likelihood of a successful transition, facilitators to successful transitioning include the following:

- optimizing provider communication from pediatric clinics
- addressing patient/family resistance caused by lack of information, stigma or disclosure concerns, and differences in practice styles
- preparing youth for life skills development, including counseling on the appropriate use of the health services, the importance of prompt symptom recognition and reporting, and the importance of self-care and medication management

- engaging in regular multidisciplinary case conferences between adult/adolescent and pediatric care providers
- implementing interventions that may be associated with improved outcomes, such as support groups and mental health consultations

Pediatric HIV Care

The implementation of the PMTCT programme has resulted in the reduction of pediatric HIV infection, however, in keeping with the universal access goals, quality HIV care continues to be provided to children who have become infected with HIV.

Early Diagnosis of HIV Infection in Infants and Children

<18 months of age

Use PCR as a screening assay to determine HIV exposure.

Use HIV DNA PCR to establish diagnosis.

- At birth (within 72 hours)
- At 6 weeks
- At 12 weeks

HIV virological assays used for the purpose of clinical diagnostic testing (usually at or after 6 weeks of age) have a sensitivity of at least 95% (ideally greater than 98%), and specificity of 98% or more, under quality-assured, standardized, and validated laboratory conditions.

>18 months of age

At 18 months a serological test is performed using ELISA methods.

Infants identified as HIV DNA PCR positive are recommended to initiate treatment as per the PMTCT guidelines.

All infants with unknown or uncertain HIV exposure (documented HIV test not available for the mother) being seen in health-care facilities at or around birth, or at the first postnatal visit (usually 4 – 6 weeks), or other child health visit, should be screened for HIV.

When to Start ART in Infants and Children

Infants and children <2 years of age: Start ART immediately upon diagnosis

Children ≥2 years and <5 years of age: ≤25% CD4 or CD4 count of ≤750 cells/mm3

Children ≥5 years of age: CD4 count of ≤500 cells/mm3

Current research demonstrates that the initiation of ART in early infancy and childhood dramatically reduces the risk of death and disease progression. Without effective treatment, an estimated one third of infected infants will have died by one year of age, and about half will have died by age two.

What to Start

Table 14: Preferred 1st and 2nd Line Regimens

Situation	Preferred 1st Line regimen	Preferred 2nd Line Regimen
Children with known infections	AZT + 3TC + NVP	ABC + dDI + LPV/r
Concomitant Conditions		
Child or adolescent with severe anemia	NVP + 2 NRTIs; **NO AZT D4T+3TC+NVP**	Boosted PI + 2NRTIs ABC + DDI + LP/r
Child or adolescent with TB	EFV + 2 NRTIs or 3 NRTIs AZT+3TC+EFV	Boosted PI + 2NRTIs AZT +3TC + ABC
Adolescent with hepatitis B	TDF + 3TC + NRTI TDF +3TC + EFV	Boosted PI + 2NRTIs TDF +3TC +LP/r

Clinical and Laboratory Monitoring in Children

For the clinical monitoring of children, the following should be included:

1. Growth, development and nutrition should be monitored monthly.
2. A baseline chest radiograph to allow assessment for respiratory complications, including lymphoid interstitial pneumonitis and TB.
3. Immunization should be administered as per PMTCT guidelines. See Annex 9.

Table 15: Laboratory Tests for HIV-Infected Children

Laboratory Test	Frequency
CD4 Count	• At the time of diagnosis of HIV infection • Every 3 months • If new clinical staging events develop or there is a failure to thrive clinically
Viral Loads	• As required or every six months • should be done to confirm clinical or immunological failure
FBC, Platelets & hemoglobin	• Every 3 months
Liver Function Tests	• Every 3 months: SGOT, SGPT, Total Bilirubin, Direct Bilirubin, Total Protein
Kidney Function Tests	• Every 3 months: BUN, Creatinine
Electrolytes	• Potassium, Sodium, Chloride
NOTE: **If child is on 2nd Line Regimen: also check cholesterol, triglyceride, uric acid, alkaline phosphate and amylase every 3 months.** **Urinalysis every 12 months, Tuberculin skin test every 12 months, electrocardiogram/echocardiogram every 3 to 5 years.**	

Adherence for Children

Regardless of their severity, adverse reactions may affect adherence to therapy. A proactive approach to managing toxicity is recommended. Discussing the potential side-effects of the ART regimen before initiation of therapy and during the early stages of treatment with the child and his or her caregivers, as well as offering support during minor and moderate adverse reactions, can increase the likelihood of adherence to therapy.

Many ARV drug toxicities are time-limited and resolve spontaneously even when the same ART regimen is continued. The child and caregivers should be familiar with the signs of toxicities that are serious and require immediate return to the health facility. This is particularly important for toxicities that can be life-threatening, including the NVP-associated Steven – Johnson syndrome, drug-induced hepatitis, lactic acidosis, pancreatitis, or ABC-associated hypersensitivity.

When to Switch to Second Line Regimen

- Clinical failure: Defined as the appearance or reappearance of WHO clinical stage 3 or stage 4 events after at least 24 weeks on ART in a treatment-adherent child.
- Immunological Failure:

  CD4 count of <200 cells/mm3 or %CD4+ <10 for a child ≥2 years to <5 years of age

  CD4 count of <100 cells/mm3 for a child 5 years of age or older.
- Virological failure: Defined as a persistent viral load above 5,000 RNA copies/ml, after at least 24 weeks on ART, in a treatment-adherent child.

Nutrition for HIV Infected Infants and Children

The importance of nutritional assessment and the nutritional requirements of infants and children on ART:

1.HIV-infected children who are symptomatic, whether on ART or not, have conditions requiring increased energy, (e.g. TB, chronic lung disease, chronic OIs or malignancies) have weight loss, or evidence of poor growth, should be provided with 25 – 30% additional calorie intake. A nutritionist should perform a follow up on these patients at the first opportunity.

2. HIV-infected children who are severely malnourished should be managed in the same way as uninfected children and be provided with 50 – 100% additional calorie intake. These patients **should also be managed in tandem with a nutritionist.**

3. HIV-infected children should receive one recommended daily allowance (RDA) of micronutrients daily. If this cannot be assured through the diet, or there is evidence of deficiency, then adequate supplementation should be given.

4. HIV-infected infants and children should receive high-dose vitamin A supplementation every 6 months if they are between 6 and 59 months of age. This is the same supplementation required for non-infected children.

5. HIV-infected children who have diarrhoea should receive zinc supplementation as a part of management.

Table 16: Type, frequency, and amounts of complementary foods required by age group

Age	Texture	Frequency	Amount at each meal*
6 months	Soft porridge; well-mashed vegetables, meat, or fruit	2 times a day plus frequent milk feeds	**2–3 tablespoons**
7–8 months	Mashed foods	3 times a day plus frequent milk feeds	**2/3 cup**+
9–11 months	Finely chopped or mashed foods, and foods that baby can pick up	3 meals plus 1 snack between meals plus milk feeds	**2/3 cup**+
12–24 months	Family foods, chopped or mashed if necessary	3 meals plus 2 snacks between meals plus milk feeds	**1 full cup**+
If baby is not breastfed, give in addition: 1–2 cups of milk per day, and 1–2 extra meals per day. + One cup = 250 mls			

HIV Drug Resistance in Children

Adding or substituting single drugs in a failing ART regimen without doing any resistance testing risks giving any new drug as ineffective therapy, which may result in rapid development of further resistance. It is therefore recommended that all changes in therapy with detectable viraemia be preceded by a resistance test, unless it is unequivocal that there is no cross-resistance with previous drugs received. Ideally resistance testing should be performed while the patient is still on the old regimen, or within a few weeks of stopping. Expert opinion should be sought in interpreting resistance genotypes.

NOTE: In the event of 2nd line regimen failure, the case should be reviewed on an individual basis by a select committee which woumd make specific recommendations for what is the best option as a third line/salvage therapy.

Special Consideration for Opportunistic Infections in Children

Tuberculosis

Isoniazid Preventive Therapy (IPT)

1. All HIV-infected infants and children exposed to TB through household contact, but with no evidence of active disease, should begin isoniazid preventive therapy (IPT).

2. Children with HIV (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.

3. Infants with HIV, 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.

4. The recommended dose of isoniazid (INH) for preventive therapy in HIV co-infection is 10 mg/kg/ daily for 6 months (maximum 300 mg/day).

Infants and Children Diagnosed with TB and HIV Co-Infection

Any child with active TB disease should begin TB treatment immediately, and should start ART as soon as tolerated and within the first 8 weeks of having started TB therapy, irrespective of their CD4 count and/or 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 ZDV + 3TC + NVP.
- The preferred first-line ARV regimen for children more than 3 years of age who are taking a rifampicin- containing regimen is ZDV + 3TC + EFV.

For all HIV-infected children, anti-TB therapy should be started immediately upon the diagnosis of TB; and ART should continue as per prescribed regimen. Make adjustments to ART regimens as needed to decrease the potential for toxicities and drug interactions:

If on a regimen of 2 NRTIs + NVP, substitute EFV for NVP if child is 3 years of age.

If on a regimen of 2 NRTIs + NVP and substitution with EFV is not possible, ensure NVP is dosed at the maximum dose of 200 mg/m2 per dose twice daily.

If on a regimen of LPV/r, consider adding RTV to a 1:1 ratio of LPV: RTV to achieve the full therapeutic dose of LPV. Regimen for TB is 2 NRTIs + EFV.

Prophylaxis to Prevent Opportunistic Infection in Children

Pneumocystis Pneumonia (PCP)

Co-Trimoxazole: (Trimethoprim/sulfamethoxazole) prophylaxis

NOTE: HIV infected infants 1 -12 months: prophylaxis is indicated for **all** regardless of CD4 count or clinical status.

1 -5 years with CD4 count <500
6 -12 years with CD4 count <200

Table 17: Co-trimoxazole dosage for children

Co-Trimoxazole dosage—single dose per day				
Age	**Weight**	**Suspension:**(40mg TMP/200mg SMX per 5ml)	**Adult Tablet:** (80mg TMP/400mg SMX)	**Adult Tablet:** (80mg TMP/400mg SMX)
<6months	<5kg	2.5ml	-	-
6months – 5yrs	5-15kg	5ml	½ tablet	-
6 -14yrs	15-30kg	10ml	1 tablet	½ tablet
>15 yrs	>30kg	NIL	2 tablet	1 tablet

Mycobacterium Avium

Azithromycin is given.

Table 18: Azithromycin dosing in children

Age	Weight	Dosage
≥6 yrs with CD4 count <50	<5 kg	20 mg/kg
2 yr to 5 yr with CD4 count <75	5-15 kg	20 mg/kg
1 yr to 2 yr with CD4 count <500	15-30 kg	20 mg/kg
<1 yr with CD4 count <750	>30 kg	20 mg/kg

NOTE: The Formula for figuring out Body Surface Area (BSA):
Ht (cm) Wt (kg) then take the square root (√) of this number to get the BSA. **If no Height is available another formula can be used that is usually quite close to the actual BSA is: Wt (kg) x 4 + 7;** Wt (kg) +9

Annex 1: WHO Clinical Staging of HIV Disease in Adults and Adolescents

Primary HIV infection
Asymptomatic **Acute retroviral syndrome**
Clinical stage 1
Asymptomatic **Persistent generalized lymphadenopathy**
Clinical stage 2
Moderate unexplained weight loss (under 10% of presumed or measured body weight) **Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)** **Herpes zoster** **Angular cheilitis** **Recurrent oral ulceration** **Papular pruritic eruptions** **Seborrhoeic dermatitis** **Fungal nail infections**
Clinical stage 3
Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations • **Unexplained chronic diarrhoea for longer than one month** • **Unexplained persistent fever (intermittent or constant for longer than one month)** • **Severe weight loss (>10% of presumed or measured body weight)** • **Oral candidiasis** • **Oral hairy leukoplakia** • **Pulmonary tuberculosis (TB) diagnosed in last two years** • **Severe presumed bacterial infections (e.g. pneumonia, empyema, meningitis, bacteraemia, pyomyositis, bone or joint infection)** • **Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis** ***Conditions where confirmatory diagnostic testing is necessary*** • **Unexplained anaemia (< 80 g/l), and or neutropenia (<500/µl) and or thrombocytopenia (<50 000/ µl) for more than one month**
Clinical stage 4
Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations • **HIV wasting syndrome** • **Pneumocystis pneumonia** • **Recurrent severe or radiological bacterial pneumonia** • **Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)** • **Oesophageal candidiasis**

- **Extrapulmonary Tuberculosis**
- **Kaposi's sarcoma**
- **Central nervous system toxoplasmosis**
- **HIV encephalopathy**

Conditions where confirmatory diagnostic testing is necessary

- **Extrapulmonary cryptococcosis including meningitis**
- **Disseminated non-tuberculous mycobacteria infection**
- **Progressive multifocal leukoencephalopathy**
- **Candida of trachea, bronchi or lungs**
- **Cryptosporidiosis**
- **Isosporiasis**
- **Visceral herpes simplex infection**
- **Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)**
- **Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)**
- **Recurrent non-typhoidal salmonella septicaemia**
- **Lymphoma (cerebral or B cell non-Hodgkin)**
- **Invasive cervical carcinoma**
- **Visceral leishmaniasis**

Source: *Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance.* 2006.

Annex 2: Dosages of Recommended Antiretrovirals

Generic name	Dose
Nucleoside reverse transcriptase inhibitors (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 once daily
Stavudine (d4T)	30 mg twice daily
Zidovudine (AZT)	250−300 mg twice daily
Nucleotide reverse transcriptase inhibitors (NtRTIs)	
Tenofovir	300 mg once daily[1]
Non-nucleoside reverse transcriptase inhibitors (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[2]
Proteases inhibitors (PIs)	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg once daily
Darunavir + ritonavir (DRV/r)	600 mg + 100 mg twice daily
Fos-amprenavir + ritonavir (FPV/r)	700 mg + 100 mg twice daily
Indinavir + ritonavir (IDV/r)	800 mg + 100 mg twice daily
Lopinavir/ritonavir (LPV/r)	400 mg + 100 mg twice daily[3]
	Considerations for individuals on TB therapy In the presence of rifabutin, no dose adjustment required In the presence of rifampicin; use ritonavir superboosting (LPV 400 mg + RTV 100 mg twice daily) or LPV 800 mg + RTV 200 mg twice daily, with close clinical and hepatic enzyme monitoring
Integrase strand transfer inhibitors (INSTIs)	
Raltegravir (RAL)	400 mg twice daily

[1]TDF dosage adjustment for individuals with altered creatinine clearance (using Cockcroft-Gault formula).
Creatinine clearance ≥50 ml/min, 300 mg once daily.
Creatinine clearance 30−49 ml/min, 300 mg every 48 hours.
Creatinine clearance ≥10−29ml/min (or dialysis), 300 mg once every 72−96 hours.
Cockcroft-Gault formula: *GFR = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr)*
[2]In the presence of rifampicin, or when patients switch from EFV to NVP, no need for lead-in dose of NVP.
[3] LPV/r can be administered as 4 tablets once daily (i.e. LPV800 mg + 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.

Annex 3: Toxicities and Recommended Drug Substitutions

ARV drug	Common associated toxicity	Suggested substitute
TDF	Asthenia, headache, diarrhoea, nausea, vomiting, flatulence Renal insufficiency, Fanconi syndrome Osteomalacia Decrease in bone mineral density Severe acute exacerbation of hepatitis may occur in HBV co-infected patients who discontinue TDF	**<u>If used in first-line therapy</u>** **AZT (or d4T if no other choice)** **<u>If used in second-line therapy</u>** **Within a public health approach, there is no option If patient has failed AZT/d4T in first-line therapy. If feasible, consider referral to a higher level of care where individualized therapy may be available**
AZT	Bone marrow suppression: macrocytic anemia or neutropaenia Gastrointestinal intolerance, headache, insomnia, asthenia Skin and nail pigmentation Lactic acidosis with hepatic steatosis	**<u>If used in first-line therapy</u>** **TDF (or d4T if no other choice)** **<u>If used in second-line therapy</u>** **d4T**
EFV	Hypersensitivity reaction Stevens-Johnson syndrome Rash Hepatic toxicity Persistent and severe CNS toxicity (depression, confusion) Hyperlipidaemia Male gynaecomastia Potential teratogenicity (first trimester of pregnancy or women not using adequate contraception)	**NVP** **bPI if intolerant to both NNRTIs** **Triple NRTI if no other choice**
NVP	Hypersensitivity reaction Stevens-Johnson syndrome Rash Hepatic toxicity Hyperlipidaemia	**EFV** **bPI if intolerant to both NNRTIs** **Triple NRTI if no other choice**
ATV/r	Indirect hyperbilirubinaemia Clinical jaundice Prolonged PR interval — first degree symptomatic AV block in some patients Hyperglycaemia Fat maldistribution Possible increased bleeding episodes in individuals with haemophilia Nephrolithiasis	**LPV/r**

LPV/r	**GI intolerance, nausea, vomiting, diarrhoea** **Asthenia** **Hyperlipidaemia (especially hypertriglyceridaemia)** **Elevated serum transaminases** **Hyperglycaemia** **Fat maldistribution** **Possible increased bleeding episodes in patients with haemophilia** **PR interval prolongation** **QT interval prolongation and torsade de pointes**	**ATV/r**

Annex 4: ARV-Related Adverse Events and Recommendations

Symptom-directed toxicity management table

Adverse events	Major first-line ARVs	Recommendations
Acute pancreatitis	d4T	Discontinue ART. Give supportive treatment with laboratory monitoring. Resume ART 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, symptomatic care. EFV rash often stops spontaneously after 3–5 days without need to change ART. 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 ART and give supportive treatment. After resolution, resume ART with a bPI-based regimen.
Dyslipidaemia	All NRTIs (particularly d4T) EFV	Consider replacing the suspected ARV
Anemia and neutropaenia	AZT	If severe (Hb <7.0 g/dl and/or ANC <750 cells/mm^3), replace with an ARV with minimal or no bone marrow toxicity (e.g. d4T or TDF) and consider blood transfusion
Hepatitis	All ARVs (particularly NVP)	If ALT is at more than five times the basal level, discontinue ART and monitor. After resolution, restart ART, replacing the causative drug (e.g . EFV replaces NVP).
Lactic acidosis	All NRTIs (particularly d4T)	Discontinue ART and give supportive treatment. After resolution, resume ART with TDF.
Lipoatrophy and lipodystrophy	All NRTIs (particularly d4T)	Early replacement of the suspected ARV drug (e.g. d4T for TDF or AZT)
Neuropsychiatric changes	EFV	Usually self-limited, without the need to discontinue ART. If intolerable to the patient, replace NVP with EFV or bPI. Single substitution recommended without cessation of ART.
Renal toxicity (renal tubular dysfunction)	TDF	Consider substitution with AZT
Peripheral neuropathy	d4T	Replacement of d4T with AZT, TDF. Symptomatic treatment (amitriptyline, vitamin B6).

Annex 5: Diagnostic Criteria for HIV-Related Clinical Events

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical stage 1		
Asymptomatic	No HIV-related symptoms reported and no signs on examination	**Not applicable**
Persistent generalized lymphadenopathy	Painless enlarged lymph nodes >1 cm, in two or more noncontiguous sites (excluding inguinal), in absence of known cause and persisting for 3 months or longer	**Histology**
Clinical stage 2		
Moderate unexplained weight loss (under 10% of body weight)	Reported unexplained weight loss. In pregnancy, failure to gain weight	**Documented weight loss (under 10% of body weight)**
Recurrent bacterial upper respiratory tract infections (current event plus one or more in last 6 months)	Symptoms complex, e.g. unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media), or tonsillopharyngitis without features of viral infection (e.g. coryza, cough)	**Laboratory studies if available, e.g. culture of suitable body fluid**
Herpes zoster	Painful vesicular rash in dermatomal distribution of a nerve supply does not cross midline	**Clinical diagnosis**
Angular cheilitis	Splits or cracks at the angle of the mouth not attributable to iron or vitamin deficiency, and usually responding to antifungal treatment	**Clinical diagnosis**
Recurrent oral ulcerations (two or more episodes in last 6 months)	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey pseudomembrane	**Clinical diagnosis**
Papular pruritic eruption	Papular pruritic lesions, often with marked postinflammatory pigmentation	**Clinical diagnosis**
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin)	**Clinical diagnosis**
Fungal nail infections	Paronychia (painful red and swollen nail bed) or onycholysis (separation of nail from nail bed) of the fingernails (white discolouration, especially involving proximal part of nail plate, with thickening and separation of nail from nail bed)	**Fungal culture of nail / nail plate material**
Clinical stage 3		
Severe unexplained weight loss (more than 10% of body weight)	Reported unexplained weight loss (over 10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass	**Documented loss of more than 10% of body weight**

	index below 18.5. In pregnancy, weight loss may be masked.	
Unexplained chronic diarrhoea for longer than 1 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, and two or more stool tests reveal no pathogens**
Unexplained persistent fever (intermittent or constant and lasting 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, without other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	**Documented fever exceeding 37.6 ^{o}C with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection**
Oral candidiasis	Persistent or recurring creamy white curd-like plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	**Clinical diagnosis**
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue, which do not scrape off	**Clinical diagnosis**
Pulmonary TB (current)	Chronic symptoms (lasting at least 2 to 3 weeks): cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats, plus EITHER positive sputum smear OR negative sputum smear AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, cavitation, pulmonary fibrosis and shrinkage). No evidence of extrapulmonary disease.	**Isolation of *M. tuberculosis* on sputum culture or histology of lung biopsy (together with compatible symptoms)**
Severe bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)	Fever accompanied by specific symptoms or signs that localize infection, and response to appropriate antibiotic	**Isolation of bacteria from appropriate clinical specimens (usually sterile sites)**
Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, rapid loss of bone and/or soft tissue	**Clinical diagnosis**

Unexplained anemia (below 8g/dl), neutropenia (below 0.5 × 10^9/l) or chronic (more than 1 month) thrombocytopenia (under 50 × 10^9/l)	No presumptive clinical diagnosis	**Diagnosed on laboratory testing and not explained by other non-HIV conditions. Not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in relevant national treatment guidelines, WHO IMCI guidelines or other relevant guidelines.**
Clinical stage 4		
HIV wasting syndrome	Reported unexplained weight loss (over 10% of body weight) with obvious wasting or body mass index below 18.5, plus EITHER unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than 1 month OR reports of fever or night sweats for more than 1 month without other cause and lack of response to antibiotics or antimalarials. Malaria must be excluded in malarious areas.	**Documented weight loss (over 10% of body weight)** **Plus two or more unformed stools negative for pathogens** **OR** **documented temperature exceeding 37.6 °C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged CXR**
***Pneumocystis* pneumonia**	Dyspnoea on exertion or nonproductive cough of recent onset (within the past 3 months), tachypnoea and fever; AND CXR evidence of diffuse bilateral interstitial infiltrates, AND no evidence of bacterial pneumonia. Bilateral crepitations on auscultation with or without reduced air entry.	**Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue**
Recurrent bacterial pneumonia (this episode plus one or more episodes in last 6 months)	Current episode plus one or more episodes in last 6 months. Acute onset (under 2 weeks) of symptoms (e.g. fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or CXR. Response to antibiotics.	**Positive culture or antigen test of a compatible organism**
Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal) of more than 1 month, or visceral of any duration	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrent HSV infection and reported for more than one month. History of previous episodes. Visceral HSV requires definitive diagnosis.	**Positive culture or DNA (by PCR) of HSV or compatible cytology / histology**
Oesophageal candidiasis	Recent onset of retrosternal pain or	**Macroscopic appearance at**

	difficulty in swallowing (food and fluids) together with oral candidiasis	**endoscopy or bronchoscopy, or by microscopy/histology**
Extrapulmonary TB	Systemic illness (e.g. fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated TB varies by site: pleural, pericardial, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy, osteitis. Miliary TB: diffuse uniformly distributed small miliary shadows or micronodules on CXR. Discrete cervical lymph node *M. tuberculosis* infection is usually considered a less severe form of extrapulmonary tuberculosis.	***M. tuberculosis* isolation or compatible histology from appropriate site, together with compatible symptoms/signs (if culture/histology is from respiratory specimen there must be other evidence of extrapulmonary disease)**
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat patches with a pink or blood-bruise colour, skin lesions that usually develop into violaceous plaques or nodules	**Macroscopic appearance at endoscopy or bronchoscopy, or by histology**
CMV disease (other than liver, spleen or lymph node)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	**Compatible histology or CMV demonstrated in CSF by culture or DNA (by PCR)**
CNS toxoplasmosis	Recent onset of a focal neurological abnormality or reduced level of consciousness AND response within 10 days to specific therapy.	**Positive serum toxoplasma antibody AND (if available) single/multiple intracranial mass lesion on neuroimaging (CT or MRI)**
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	**Diagnosis of exclusion, and, if available, neuroimaging (CT or MRI)**
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasingly severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	**Isolation of *Cryptococcus neoformans* from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF/blood**
Disseminated non-	No presumptive clinical diagnosis	**Diagnosed by finding**

tuberculous mycobacteria infection		**atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding lung**
Progressive multifocal leukoencephalopathy (PML)	No presumptive clinical diagnosis	**Progressive neurological disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuroimaging or positive polyomavirus JC (JCV) PCR on CSF**
Cryptosporidiosis (with diarrhoea lasting more than 1 month)	No presumptive clinical diagnosis	**Cysts identified on modified ZN microscopic examination of unformed stool**
Chronic isosporiasis	No presumptive clinical diagnosis	**Identification of *Isospora***
Disseminated mycosis (coccidiomycosis, histoplasmosis)	No presumptive clinical diagnosis	**Histology, antigen detection or culture from clinical specimen or blood culture**
Recurrent non-typhoid salmonella bacteraemia	No presumptive clinical diagnosis	**Blood culture**
Lymphoma (cerebral or B cell non-Hodgkin) or other solid HIV- associated tumours	No presumptive clinical diagnosis	**Histology of relevant specimen or, for CNS tumours, neuroimaging techniques**
Invasive cervical carcinoma	No presumptive clinical diagnosis	**Histology or cytology**
Visceral leishmaniasis	No presumptive clinical diagnosis	**Histology (amastigotes visualized) or culture from any appropriate clinical specimen**
HIV-associated nephropathy	No presumptive clinical diagnosis	**Renal biopsy**
HIV-associated cardiomyopathy	**No presumptive clinical diagnosis**	**Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography**

Source: Revised WHO *Clinical staging and immunological classification of HIV and case definition of HIV for surveillance*. 2006.

Annex 6: Dosing of Pediatric Antiretrovirals

Initial ART for Pediatrics

Zidovudine (AZT) supplied in 50 mg / 5 ml suspension, or available in 300 mg tablet in combination with Lamivudine 150 mg (Duovir, Combivir)

Premature Babies	**1.5 mg/kg BID until 2 weeks of age; then 2 mg/kg TID until 6 weeks of age**
Full term babies	4 mg/kg BID for 6 weeks
6 wks to 13 yrs:	180 – 240 mg/m²/BID
Adolescent:	Adult dose (300mg BID)

Note: No food restrictions

Side effects: Anemia, neutropenia, cardiomyopathy, restlessness, mild headaches, nausea, fatigue. Monitor: CBC

Lamivudine (3TC) supplied in 50 mg /5 ml suspension

Recommended dosage:

Infants, < 30 days:	**2 mg/kg BID**
1 month – 12 years:	4 mg/kg BID, maximum of 150 mg/BID
Adolescents, wt<50kg:	4 mg/kg BID
Adolescents, wt>50kg:	Adult dose (150mg BID)

NOTE: No food restrictions; side effects: Pancreatitis, headache, GI upset, fatigue

Nevirapine (NVP) supplied in 50 mg/ 5 ml suspension or 200 mg tablets

PMTCT: 2mg/kg once immediately after birth

Recommended dosage:

Age	Dosage
2 months to 8 years:	7 mg/kg BID *initial dose 4mg/kg/daily x 14 days then advance
8 years and older:	4 mg/kg BID, not to exceed 400 mg for total daily dose *initial dose 4 mg/kg/daily x 14 days then advance
Adolescent:	Adult dose (200 mg BID)

WHO recommends 120-200 mg/m² BID, but the above recommended dosages is what is currently being used in Belize.

No food restrictions are applicable

Side effects: Hepatotoxicity, Rash (within first 6 weeks of treatment) that can evolve to severe Stevens-Johnson syndrome

Side effects of combination therapy (not attributed to one particular ARV) are changes in distribution of body fat that may include: loss of fat in legs, arms and face, and an increase of stomach fat, breast size and "buffalo hump."

2nd Regimen for Pediatric Antiretroviral Therapy

Abacavir (supplied in 20 mg/ml suspension)

Recommended dosage:

Age	Dosage
3 months to 16 yrs:	8 mg/kg/BID
16 yrs and older:	adult dose (300 mg BID)

No Food Restrictions

Side effects: Hypersensitivity in 8% of patients that can be life-threatening—rash, fever, abdominal pain, nausea, vomiting (usually occur in first 3 weeks of initiation)

Monitor: CBC, Creatinine clearance

Didanosine (100 mg chewable tablets or 125 – 250 tablet presentation)

Recommended dosage:

Age	Dosage
8 months to 12 years:	120 mg/m²/BID
Adolescents, wt > = 60 kg:	Adult dose (250 mg/BID as buffered powder)

To be taken on empty stomach, must be refrigerated once powder is mixed with antacid.

Side effects: Diarrhea, peripheral neuropathy, diarrhea, abdominal pain, nausea

Monitor: Potassium, uric acid, CBC, PLA, LFT's, Bilirubin, albumin

Kaletra (Lopinavir/Ritonavir) supplied in 80 mg / 20 mg suspension

Recommended dosage:

Weight	Dosage
7-15 kg:	12/3 mg/kg/BID
15-40 kg	10/2.5 mg/kg/BID
>40 kg:	Adult dose (400/100 mg BID)

Suspension to be taken WITH FOOD (has a very bad taste and children c/o "burning sensation," which may makie it very difficult to have optimal adherence with this medication, some children have vomiting due to medication. Must be refrigerated.

Side effects: elevated cholesterol and triglycerides, liver toxicity, exacerbation or new onset diabetes mellitus, nausea, diarrhea, abnormalities in body fat distribution

Monitor: Triglycerides, cholesterol, LFT's, electrolytes, glucose

Annex 7: Tanner Stages of Physical Development

Definitions of Stages

Pubic Hair (male)

Tanner I

no pubic hair at all (prepubertal Dominic state) [typically age 10 and younger]

Tanner II

small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females) [10–11.5 yrs]

Tanner III

hair becomes more coarse and curly, and begins to extend laterally [11.5–13 yrs]

Tanner IV

adult-like hair quality, extending across pubis but sparing medial thighs [13–15 yrs]

Tanner V

hair extends to medial surface of the thighs [15+]

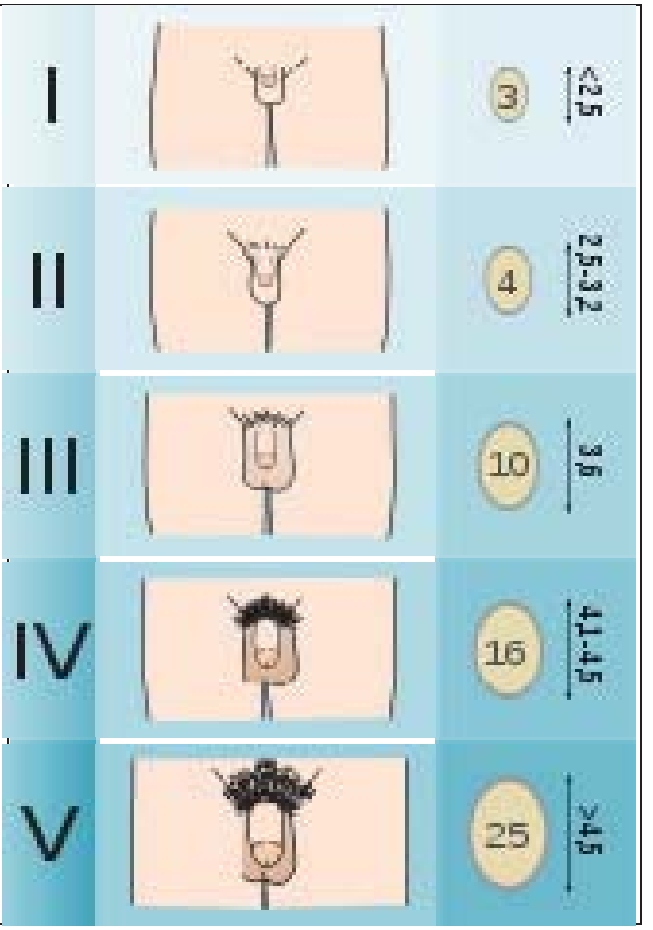


Illustration of the Tanner scale for males. Adapted from text by Lawrence Neinstein, MD

Genitals (male)

Tanner I

prepubertal (testicular volume less than 1.5 ml; small penis of 3 cm or less) [typically age 9 and younger]

Tanner II

testicular volume between 1.6 and 6 ml; skin on scrotum thins, reddens and enlarges; penis length unchanged [9-11 yrs]

Tanner III

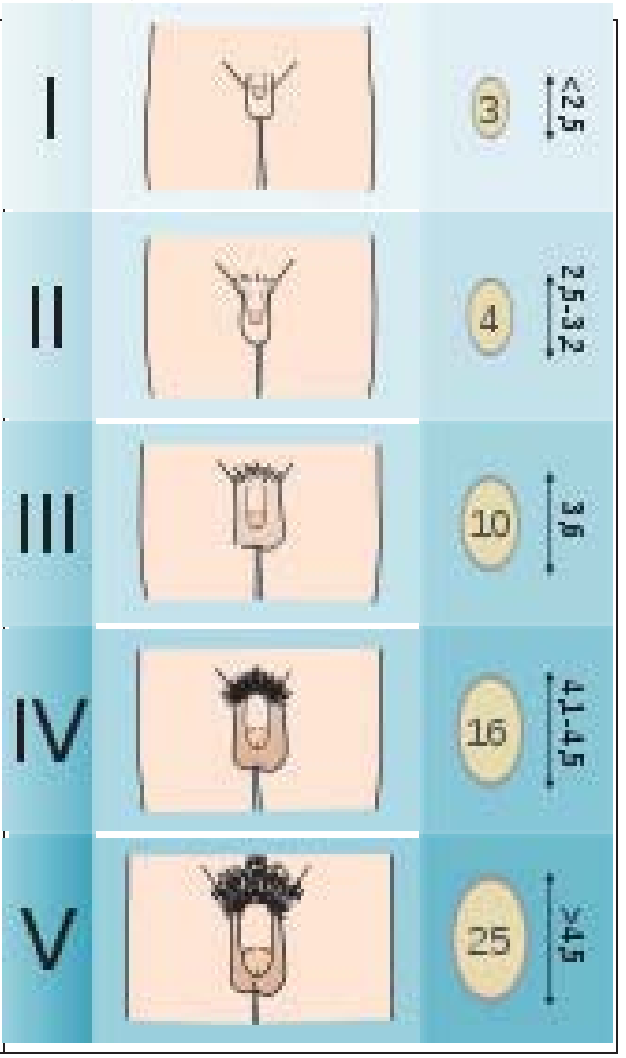
testicular volume between 6 and 12 ml; scrotum enlarges further; penis begins to lengthen to about 6 cm [11-12.5 yrs]

Tanner IV

testicular volume between 12 and 20 ml; scrotum enlarges further and darkens; penis increases in length to 10 cm and circumference [12.5-14 yrs]

Tanner V

testicular volume greater than 20 ml; adult scrotum and penis of 15 cm in length [14+ yrs]



Adapted from text by Lawrence Neinstein, MD

Breasts and Genitalia (female)

Tanner I

no glandular tissue: areola follows the skin contours of the chest (prepubertal) [typically age 10 and younger]

Tanner II

breast bud forms, with small area of surrounding glandular tissue; areola begins to widen [10-11.5 yrs]

Tanner III

breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast [11.5-13 yrs]

Tanner IV

increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast [13-15 yrs]

Tanner V

breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla area. [15+ yrs]

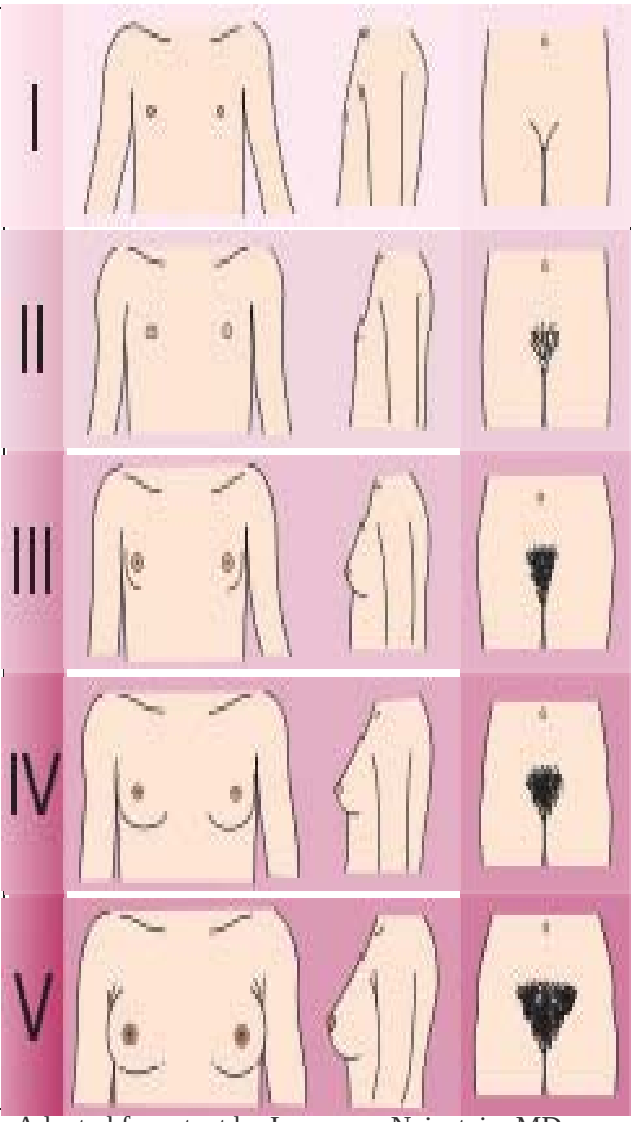


Illustration of the Tanner scale for females. Adapted from text by Lawrence Neinstein, MD

Annex 8: WHO Staging for HIV Infection and Diseases in Children (<15 yrs)

Clinical Stage I
- **Asymptomatic** - **Generalized lymphadenopathy**
Clinical Stage II
- **Hepatosplenomegaly** - **Papular pruritic eruptions** - **Seborrhoeic dermatitis** - **Extensive human papilloma virus infection** - **Extensive molluscum contagiosum** - **Fungal nail infections** - **Recurrent oral ulcerations** - **Lineal gingival erythema (LGE)** - **Angular cheilitis** - **Parotid enlargement** - **Herpes zoster** - **Recurrent or chronic RTIs (otitis media, otorrhoea, sinusitis)**
Clinical Stage III
Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations **Moderate unexplained malnutrition not adequately responding to standard therapy** **Unexplained persistent diarrhoea (14 days or more)** **Unexplained persistent fever (intermittent or constant, for longer than one month)** **Oral candidiasis (outside neonatal period)** **Oral hairy leukoplakia** **Acute necrotizing ulcerative gingivitis/periodontitis** **Pulmonary TB** **Severe recurrent presumed bacterial pneumonia** ***Conditions where confirmatory diagnostic testing is necessary*** **Chronic HIV-associated lung disease including brochiectasis** **Lymphoid interstitial pneumonitis (LIP)** **Unexplained anaemia (<80g/l), and or neutropenia (<1000/µl) and or thrombocytopenia (<50 000/µl) for more than one month**

Clinical Stage IV

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

Unexplained severe wasting or severe malnutrition not adequately responding to standard therapy
Pneumocystis pneumonia
Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration)
Extrapulmonary Tuberculosis
Kaposi's sarcoma
Oesophageal candidiasis
Central nervous system toxoplasmosis(outside the neonatal period)
HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary

CMV infection (CMV retinitis or infection of organs other than liver, spleen or lymph nodes; onset at age one month or more)
Extrapulmonary cryptococcosis including meningitis
Any disseminated endemic mycosis (e.g. extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)
Cryptosporidiosis
Isosporiasis
Disseminated non-tuberculous mycobacteria infection
Candida of trachea, bronchi or lungs
Visceral herpes simplex infection
Acquired HIV associated rectal fistula
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy (PML)
HIV-associated cardiomyopathy or HIV-associated nephropathy

The presumptive diagnosis above is designed for use where access to confirmatory diagnostic testing for HIV infection by means of virological testing (usually nucleic acid testing, NAT) or P24 antigen testing for infants and children aged under 18 months is not readily available

Annex 9: WHO Immunization Recommendations

Age of Infant	Vaccine
2 months (8 weeks)	DPT/ Hep B/ HIb-1, IPV-1
3 months (12 weeks)	BCG*
4 months (16 weeks)	DPT/ Hep B/ HIb-1, IPV-1
6 months (24 weeks)	DPT/ Hep B/ HIb-1, IPV-1 Influenza 1st
7 months	Influenza 2nd
1 year	MMR 1st
2 years	MMR 2nd
4 ½ years	DPT, IPV-1

Key:

BCG = Bacille Calmette Guérin

***BCG – give to all children, except HIV Infected Infants**

IPV = Inactivated polio vaccine

DPT/ Hep B/ Hib = diphtheria, pertussis, tetanus vaccine, Hepatitis B , Haemphilus Influenza b Vaccine

ANNEX 10: REFERENCES

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GETTING TO ZERO