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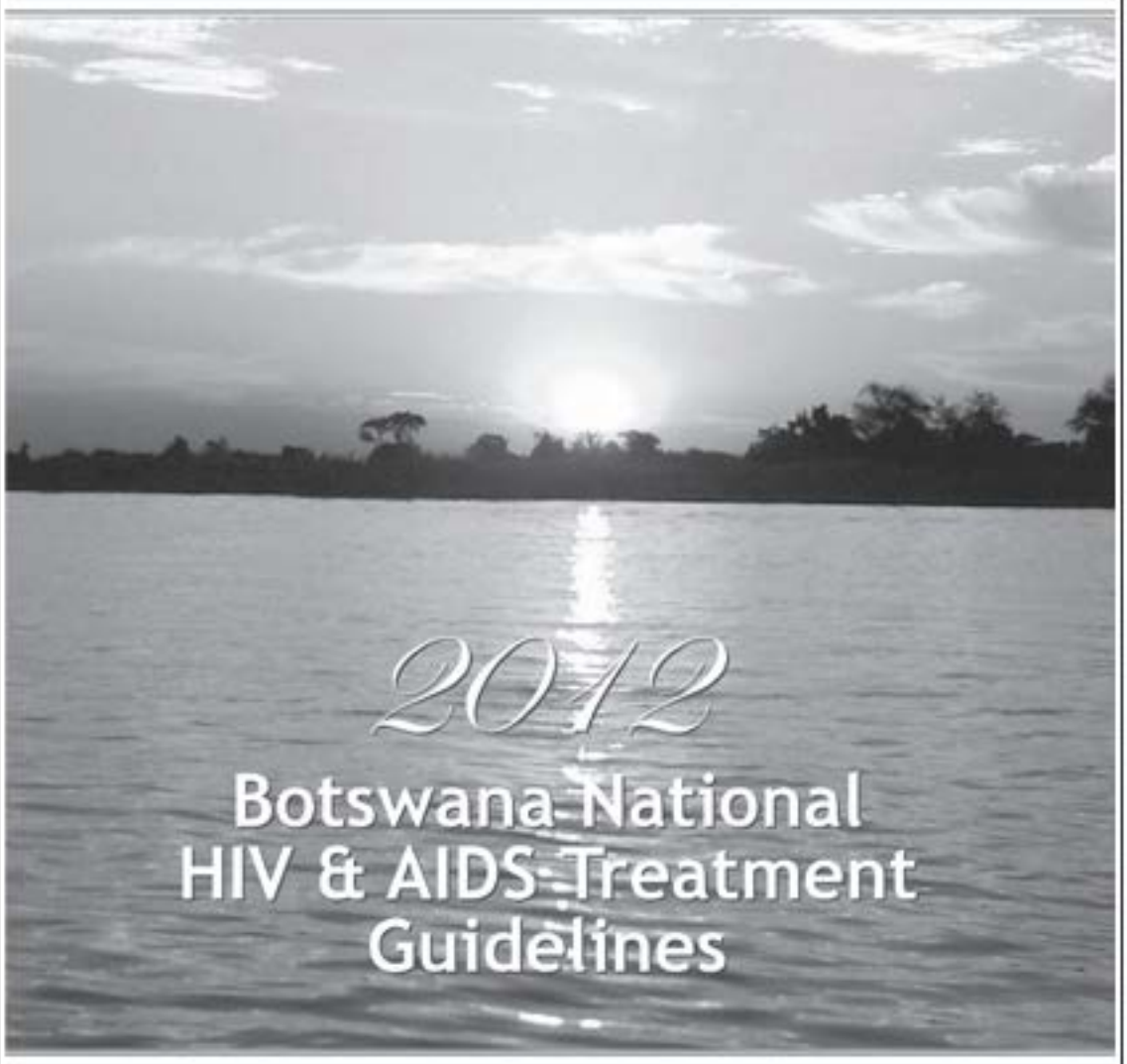

2012

Botswana National HIV & AIDS Treatment Guidelines

MINISTRY of HEALTH

Masa

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Ministry of Health

P/Bag 0038, Gaborone

BOTSWANA

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Abbreviations

>, ≤	greater than, less than or equal to
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATT	anti-tuberculosis therapy
ARL	AIDS-related lymphoma
ART	antiretroviral therapy
ARV	antiretroviral
BD	twice a day
BMD	bone mineral density
BMI	body mass index
BNTP	Botswana National Tuberculosis Programme
CDC	United States Centers for Disease Control
CHBC	community home based care
CMV	cytomegalovirus
CSF	cerebral spinal fluid
CSW	commercial sex worker
CTX	cotrimoxazole
CrCl	creatinine clearance
DBS	dried blood spot
DHAPC	Department of HIV/AIDS Prevention and Care
DMPA	depomedroxyprogestrone
DRU	drug regulatory unit
DS	“double-strength” CTX (= 2 “single-strength” CTX)
DNA PCR DNA	polymerase chain reaction
E	ethambutol
ELISA	enzyme-linked immunosorbent assay
FBC	full blood count
FDCs	fixed-dose combinations
FMT	failure management team
GFR	glomerular filtration rate
H	isoniazid

HAART	highly active antiretroviral therapy
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCW	healthcare worker
HD	hemodialysis
Hgb	hemoglobin
HIV	human immunodeficiency virus, type 1 (HIV-1)
HIV-DR	HIV drug resistance
hrs	hours
HSV	herpes simplex virus
ICP	intracranial pressure
INH	isoniazid
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
IUCD	intrauterine contraceptive device
IV	intravenous
IVIG	intravenous immunoglobulin
kg	kilogram
KS	Kaposi sarcoma
LEEP	loop electrosurgical excision procedure
LIP	lymphoid interstitial pneumonitis
LP	lumbar puncture (spinal tap)
MAC	mycobacterium avium complex
mg	milligram
µL	milliliter
mmol	millimole
mos	months
µL	microliter (cubic millimeter, mm3)
MDR-TB	multidrug-resistant tuberculosis
MOH	Botswana Ministry of Health
MSM	men who have sex with men
MTCT	mother-to-child transmission (of HIV)

NHL	non-Hodgkin's lymphoma
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OD	once daily
OI	opportunistic infection
PCNSL	primary central nervous system lymphoma
PCP	pneumocystis jiroveci (former carinii) pneumonia
PEP	post-exposure prophylaxis
PI	protease inhibitor
PID	pelvic inflammatory disease
PMTCT	prevention of mother-to-child transmission (of HIV)
PO	by mouth, orally
PrEP	pre-exposure prophylaxis
PVL	priority viral load
q	every, e.g., q3hours= every 3 hours
QID	four times a day
R	rifampicin
RBT	rifabutin
RFP	rifapentine
S	streptomycin
sdNVP	single-dose nevirapine
SJS	Stevens-Johnson syndrome
SMC	safe male circumcision
STI	sexually transmitted infection
SMX	sulfamethoxazole
SS	single-strength CTX (TMP 80mg/SMX 400mg)
TAM	thymidine analogue mutation
TAP	triple anti-retroviral prophylaxis
TB	mycobacterium tuberculosis
TDS	three times a day
TC	total cholesterol
TG	triglycerides

TMP	trimethoprim
ULN	upper limit of normal
VL	viral load
WHO	World Health Organization
VZV	varicella-zoster virus
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide

Anti-retroviral Abbreviations:

ATA	atazanavir
AZT	zidovudine, ZDV
3TC	lamivudine
FTC	emtricitabine
d4T	stavudine
DAR	darunavir
ddI	didanosine
ABC	abacavir
TDF	tenofovir
NVP	nevirapine
EFV	efavirenz
LPV/r	ritonavir-boosted lopinavir [“Kaletra,” “Aluvia”]
NFV	nelfinavir
SQV	saquinavir
RAL	raltegravir
RTV	ritonavir
r	low dose ritonavir, used as a “booster”)

ON-LINE HIV & AIDS EDUCATIONAL INFORMATION FOR CLINICIANS:

www.medscape.com/hiv

www.aidsmap.com

www.clinicaloptions.com/hiv

www.iasociety.org

www.hopkinsiaids.edu

www.bipai.org/HIV-curriculum

www.aidstar-one.com

www.hivanonymous.com

Foreword

After ten years, the success of Botswana's anti-retroviral treatment programme is clear. With documented clinical excellence, outstanding treatment outcomes and significant decreases in HIV incidence - especially among the youth - the Botswana National Anti-retroviral Treatment Programme will remain an important example of how strong political will, financial commitment and community engagement can overcome the greatest adversity. The time has come to build upon this success by strengthening our national healthcare infrastructure in order to ensure the long-term sustainability of HIV/AIDS prevention and care services.

At the same time as the release of these revised HIV/AIDS clinical care guidelines, the Department of HIV/AIDS Prevention and Care will be merged with the Department of Public Health. This ambitious move is aimed at strengthening the delivery of healthcare to everyone in Botswana regardless of their HIV status. By integrating anti-retroviral treatment across all sectors of health, HIV-infected patients will benefit from comprehensive health services paving the way for further gains in wellbeing and decreases in co-morbidities and mortality.

These are exciting times which call for bold innovation and vision. We therefore welcome this 2012 edition of the Botswana National HIV/AIDS Treatment Guidelines as a step toward full and comprehensive HIV/AIDS service delivery across all units within the Ministry of Health, at all districts and at all points of care.

Mrs. Shenaaz El-Halabi

Deputy Permanent Secretary

Ministry of Health

1 April 2012

*The **time** has now come to build upon this success by **strengthening our national healthcare infrastructure** in order to ensure the long-term sustainability of HIV/AIDS prevention and care services*

Preface

The 2012 edition of Botswana National HIV/AIDS Treatment Guidelines introduces a new level of optimized care for those infected with HIV. With expanded access to ART for adults and children at higher CD4 counts, more HIV positive individuals will be provided with life sustaining treatment and benefit from earlier ART initiation. Improvements in the delivery of PMTCT with the transition to Triple ART Prophylaxis, will also go far to ensure that 2016 indeed becomes the beginning of an AIDS free generation. Improvements in the selection and convenience of ART regimens for adults and children will further improve treatment outcomes. The inclusion of two new chapters – one focusing on Pediatrics and another on Cancer and HIV – enable clinicians to address the special needs of these populations. Expansion of the TB/HIV chapter also reflects the progress of TB and HIV clinical integration.

Most importantly, these clinical improvements will not only impact health on an individual level, but also within the community, as greater access to ART will serve as a central component of our combination prevention strategy. HIV prevention is the key to financial sustainability efforts and therefore utilizing ART most efficiently is critical. Improving upon the delivery of sexual and reproductive health services will likewise benefit families as pregnancies are well planned and welcomed.

It is our patients' wellbeing that matters most. We sincerely hope that these 2012 revisions go a long way to improve the lives and clinical outcomes of those who require our care and support.

Finally, we appreciate the wide range of clinical expertise that contributed to making the 2012 HIV and AIDS Clinical Care Guidelines a reality.

Dr. Refeletswe Lebelonyane

Director, Department of HIV/AIDS Prevention and Care

Ministry of Health

1 April 2012

HIV prevention is the key to ***financial sustainability efforts*** *and therefore* ***utilizing ART most efficiently is critical***

Acknowledgements

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- With special acknowledgement to **Dr. Daniel Baxter** who set the original groundwork for these revisions in 2008.

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Department of HIV/AIDS Prevention and Care, Ministry of Health

1 April 2012

UNDERLYING PRINCIPLES AND RATIONALE OF THE 2012 BOTSWANA NATIONAL HIV & AIDS TREATMENT GUIDELINES: 1 APRIL 2012, EDITION:

- In accordance with the 2010 recommendations of the WHO, the Ministry of Health has improved access to ART by expanding eligibility criteria to all adults with CD4 counts ≤ 350 cells/µL. This change is also reflected in pediatric populations; all children ≤ 24 months of age as well as children from 2 – 5 years with CD4 counts ≤ 750 cells/µL or CD4 ≤ 25% will be eligible to begin ART. As a result of this eligibility change an estimated 7,400 deaths will be averted as well 12,700 HIV infections over the next five years.
- In accordance with Vision 2016 in order to guarantee an AIDS Free Generation, Triple ART Prophylaxis (TAP) will be provided to all HIV-infected pregnant women. As a result, mother to child transmission rates are expected to fall below 1% annually.
- Previously, in animal studies and retrospective human case reports, it was believed that efavirenz use in pregnant HIV-infected women (particularly during the first trimester) was linked to an increase in central nervous system birth defects. However, meta-analyses of available evidence to date have found no such increase risk when compared with exposure to other anti-retrovirals. *(Ford N, Calmy A, Mofenson, et al. Safety of efavirenz in the first-trimester of pregnancy: an updated systematic review and meta-analysis. AIDS 2011, 25(18): 2301-4.)*

  Therefore, given the convenience of using a 1 dose daily fixed dose combination of TDF/FTC or 3TC/EFV (Atripla) and the low toxicity profile, ***all patients regardless of their reproductive status will be initiated on Atripla***. While we expect no significant increase in central nervous system birth defects as a result of this policy, HIV clinicians, gynecologists and pediatricians should remain vigilant in reporting such cases directly to the DHAPC and the DRU. Plans to implement a national birth defect registry are underway to monitor any increases due to EFV use in pregnancy.
- Likewise, previous concerns over the possible dangers of tenofovir use during pregnancy have changed. The 2010 WHO guidelines support TDF use during pregnancy. These 2012 revisions are now aligned and support the use of tenofovir, before, during and after pregnancy.
- Until recently, Fixed Dose Combinations were only available for adult use. Now Pediatric FDCs have become widely available and should be used instead of individual dose regimens for children whenever possible. We expect that the added convenience of no longer using syrups or complicated regimen dosing will greatly improve pediatric adherence and long-term treatment outcomes.
- Since 2008 the use of d4T in adults, unless under rare circumstances, is no longer recommended due to toxicities. ***This recommendation continues and now includes all pediatric patients***. Any patient (adult, adolescent or pediatric) remaining on d4T should have clear clinical indications which require its use. Otherwise, ***all remaining adult patients on d4T will be switched to the most appropriate NRTI substitution and pediatric patients currently receiving d4T/3TC containing regimens will be switched to ABC/3TC***.
- The inclusion of two new chapters: Pediatrics and Cancer/HIV, is provided to address the growing complexities of these special populations.

- Customizing care to meet the particular challenges of children and adolescents infected with HIV will continue to be required now and in the years ahead. Furthermore, pediatric ART treatment failure rates are documented to be higher than those of adults. Optimizing treatment regimens to improve convenience and decrease long-term toxicities is therefore essential.
- Adult and pediatric HIV patients suffering from cancer often face serious clinical challenges. Ensuring that they receive the best possible comprehensive HIV care, in addition to optimal chemotherapy and radiotherapy, requires that screening, prevention and appropriate treatment of cancer in the setting of HIV becomes a clinical priority.
- Evidence based clinical trials have now clearly demonstrated the advantages of beginning ART in TB/HIV co-infected patients as soon as possible. New recommendations for the initiation of ART in TB patients, as well as guidance on ART regimen selection and administration, have therefore been updated and revised.

1.0 HIV PREVENTION

1.1 Prevention of Sexual Transmission

Prevention of HIV transmission is the critical factor that will allow Botswana to continue to sustain a successful fight against HIV and AIDS. At every opportunity healthcare workers must make every effort to screen and test all patients for HIV. Frank discussions regarding sexual behavior, including participation in multi-concurrent partnerships, discordant couples, sexual orientation and correct and consistent use of condoms should be routinely initiated. In this way, prevention messages and health education can be targeted and address the specific and unique needs of individuals.

Healthcare providers should help patients understand that:

- In order for monogamy to be an effective HIV prevention method it must be 100% mutual and 100% consistent.
- Always participating in safe sex practices protects lives and prevents the spread of HIV.
- Taking responsibility for one's sexual and reproductive health is essential to ensure longevity, health and well-being.
- HIV co-infected and HIV discordant couples should carefully plan all pregnancies.
- HIV-infected partners in discordant relationships will greatly limit transmission to their partners by adhering to their ART.
- Improving honest communication regarding sexuality with their partners within monogamous or non-monogamous sexual networks can prevent the spread of HIV.

Issues regarding sexual and reproductive health must be reviewed at every patient visit. Any safe sex discussion which presents all sexual activity as dangerous or "risky" is likely to fail.

Issues to Address Regarding Safe/Safer Sex:

- Consistent and proper condom use for rectal and/or vaginal intercourse remains the core of "safe sex" messages.
- Proper condom use must be reviewed with the patient, including proper handling and disposal of used condoms, as well as proper hand and genital cleansing after sex to prevent inadvertent transfer of genital secretions between partners.
- A frank review of the risks of various sexual activities and behaviors to avoid misconceptions.
- Sexual kissing is "safe sex."
- Mutual masturbation is "safe sex," as long as transfer of genital secretions between partners is avoided.
- The HIV transmission risk of oral-genital sex is not known, but is low.
- Prompt identification and treatment of STIs is crucial.
- ***HIV transmission can occur at any viral load, including at suppressed or "undetectable" values.***

Eradicating Sexual Myths & Misconceptions:

Sexual myths and misconceptions often interfere with safe sex messages, and must be addressed candidly with patients. Such myths include the following:

- A woman with a wet or well-lubricated vagina is promiscuous, and application of agents to decrease such wetness—which results in "dry sex"—is necessary to prevent the impression of promiscuity.
- Self-masturbation is unnatural, or a cause of loss of fertility or energy.
- Sex with a virgin or infant will cure HIV infection.
- Condoms have worms or spread HIV.
- Condoms have large pores which permit HIV transmission.
- Showering after unprotected intercourse will prevent HIV infection.

Special Considerations: Addressing Adolescents:

- Parents and clinicians must initiate frank discussions of sex with adolescents, including non judgmental discussions of safe sex methods to satisfy sexual needs

1.2 Combination HIV Prevention

Recent clinical trials, many conducted in Botswana, have shown significant decreases in HIV transmission with the use of single HIV prevention methods. Using these individual methods (with a range of efficiency rates) in combination will provide the best protection to prevent HIV transmission in the years ahead. Clinicians should therefore familiarize themselves with prevention options in order to provide clients (especially those in discordant couples) with the latest information on viable methods to prevent the spread of HIV. Combination HIV prevention methods include the following:

1.2.1 Safe Male Circumcision (SMC)

Male circumcision has been proven to reduce a man's risk of HIV acquisition during vaginal intercourse by up to 60%. Therefore, Department of HIV/AIDS Prevention and Care has embarked on an ambitious campaign to provide access to SMC to all eligible males throughout the country. Clinicians should make every effort to refer individuals for local SMC services.

> ***As circumcision does not eliminate the risk of HIV transmission, all males must be encouraged to continue to practice safe sex and always use condoms regardless of their circumcision status.***

Once circumcised, to prevent enhanced HIV acquisition (and subsequent transmission) via an unhealed surgical scar, it is imperative that SMC patients be counselled not to resume sexual activities until complete healing of the surgical scar has been verified by a clinician experienced in such determination; this would ideally be the practitioner who performed the procedure.

There are two routes of referral into SMC services:

Referral Cards

For use by VCTs and non-circumcising public health facilities to refer male patients who test HIV negative at their facilities.

Referral Slips

For use by mobilization/demand creation activities (road shows, health fairs, house to house visits, etc.) to refer men who participate in such events.

(See Annex 1: SMC Referral Slips, page No. 154)

Minimum Package for SMC

- Pre-operative provider-initiated HIV testing and counseling
- Active exclusion of symptomatic STIs and syndromic treatment if detected
- Provision of condoms and promotion of correct and consistent condom use
- Post-operative wound care and abstinence instructions
- Age-appropriate counseling on risk reduction
- Active linkage to other HIV prevention, treatment, care and support services

1.2.2 Anti-Retroviral Treatment as HIV Prevention

Recent clinical research has shown that use of ART by the HIV-infected partner in discordant couples is highly effective against HIV transmission. This evidence reinforces the importance for all Batswana to know their HIV status and be placed on ART as soon as they become eligible. Knowing one's status and initiating ART treatment ***before becoming ill*** will not only improve the prognosis of HIV patients, but also reduce HIV transmission and ensure the long-term sustainability of the Botswana National ART programme.

Therefore, the Ministry of Health, DHAPC, in conjunction with development partners will embark on a national programme to enhance HIV prevention efforts by improving access to all HIV prevention services including SMC, HIV testing and counselling, PMTCT and early access to ARV treatment and care. These efforts and strategies to improve retention in care and adherence to life-long treatment will allow ART to be optimally effective.

1.2.3 Pre-Exposure Prophylaxis

Prophylaxis with ART by the ***HIV uninfected*** (pre-exposure prophylaxis (PreP)) has also been studied in clinical trials within Botswana with encouraging results. However at this time, the Ministry of Health does not recommend the wide spread use of ART in the HIV-uninfected population.

The use of PreP in discordant couples desiring children is in use at some private health facilities in Botswana. However, at the time of this printing, a national policy on the safe implementation and wide spread use of PreP in a variety of settings, including MSM, CSW and cases of pregnancy in discordant couples, remains to be established.

1.3 Prevention of Healthcare Workplace Transmission

"Universal precautions" are defined as healthcare practices which assume that all bodily fluids are infectious. They should be used by healthcare workers when interacting with any patient and include safe injection practices, as follows:

- Use gloves when performing invasive procedures, including cannula placement
- Avoid recapping needles
- Avoid reinserting used needles into multiple dose vial or fluid bag
- Never place needles into mattresses, even temporarily.
- Immediately dispose of needles in a sharps container at the end of a procedure.

All healthcare workers, regardless of their HIV status, must practice universal precautions when handling all body fluids, especially since HBV, HCV and other serious pathogens are even more transmissible than HIV.

- Home healthcare workers and family members are not at an increased risk of HIV acquisition, as long as they follow universal precautions in handling and disposal of infectious materials. Where protective gloves are not easily available, hand washing and avoidance of exposure between non-intact skin and infectious secretions should be stressed.

- HIV-infected HCWs, including those who perform invasive procedures, do not pose any risk of HIV transmission to their patients, as long as they adhere to routine infection control policies and universal precautions

1.4 Management of Sexually Transmitted Infections

STIs play an important role in HIV transmission and acquisition, and their proper control and management must be part of every HIV prevention program. In HIV-infected patients, STIs such as herpes simplex virus (HSV) and syphilis have been shown to significantly enhance HIV transmission and acquisition, elevate viral load, and lower CD4 cell count.

- In patients of unknown HIV serostatus, STIs are important markers of high risk behavior and possible exposure to HIV, indicating the need for obligatory HIV testing and safe sex counseling.
- Management of STIs must follow the "syndromic"approach, wherein STI signs/symptoms are matched to a specific STI syndrome.

(See Annex 2: STI Treatment Algorithms, page No. 155)

2.0 SCREENING AND TESTING FOR HIV INFECTION

The critical importance of HIV screening for all age groups cannot be over emphasized. HIV testing should continue to be universal, routine, and on an "opt out" basis. HIV testing should be conducted in all clinical and outreach settings throughout the country by all healthcare providers

2.1 Diagnosis of HIV Infection in Patients 18 Months of Age and Older

The double rapid test is now the preferred method of HIV testing in patients 18 months of age and older. Rapid tests have been found to be feasible, accurate, timely, and useful both in providing prompt access to antiretroviral prophylaxis and treatment and in reducing perinatal HIV transmission. The ELISA, which remains "the gold standard" for testing, is generally used for selected specimens which are sent to the laboratory, and for mass screening of large numbers of patients such as testing in blood banks and reference laboratories. The testing algorithm for ELISA and rapid HIV testing in Botswana is as follows:

- Two concordant parallel rapid HIV tests, or
- Two concordant parallel ELISA tests

Positive Results:

Any specimen that is reactive on parallel ELISA testing or parallel rapid testing is considered HIV antibody positive, and is diagnostic for HIV infection for anyone over 18 months of age. ***Further confirmatory testing is not indicated***.

Negative Results:

Any specimen that is not reactive on parallel ELISA testing or parallel rapid testing is HIV antibody negative, and indicates that the patient is either uninfected or in the "window period" of infection.

- **Advise patients found to be negative and who plan to remain sexually active to complete HIV testing annually.**

Discordant Results:

Any specimen that shows discordant test results (i.e., one is positive and the other is negative) must be retested ***at that visit*** to exclude clerical or technical errors.

Concordant results after this repeat testing step shall be indicated as a positive or negative result.

A specimen that remains discordant in the repeat testing step is considered indeterminate, and the following algorithm should be followed:

- Advise the patient to return in 2-4 weeks for repeat testing by rapid test, during which time abstinence or safe sex should be practiced.
- Repeat rapid test 2-4 weeks later. If results are still discordant, a blood specimen should be taken at the visit and sent to a reference laboratory for further testing using ELISA and/or Western blot. If the above specimen remains indeterminate, further investigative tests

such as molecular techniques (HIV DNA PCR or HIV RNA PCR) should be used. The full history regarding the previous testing of the specimens should be submitted with the specimen. ***Alert laboratory personnel to track the specimen and results***. *(See chapter 9, section 9.7: HIV Specialist Panel for laboratory contact numbers)*

- During the investigation period, advise the patient to continue either abstinence or safe sex practices pending final result.

2.2 Diagnosis of HIV Infection in Pregnant Women

Prompt and accurate HIV diagnosis in pregnant women is essential for referral for Triple ARV Prophylaxis (TAP), as well as for the mother's health. All pregnant women must be tested for HIV as matter of priority.

Positive Results:

All pregnant women who test HIV positive must immediately have blood collected for CD4 count to determine ART eligibility status. Regardless of CD4 count, all pregnant HIV-infected women qualify for Triple ART Prophylaxis during their pregnancy. Therefore immediately refer all women found to be HIV-infected to local PMTCT services.

Negative Results:

Pregnant women who test HIV-negative must receive ongoing counselling regarding safe sex practices in order to avoid undetected HIV infection during pregnancy.

- Re-test all pregnant women at either 36 weeks gestation or at onset on labour, whichever comes first, in order to detect HIV infection acquired since their last test result during pregnancy.
- Inform all pregnant women that HIV testing should be completed annually after delivery.
- Advise all post-partum HIV uninfected women who choose to breastfeed to have an HIV test every three months while breastfeeding. If mothers are found to be HIV-infected, their children must also be screened for HIV as discussed in Section 2.4 below.

Discordant Results in Pregnant Women:

Repeated discordant rapid test results require priority ELISA testing at that visit, with results available within five days of testing. Laboratory personnel should also be alerted to track the specimen and results. *(See chapter 9, section 9.7: HIV Specialist Panel for laboratory contact numbers)*

If the ELISA test remains discordant, use Western Blot and viral load, for results within five days of testing. If these tests are equivocal or discordant, contact an HIV Specialist immediately.

(See Annex 3: Diagnosis of HIV Infection in Patients 18 Month of Age or Older, page 162)

2.3 Diagnosis of HIV Infection in Adolescents

The attorney General advises that the *Botswana Family Planning General Policy Guidelines and Service Standards* guide the testing of minors. This policy states that: "…teenagers are to be provided with appropriate family planning methods on request after adequate counselling." In other words, if the counsellor is satisfied that a young person is mature enough to fully understand his or her behavior and the consequences of that behavior, parental consent is not necessary in order to receive services.

Pregnant adolescents do not need the consent of their parents to be tested for HIV or to join the PMTCT programme, and parents do not have to be present during counselling. Adolescents may choose to have a parent or another adult with them to provide the necessary support. This option should be discussed with the client and encouraged. It is also important for family members who will be assisting with the baby to be involved.

- Disclosure of positive results to adolescents must be done in a supportive environment. *(See Chapter 8, Section 8.2)*

2.4 Diagnosis of HIV Infection in Patients less than 18 Months of Age

Test all HIV-exposed babies in Botswana using DNA polymerase chain reaction (PCR) testing at 6 weeks of age to determine their HIV status, with immediate follow-up DNA PCR to confirm a positive result.

Studies have shown that HIV DNA PCR is a sensitive technique that detects specific HIV viral DNA in a patient's peripheral blood mononuclear cells (PBMCs). The sensitivity of a single HIV DNA PCR test performed at ≤48 hours of age is less than 40% but sensitivity increases to more than 90% by 2-4 weeks of age.

- Infants presented between 4 and 6 weeks of age should have HIV DNA PCR performed at that visit, in order not to miss testing at 6 weeks of age.
- Dried blood spot (DBS) collected on filter paper is the recommended method of specimen collection for early infant diagnosis (EID) of HIV infection (compared to drawing venous blood).

Positive Results: ***Immediately refer infants whose first DNA PCR is positive, for ART initiation, without waiting for the confirmatory DNA PCR. However, confirm HIV infection by a repeat HIV DNA PCR on a second specimen as soon as possible after the first test result becomes available.***

Negative Results:

Infants who do not have continued post-partum exposure to HIV (such as through breastfeeding) and who test negative for HIV with a 4-6 week DNA PCR test should be retested at 18 months with a double rapid test.

Breastfed Babies with a negative DNA PCR at 4-6 weeks ***should have repeat HIV testing 6 weeks after complete cessation of breastfeeding***. The type of HIV test performed will depend upon the age of the patient.

- If DNA PCR is used and is positive, it should be repeated immediately, but ***do not wait for the confirmatory PCR to return before referring for ART initiation***.

If DNA PCR Results are not readily available:

- Clinically evaluate HIV-exposed babies monthly, including WHO clinical staging, since HIV-infected babies are at high risk of severe illness and death. Initiate ART for WHO clinical staging 3 or 4.

An HIV-exposed baby without an available DNA PCR who presents with WHO clinical stage 2 must be discussed with a pediatric HIV Specialist for consideration of ART initiation while a definitive diagnosis by PCR is pending.

2.5 Antibody Testing in Early Infant Diagnosis of HIV Infection:

HIV antibody testing in infants does not establish the presence of HIV infection because of transplacental transfer of maternal antibodies during pregnancy. Maternal HIV antibody may persist in infants under the age of 18 months and give a false-positive antibody test in an uninfected child. However, studies have shown that two or more negative HIV antibody tests performed at > 6 months of age can be used to definitively exclude HIV infection in HIV-exposed children with no clinical or virologic laboratory evidence of HIV infection.

Studies have also shown that the absence of HIV infection in infants with negative virologic tests can be confirmed by performing serology between age 12-18 months. It is known that the proportion of infants who seroconvert between 15 and 18 months is close to 100%, and as many as 95% of infants may seroconvert by 12 months of age; factors that might influence the time to seroreversion include the staging of maternal disease as well as the sensitivity of the assay.

2.6 Protocol for Opt-Out HIV Testing

- Ensure that patients understand that an HIV test will be performed; explain the medical reasons for the test and that the test results will remain confidential.
- If the patient does not voice objections to the HIV testing, consent should be obtained at that time. Verbal communication is adequate in obtaining consent for RHT.
- If the patient refuses HIV testing, explore the reason(s) for the refusal, and address the patient's concerns.
- If the patient still refuses, then he/she should be referred for full pre-test counseling on site if available or at the nearest VCT facility.
- Provide pre-test counseling whenever requested.

Patients should always be encouraged to test for HIV. However, at no time should the patient be pressured or coerced to undergo HIV testing.

2.7 HIV Pre & Post-Test Counseling

Pre-Test Counseling

Pre-Test Counselling is a confidential dialogue between the client and service provider aimed at assisting an informed decision about HIV testing. However, health care providers must remain mindful that a frightening or burdensome pre-test counselling session may discourage client uptake of HIV testing. Information for pre-test counselling sessions should include the following points:

- Correction of misconceptions and filling gaps in information about HIV/AIDS.
- Discussion of the benefits of HIV testing.
- Discussion of the implications of a positive or negative HIV test result.
- Explanation of HIV rapid test process and the meaning of HIV test results.

- Exploration of personal HIV risk behaviors and options for reducing risk.
- Exploration of support system and discussion of disclosure mechanisms.
- Assessment of client's readiness for HIV testing.
- Obtaining verbal consent for HIV testing.

Post-test counseling

Post-test counselling should be performed after the HIV test result is available and should be tailored according to the test result. However, regardless of HIV status results:

- Safe sex practices should be reviewed in detail with all testing clients.
- Routine TB screening should be completed in all clients regardless of HIV status
- Sexual reproductive health and family planning should be discussed.

Positive Results:

- Review referral procedures for follow-up care, including prompt referral for CD4 and clinical screening to determine ART eligibility status.
- Encourage patients to disclose their HIV status to a close friend or family member for social and family support.
- If indicated, refer patients to a social worker and/or other community support services as indicated.
- Always emphasize hope, encouragement and support for patients with positive results.

Negative Results:

- Discuss risk reduction plans including decreases in multiple concurrent partnerships, substance abuse, consistent condom use, and follow up annual HIV testing.
- Advise patient to encourage their sexual partners, friends and family to annually test for HIV.

3.0 PRE-ART CARE: CD4 AND CLINICAL SCREENING & CARE

3.1 Determination of ART Eligibility by CD4 Cell Count or % and/or WHO Clinical Stage

It is mandatory, upon HIV diagnosis, to promptly refer all patients for CD4 and clinical screening to treat opportunistic infections and determine the degree of immunologic deficiency and patient eligibility for ART.

The initial CD4 screening/monitoring visit is an important opportunity for patients to also receive preventive and supportive care, and to begin the education process about HIV disease and ART.

The CD4 evaluation visit must include:

- Physical examination and screening for TB and other opportunistic infections
- Referrals for baseline Pap smear screening for HIV-infected women if not completed within the last 3-5 years
- Discussion regarding sexual and reproductive health choices and partner testing

A Botswana-specific WHO staging classification categorizes patient symptoms and history into one of four stages, as outlined below for pediatric patients and for adult/adolescent patients:

Table 3.1: WHO Staging for Pediatrics

Clinical Stage 1: ASYMPTOMATIC
Asymptomatic
Persistent generalized lymphadenopathy
Clinical Stage 2: MODERATE DISEASE
Persistent unexplained hepatosplenomegaly
Papular pruritic eruptions
Extensive HPV infection
Extensive molluscum contagiosum
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Lineal gingival erythema
VZV
Recurrent or chronic upper respiratory infections (otitis media, tonsillitis, sinusitis)
Fungal nail infections
Clinical Stage 3: ADVANCED DISEASE
Unexplained moderate malnutrition
Unexplained persistent diarrhea for 14 days
Unexplained persistent fever for 1 month
Persistent thrush after 6 weeks of age
Persistent oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/peridontitis
Pulmonary or lymph node TB
Severe recurrent bacterial pneumonia
Lymphoid interstitial pneumonitis
Chronic HIV-related lung disease, including bronchiectasis
Unexplained anemia (<8gm%), neutropenia (<500/μL) or thrombocytopenia (<50,000/μL)
Clinical Stage 4: SEVERE DISEASE
Severe wasting, stunting, or malnutrition
Pneumocystis pneumonia
Severe recurrent bacterial infections, excluding pneumonia (e.g., meningitis, osteomyelitis)
Chronic HSV infection >1 month
Extra-pulmonary TB other than lymph node TB
Kaposi's sarcoma
Esophageal candidiasis
CNS toxoplasmosis
HIV encephalopathy
CMV infection (e.g., retinitis, gastroenteritis)
Extra-pulmonary cryptococcosis, including meningitis
Disseminated endemic mycosis
Chronic cryptosporidiosis or isosporiasis
Disseminated non-TB mycobacterial infection
Cerebral or non-Hodgkin's lymphoma
Progressive multifocal leukoencephalopathy
HIV-related cardiomyopathy or nephropathy

Table 3.2: WHO Staging for Adolescents and Adults

Clinical Stage 1: ASYMPTOMATIC
Asymptomatic
Persistent generalized lymphadenopathy
Clinical Stage 2: MODERATE DISEASE
Unexplained moderate weight loss <10% of baseline weight
Recurrent upper respiratory infections (sinusitis, otitis media, tonsillitis, pharyngitis)
Mono-dermatomal VZV
Recurrent oral ulceration
Papular pruritic eruptions
Seborrheic dermatitis
Fungal nail infections
Clinical Stage 3: ADVANCED DISEASE
Unexplained weight loss >10% of baseline
Unexplained chronic diarrhea for more than one month
Unexplained persistent fever (>37.5C, intermittent or constant) for more than one month
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary TB
Severe bacterial infections (e.g., pneumonia, meningitis, PID,* bone/joint infection, bacteremia)
Multi-dermatomal, recurrent mono-dermatomal, or ophthalmic VZV*
Necrotizing ulcerative gingivitis, peridontitis, stomatitis
Unexplained anemia (<8gm%), neutropenia (<500/µL), and/or thrombocytopenia (<50,000/µL)
**Not part of international WHO staging, but added as frequent Botswana-specific HIV-related "advanced" conditions meriting HAART*
Clinical Stage 4: SEVERE DISEASE
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic HSV infection (orolabial, genital, rectal for more than one month or visceral at any site)
Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
Extra-pulmonary TB
Kaposi's sarcoma
CMV (retinitis or infection of other organs)
CNS toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis, including meningitis
Disseminated non-TB mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis, isosporiasis
Disseminated mycosis
Recurrent septicemia
Lymphoma (cerebral or non-Hodgkin's)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy and cardiomyopathy

Additional footnotes to WHO adult/ adolescent clinical staging:

- A single, non-recurrent episode of mono-dermatomal VZV infection is a stage 2 condition. Recurrent mono-dermatomal VZV, a single episode of multi-dermatomal VZV, or ophthalmic VZV should be regarded as stage 3 conditions.
- ii. Recurrent severe PID is a WHO stage 3 condition. The above additions to adult/ adolescent WHO staging are Botswana-specific, and reflect the VZV and PID disease burdens in the country.

3.2 CD4 & Clinical Screening Visit

The CD4 and clinical screening visit should also include preventive and supportive care as needed:

- Patient education about HIV transmission and prevention, including counseling regarding notification of all known past sexual partners
- Encouragement to disclose HIV status to close family members and/or friends (not advised for adolescents), a step which ultimately will improve adherence to ART
- Frank and open discussion about safe sex, family planning, and future reproductive choices and planned pregnancy. (Encourage HIV-infected women to notify their practitioners if they become pregnant, or if they plan to become pregnant).
- When clinically indicated, initiation of CTX prophylaxis
- Referral for baseline Pap smears for sexually active women who have not completed a Papsmear in the past 3-5 years
- Screening for TB; in children include screening for any TB contacts
- Patient education about HIV disease and the critical importance of adherence to medications and scheduled appointments
- Reinforce understanding that ART is lifelong and is not a cure
- Social service referral for evaluation of any assistance needs, e.g., food baskets
- Emphasis on smoking cessation and avoidance of recreational drugs and alcohol
- Avoidance of traditional, herbal, and alternative medicines, including anything ingested, as well as practices such as piercing, enemas, and bloodletting
- Importance of overall wellness with regular exercise, proper nutrition, and sleep
- Dental referral, when indicated and available
- Screening for depression or other mental illness, with treatment and referrals as indicated
- Nutritional counseling, and if indicated, referral to nutritionist, if available
- Information about community services available for people living with HIV/AIDS
- Referral to appropriate websites and online information and services, such as:
  AIDSTAR-One Promising Practices Database: (http://www.aidstar-one.com promising practices database/g3ps/teen club peer support group HIV positive adolescents)

Patients Found to be Eligible for ART

Make every effort to ensure that patients who are eligible for ART initiation understand the importance of prompt presentation at a health facility to begin ART immediately. Even short delays (less than one month) in initiating treatment are associated with increased mortality, especially for individuals with very low CD4 counts (≤100 cells/μL). Include information about the referral processes for treatment and follow-up care, including specific appointments for ART initiation.

Once a patient's CD4 result qualifies them for ART, develop mechanisms to track eligible patients into ART care. Possible methods include asking patients to return to your facility after ART has been started or to communication via some other method (i.e., calling, sms or emailing the clinic).

Patients NOT Eligible for ART

All preventive and supportive care measures outlined above should also be provided at follow-up CD4 monitoring visits for those who are not yet eligible for ART.

Periodic monitoring of adults to assess disease progression and to identify eventual eligibility for ART initiation should be scheduled as follows:

- For CD4 counts > 350 and ≤500 cells/µL, follow-up visits every 3 months
- For CD4 counts > 500 cells/µl, follow up visits every 6 months
- Monitoring frequency should be increased if indicated by clinical condition,e.g., new WHO stage 2 conditions.

3.3 Cotrimoxazole Prophylaxis

CTX prophylaxis must be given OD, for all ages, in order to provide protection against diarrheal and respiratory pathogens. *(For children see Chapter 8, Section 8.4)*

3.3.1 Infants (including HIV-exposed infants)

CTX prophylaxis must be given to all HIV-exposed babies, starting at 6 weeks of age and maintained until at least six weeks after cessation of risk of HIV transmission.

- Discontinue CTX in babies ***not breastfed*** and with a negative DNA PCR at 6 weeks of age.
- Continue CTX in breastfed babies until they have tested HIV negative 6 weeks after breastfeeding has stopped.
- Continue CTX in HIV-infected babies until at least 12 months of age, regardless of CD4 count or % and clinical condition.

3.3.2 CTX Prophylaxis for Adolescents and Adults

CTX prophylaxis must be given to all adults and adolescents with severe immunosuppression, as evidenced by a CD4 cell count < 200 cells/µL, or any active, current WHO clinical stage 3 or 4 condition.

- If the CD4 count is pending, but the patient has an active WHO stage 3 or 4 condition, do not delay initiation of CTX prophylaxis.
- CTX prophylaxis is not contraindicated during pregnancy, and must be given to the pregnant patient according to criteria used for all adult patients.
- CTX prophylaxis may be safely administered during breastfeeding, if clinically indicated as above.
- Continue CTX or dapsone until the CD4 count remains > 200 cells/µL for at least 3 months.
- Restart CTX or dapsone if the CD4 count falls below 200 cells/µL.
- Stop CTX or dapsone, when the active WHO stage 3 or 4 condition has resolved or been stable for at least 6 months.

3.3.3 CTX Prophylaxis Adolescent and Adult Dosing

- CTX must be given 960 mg OD (two 480 mg single-strength tablets).

3.3.4 Special Considerations for Cotrimoxazole Prophylaxis: TB/HIV

- CTX prophylaxis, in OD dosing, should be administered to patients of all ages being treated for active TB, in standard doses, regardless of CD4 cell count.
- If the CD4 count threshold and clinical criteria for continued prophylaxis are not met, CTX should be stopped at the end of TB treatment.

3.3.5 Special Considerations Cotrimoxazole Prophylaxis: Use of Dapsone for Sulfa Allergy

Although an alternative drug for patients with severe sulfonamide allergy, dapsone is also a "sulfa" drug and may likewise cause allergic reactions. On-going patient education and clinical monitoring are therefore required.

- Dapsone dosage: 100 mg PO OD.

3.4 Nutritional Support for HIV-Infected Adolescents and Adults

Importance of Adolescent Nutrition

The adolescent period is an important part of development during which the body undergoes physical and emotional change as it matures. This creates high energy and nutrient demand, hence the need to underscore the importance of nutrition in any programme that provides services to adolescents. HIV infection enhances this demand even more. Because nutrition and physical growth are integrally related, inadequate energy and nutrients can slow or stop linear growth (stunting) and delay sexual maturation.

Adolescents have different needs according to their stage of development. During early adolescence (10-13 years) there is a growth spurt and development of sexual characteristics; in mid-adolescence, the physical changes have been completed and thinking is now more concrete and reflective. In late adolescence, the body now assumes adult form and personality becomes more settled. Adequate nutrition is required to reach full potential.

> ***The goal of nutrition for HIV-infected adolescents is to provide adequate nutritional support to promote optimal adolescent growth and development during puberty.***

<u>Nutritional Interventions for HIV-Infected Adolescents and Adults</u>

- Complete nutrition counseling and education with each patient. This is essential in order to encourage increased energy intake, thereby mitigating weight loss and loss of lean body mass.
- When appropriate and feasible, encourage families to develop alternative food sources, i.e., home gardening. This has been found to be useful in providing nutritional food for adolescents and their families in some developing countries, including Botswana.
- Refer families for food assistance in cases of potential food insecurity. This is particularly important for all HIV-infected pregnant and lactating women, particularly adolescents.

The following are recommended steps in providing nutritional care and support for HIV-infected adolescents:

- ***Nutritional Assessment and Screening:*** Dietary recommendations should be tailored to meet any issues identified during the assessment and screening. Monitor interventions on a regular basis. Anthropometric measures, dietary recall, biochemical assessment, environmental and behavioral influences must form part of a comprehensive nutritional assessment.
- N***utritional Education and Counseling:*** Provide education on keeping good dietary habits in order to remain healthy. Assist them with information on how to manage any common gastrointestinal conditions. Continue to build trusting relationships with adolescent patients in order to guide them on the importance of good nutritional adherence. Involve care-givers as much as possible and discuss any nutritional issues or challenges that exist within the home environment.
- M***anagement of Diet-Related HIV Problems:*** Manage pathologies of the GI tract which may impact negatively on food or nutritional intake.
    - Modify diet as necessary to ensure nutrient intake and prevent weight loss.
    - Be aware that nausea, vomiting, anorexia, mouth ulcers and malabsorption can alter taste and that this occurs commonly.
    - Close follow-up and monitoring is recommended; document progress or deterioration.
- ***Food Security:*** The HIV epidemic has left many adolescents as heads of families caring for an ill parent or their own siblings. Food security often becomes a priority for them, thus leaving them open to exploitation.

> ***Screen all adolescents for possible risks of food insecurity and address them effectively.***

Refer patients who are experiencing food shortages which are negatively affecting their health to the local social work office in order to be evaluated for food basket eligibility.

<u>The following dietary recommendations should be made to all HIV-infected adolescents and adults, regardless of immune and clinical status:</u>

- Daily multiple vitamins in patients with poor food intake or wasting
- Use of good hygiene with food preparation
- High-protein diets
- A minimum of five portions of vegetables and fruit every day
- Thorough cooking of meat and avoidance of raw/under-cooked meat, eggs, and seafood
- Discourage the use of special “immune boosters,” and alternative medicines which are of unproven benefit and are often very expensive.
- Advise patients to come and discuss any unusual nutritional supplementation ***before beginning such regimens***.

3.4.1 Use of Ingested Traditional Medicines

Encourage patients to disclose their use of any traditional medicines.

Advise patients to avoid the use of all ingested traditional medicines as they may adversely affect appetite and digestion and cause adverse drug interactions. In some cases, traditional medicine use is associated with liver or kidney failure. However, spiritual healing and other non-parenteral, noninvasive practices should not be discouraged, since such traditional healing may provide important cultural and spiritual support to patients.

3.5 Other Routine Interventions in HIV/AIDS Care

- Advise boiling drinking water for 20 minutes when there is contamination of the water supply. Consider general CTX prophylaxis during diarrheal outbreaks.
- Patients in areas with a high prevalence of malaria should be encouraged to use insecticide-treated bed nets at night. CTX prophylaxis should also be considered.
- Hepatitis B vaccination should be encouraged for all healthcare workers, especially those who are HIV-infected, and who handle blood and other body fluids.
- Yellow Fever vaccination may be administered to HIV-infected patients with CD4 counts >200, who do not have any WHO Clinical Stage 3 or 4 conditions.

4.0 INDICATIONS FOR INITIATION OF ART

(For Infants and Children see Chapter 8, Section 8.5)

4.1 Indications for ART Initiation in Adolescents and Adults

For all adults and adolescents (regardless of pregnancy status), either one of the following conditions require ART initiation:

- WHO clinical stage 3 or 4, or
- Any CD4 cell count ≤ 350 cells/μL (previously ≤ 250 cells/μL)

4.2 Special Considerations for ART Initiation

If an HIV-infected patient has a WHO clinical stage 3 or 4 condition, the patient's clinical condition is poor, and the CD4 cell count or % is pending, do not wait for the CD4 count or % to return:

- Initiate ART on the basis of WHO clinical stage 3 or 4 condition
- Do not delay CTX prophylaxis.

However, when beginning ART in an adult/adolescent without an available CD4 count, consideration must be given to the possibility that the patient might have a high baseline CD4 count. Therefore, start patients requiring initiation without baseline CD4 counts on EFV-based ART (or LPV/r if EFV is not appropriate) because of the increased risk of NVP-induced hepatotoxicity with high baseline CD4 count. *(See Chapter 5, Section 5.2)*

4.2.1 Other HIV-related conditions which may justify ART

- Severe WHO stage 2 conditions, e.g., severe dermatitis
- Disproportionately low CD4% (≤ 15%) in an adult with absolute CD4 count > 350 cells/μL.
- In all such patients, consult an HIV Specialist for possible ART initiation.

5.0 ART INITIATION AND FOLLOW-UP

5.1 Baseline Evaluation and Preparation for ART Initiation Adolescent and Adult

1. **Complete a full physical examination and review of systems to identify any acute OIs or other serious medical conditions which require treatment before ART initiation.**

Special attention should focus on signs or symptoms of:

- ***Meningitis:*** neck stiffness, confusion, headache, fever, focal neurologic signs
- ***TB*** (pulmonary and extrapulmonary): cough, respiratory difficulty, enlarged lymph nodes, fever, night sweats
- ***KS:*** lesions, anemia, weight loss, fatigue
- ***Wasting:*** significant weight loss, intermittent or continuous diarrhea, weakness, fever
- ***PID:*** vaginal discharge, pain, fever, menstrual difficulties

2. **Evaluate patient/caregiver readiness for ART and determine potential challenges regarding issues of adherence and disclosure.**

Assess Patient/Caregiver:

- Understanding and knowledge of ART
- Willingness to begin ART
- Willingness to include an adherence partner
- Understanding that ART requires strict adherence for success
- Understanding that ARV treatment is life-long
- Current level of disclosure – family? friends? partners?
- Barriers to disclosure

3. **Evaluate all patients for any previous history of ART exposure, especially sdNVP for PMTCT in women and children**

4. **Complete all baseline laboratory evaluations.**

Document all initial medical information and findings clearly on the medical record.

5.1.1 Adherence Partners

All patients should be strongly encouraged to bring an adherence partner at ART initiation, and healthcare workers must actively include the adherence partner in adherence discussions.

- However refusal to bring an adherence partner is not a reason to defer ART. Once every effort has been made to convince the patient to have an adherence partner, ART must not be withheld.

Be mindful that successful adherence is strongly correlated to a patient's ability to disclose of their HIV status to others.

- Only in rare instances should ART initiation be indefinitely postponed; such patients may be those with severe neuro-cognitive impairment or psychosocial obstacles for which family or friends are not available for adherence support. Always consult an experienced HIV clinician in such cases.

5.1.2 Baseline Laboratory Tests (to be completed within the last 3 months)

- CD4 cell count or %.

  (If any previous CD4 count or % has made the patient eligible for ART, do not repeat for eligibility purposes, unless clinically indicated or not completed within the last 3 months.)

- FBC and chemistry, to include ALT/AST, urea, creatinine, glucose, electrolytes (sodium and chloride)
- RPR (adults and adolescents)
- Baseline Pap smears for all sexually active women (If none documented within the last 3-5 years)

Add:

- ***For PI-based ART:*** total cholesterol (TC) and triglycerides (TG)
- ***For TDF-containing ART:*** calculation of creatinine clearance (see below)
- ***Chest X-ray****: If the patient has symptoms suggestive of respiratory disease, in which case ART initiation may be delayed, pending investigation results. However, do not delay ART in critically ill patients (e.g., suspected TB patients with advanced AIDS). Consult an HIV Specialist for assistance, if necessary.*

5.2 Recommended First and Second Line Regimens for Adults and Post-Pubertal Adolescents

Before initiating ART in female adults and adolescents, establish whether there has been a history of sdNVP for PMTCT within the previous 6 months.

Standard First Line Regimens in New Treatment-Naïve Patients:

TDF + FTC (or 3TC) + EFV (as a single dose combination: Atripla)

If EFV intolerant, CD4 cell count ≥ 250 (women) or > 400 (men) cells/µL:

TDF + FTC (or 3TC) + LPV/r

If EFV intolerant, CD4 cell count ≤250 (women) or ≤400 (men) cells /µL:

TDF + FTC (or 3TC) + NVP

If women received sdNVP within the prior 6 months:

TDF + FTC (or 3TC) + LPV/r

(Note: TDF + FTC or 3TC is also available as a fixed dose combination known as Truvada. AZT + 3TC as fixed dose combination known as Combivir)

- Adult patients currently on a fully suppressive modified First Line regimen of d4T + 3TC (or ddI) + EFV or NVP should be switched to : **TDF + FTC + EFV or NVP**
- Adult patients who are currently on a fully suppressive second line regimen of d4T+ ddI + LPV/r should be switched to: **TDF + FTC + LPV/r**

Standard Second Line Regimen for those who fail the First Line Regimen of :

TDF + FTC (or 3TC) + EFV or NVP switch to: **AZT + 3TC + LPV/r (Kaletra or Aluvia)**

AZT + 3TC + NNRTI switch to: **TDF + FTC + LPV/r**
(including women started on AZT-based ART during pregnancy)

ABC + 3TC + NNRTI switch to: **TDF + FTC + LPV/r**
(if renal insuffiency or anemia, discuss with an HIV Specialist)

Patients who are currently on the previous (2005 or 2008) recommended Guidelines first line regimen of AZT +3TC + NNRTI or TDF+3TC+NVP should be maintained on this regimen, as long as it is fully suppressive, there are no AZT-related side effects, (e.g., lipoatrophy, peripheral neuropathy) and there are no serious adherence issues.

5.2.1 Virologic Failure in LPV/r Containing First Line Regimens

- When women, infants and children who were placed on LPV/r First Line regimens due to a prior history of sdNVP exposure have virologic failure, a genotypic resistance assay must be performed. Promptly discuss such cases with an HIV Specialist since it is unclear whether NNRTI-based second line regimens will be effective. Do not wait for the assay to return before discussing the case with an HIV Specialist.
- Women and men initiated on LPV/r-based regimens because of baseline CD4 cell count > 250 cells/µL and > 400 cells/µL, respectively, may be switched to EFV-containing second line regimens.
- Always complete a full adherence check in all cases of virologic failure

  (See Chapter 9, Sec 9.3)

Table 5.1: Standard First and Second Line ART Regimens in Botswana

First Line	Second Line	Modifications to Second Line
AZT+3TC+EFV (CBV+EFV) **AZT+3TC+NVP** (CBV+NVP) *AZT+ddI+EFV* *AZT+ddI+NVP*	**TDF+FTC+ALU** (TRU+ALU)	If renal insufficiency: **ABC+3TC+ALU**
TDF+3TC+EFV **TDF+3TC+NVP**	**CBV+ALU**	If anemia: (Hbg <7) **ABC+3TC+ALU**
d4T+3TC+EFV *d4T+3TC+NVP* *ddI+3TC+EFV* *ddI+3TC+NVP*	**TDF+FTC+ALU** (TRU+ALU)	If renal insufficiency and no anemia **CBV+ALU** If renal insufficiency AND anemia **ABC+3TC+ALU**

If EFV intolerant and CD4>250 women or CD4>400 men: use LPVr instead of EFV or NVP
If EFV intolerant and CD4<250 women or CD4<400 men: use NVP instead of EFV

For women who have used sdNVP: use LPVr
If LPVr intolerant consider use of Atazanavir only in consultation with an HIV Specialist

If First Line Regimen contain LPVr, second line regimen should include EFV or NVP depending on CD4 counts
Discuss with an HIV Specialist

5.3 Managing Side Effects and Potential Complications

All adverse side effects to ART or any other medication used to treat HIV patients should be properly reported on an *Adverse Reaction Reporting Form*.

(See Annex 4: Adverse Side Effects Form, page No. 163)

Observing pharmacovigilance in order to detect, assess, understand and prevent adverse effects or any other drug-related problem is essential to ensure the safe use of ART now and in the future.

It is important for HIV clinicians to develop a positive and pro-active attitude toward pharmacovigilance so that reporting adverse reactions become an accepted and understood routine.

Definitions:

- An ***Adverse drug reaction (ADR)*** is a response to medicine which is noxious (an unexpected therapeutic response) and unintended, and which occurs at doses normally used in man.
- A ***side effect*** is any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug.
- An ***unexpected adverse reaction*** is an adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristic of the drug.
- A **serious adverse event** is any event that is: fatal, life-threatening, permanently/ significantly disabling, requires or prolongs hospitalization, causes a congenital anomaly, requires intervention to prevent permanent impairment or damage.

What to Report:

- For "new" drugs report all suspected reactions, including minor ones.
- For established or well-known drugs report all serious or unexpected (unusual) ADRs.
- Report if an increased frequency of a given reaction is observed.
- Report all suspected ADRs associated with drug-drug, drug-food or drug-food supplements (including traditional, herbal or complementary products) interactions.
- ***Report ADRS in special fields of interest such as drug abuse or drug use in pregnancy and during lactation causing ADRs or side effects (e.g. birth defects with EFV use or reports of recreational uses of EFV)***
- Report when suspected ADRs are associated with drug withdrawals.
- Report ADRs occurring from overdose or medication error.
- Report when there is a lack of efficacy or when suspected pharmaceutical defects are observed.

Who Should Report:
Professionals working in healthcare are the preferred source of information in pharmacovigilance. These include family practitioners, medical specialists, nurses and pharmacists and pharmacy technicians.
Where to Send Report Forms:

Mail the ADR to the Drug Regulatory Unit (DRU). Retain a copy in the patient's care and for the clinic. Send or fax to:
Drug Regulatory Unit
Ministry of Health Enclave
P/Bag 0038 Gaborone
Botswana
Ph: +267-363-2383/2378/2381
Fax: +267-317-0169

5.3.1 Potential for Renal Failure and Tenofovir use

- ***For patients initiated on TDF-containing regimens: Creatinine clearance (CrCl) must be calculated and recorded at the baseline, 3 and 6 month post-initiation visits, and, if stable, every 6 months thereafter.*** Remember to clearly document routine monitoring of CrCl in all medical records.
- ***Reliance on serum creatinine or urea as a surrogate for creatinine clearance is not appropriate, since significant declines in GFR can occur before these blood tests become abnormal.***

Calculating Creatinine Clearance:

CrCl in cc/minute can be estimated from formulas using patient sex, age, weight, and serum creatinine (in micromole/L):

Males: 1.22 x [(140 - age in yrs) x wt (kg)]/ [serum Cr]

Females: 1.037 x [(140 – age in yrs) x wt (kg)]/ [serum Cr]

(Remember to use the weight and serum Cr from the same date)

5.3.2 Renal Insufficiency and Monitoring Creatinine Clearance

- When baseline CrCl is <60 cc/minute:
    - Recalculate the creatinine clearance 2-3 days later, repeating serum creatinine and patient weight. (If possible verify with another set of scales)

- If repeat CrCl is still <60 cc/minute and >30cc/minute:
  * Initiate **ART with AZT + 3TC + EFV**, or if there is significant baseline anemia, **ABC + 3TC + EFV.**
  * Patients initiated on AZT-containing regimens should continue these regimens indefinitely. ***However, for patients initiated on ABC, monitor CrCl every 3 months, until it is >60 cc/minute, at which time switch to TDF.***

Do not re-challenge with TDF if the original source of renal insufficiency was TDF-induced.

  * If renal insufficiency continues with either AZT or ABC use and creatinine clearance remain <60 cc/minute, then consult an HIV Specialist.
- For those with a repeat CrCl <50 cc/min: initiate as above but with the following renal dose adjustments:

Renal Adjustments for 3TC:

* CrCl 30-50cc/minute: 150 mg. OD
* CrCl 15-29 cc/minute: 150 mg. once then continue 100 mg. OD
* CrCl 5-14 cc/minute: 150 mg. once then continue 50 mg. OD
* CrCl ≤5 or dialysis: 50 mg. once then continue 25 mg. OD

  (Note: take dose after HD session on dialysis days)

Renal Adjustments for AZT:

* CrCl<15cc/minute or hemodialysis: 300 mg. OD:

5.3.3 Special Considerations with TDF Use

Proceed with caution when initiating TDF-containing regimens in patients with:

- Renal disease (i.e., insufficiency, chronic infection, kidney stones)
- Poorly controlled diabetes or hypertension

Monitor such patients closely and discuss alternate regimen choices with an HIV Specialist, when necessary.

5.3.4 Tenofovir Use in Pregnancy

In 2010, the WHO recommended use of TDF in pregnancy as there was "limited data on potential maternal and infant bone toxicity with use of TDF."

Therefore, in order to allow women of reproductive potential to also benefit from once-a-day dosing schedules of Atripla, TDF use during all trimesters of pregnancy is now endorsed.

5.3.5 Managing Hepatitis

Patients co-infected with HIV and chronic HBV or HCV progress more often and more rapidly to cirrhosis, end-stage liver disease and hepatocellular carcinoma than those infected with HBV or HCV alone. Management requires that co-infected patients are placed on ART regimens with activity against the hepatitis virus, namely TDF, 3TC or FTC. Special caution should be exercised with the discontinuation of these drugs.

NVP-induced hepatitis must also be monitored and carefully managed in those patients who are initiated on NVP containing regimens.

Discontinuation of TDF + FTC (or 3TC) with chronic HBV Infection:

- In patients with HBV and HIV co-infection, discontinuation of TDF + FTC (or 3TC), which have anti-HBV activity, may cause a "hepatitis flare" and is generally not recommended.
- However, in the rare instance when TDF + FTC or 3TC must be stopped, monitor AST and ALT, 2 and 4 weeks post-discontinuation, with patient education about hepatitis symptoms.
- In patients with suspected HBV flare, discuss management with a HIV Specialist.
- If ART needs to be modified due to virologic failure, the ARV drugs active against HBV (TDF, 3TC or FTC) should be continued in combination with other suitable ARV drugs to achieve full viral suppression.

5.3.6 NVP-associated rash and hepatotoxicity

Always educate patients/caregivers about the following signs and symptoms of hepatitis:

Nausea, jaundice, abdominal pain, hepatic tenderness, hepatomegaly, fatigue and malaise; elevated transaminases typically seen on laboratory testing.

- The initial dose of NVP should be OD for two weeks for all age ranges.
- After 2 weeks, follow up for clinical evaluation for any side effects and for AST/ALT testing.
- If there are no apparent clinical signs or symptoms of NVP side effects, increase NVP to BD, with follow-up in another 2 weeks for repeat clinical evaluation and repeat AST/ALT.

> If LFTs are elevated 3x the ULN and the patient is symptomatic for hepatitis or if LFTS are >5 ULN without symptoms, stop all ART and discuss case management with an HIV Specialist.

If a benign rash (no mucosal involvement) develops within the first 2 weeks of NVP initiation:

* Maintain OD dosing, and obtain AST/ALT to rule out prodrome of hepatitis.
* Wait until rash resolves before dose-escalation to BD. If benign rash re-occurs after BD dose escalation, continue BD dose but monitor patient closely and repeat AST/ALT.
* Do not use systemic steroids to prevent or treat benign NVP/EFV associated rash.

Skin toxicity is most commonly a mild, self-limited rash that does not warrant discontinuation of NVP. However, though rare, severe skin toxicity can occur, including potentially fatal Stevens-Johnson syndrome.

If a serious/severe rash develops with any mucosal involvement:

- Stop all ARVs, including cotrimoxazole
- Prescribe Prednisolone: 60mg PO OD for 5 days with a taper to 40 mg. PO OD x 5 days, then 30 mg. PO OD for 5 days
- Continue to monitor AST/ALT closely

- If rash appears bullous and is progressing to full Stevens-Johnson syndrome, admit for in-patient care and consideration of IV antibiotic coverage. *(See Section 5.3.9 C below).*
- However, if the rash is not severe enough for hospitalization, monitor patients closely (every day or every other day) to make sure the rash is no longer progressing.
- Do not re-challenge with NVP after the rash resolves.

Remember: Do not initiate NVP in patients with high CD4 counts (Women >250 cells/µL; men > 400 cell/µL).

5.3.7 Switching patients from EFV to NVP

The risk for hepatitis may not be as great when patients have been on fully suppressive non-NVP-based ART, with an ART-induced CD4 cell count increase to >250/µL (women) or >400 cell/µL (men), so when clinically necessary a switch from EFV to NVP can be made with caution.

- In instances of intolerance to EFV or first line PI's (e.g., persistent EFV-induced CNS side effects or gynecomastia, LPV/r-induced chronic vomiting or diarrhea), switching from EFV or LPV/r to NVP can be initiated, provided:
  - Viral load is undetectable
  - There is no hiatus between discontinuation of EFV (or LPV/r) and replacement with NVP. **(In such cases, dose escalation of NVP is not required, and the BD dose can be started as the CYP450 enzymes have already been induced.)**
  - Patients are monitored for any NVP-induced hepatitis and educated appropriately.

However, if EFV-associated hepatitis or SJS developed initially from EFV use, LPV/r should be substituted for EFV once the patient recovers, since recurrence of toxicity after switching from EFV to NVP is far more likely than vice-versa.

5.3.8 Switching patients from NVP to EFV

Because there is up to 50% cross-reactivity between NVP and EFV, any substitution of EFV for a NVP-associated toxicity must include careful patient education and clinical/laboratory follow-up.

- For mild hepatitis or early SJS due to NVP, which does not progress to florid disease, and from which the patient recovers promptly, it may be possible to substitute EFV for NVP after the patient recovers.
- If there is any concern that replacement of NVP with EFV may risk recurrence of the toxicity, then use LPV/r instead.

5.3.9

a) Managing Lactic Acidosis

Lactic acidosis is a life-threatening complication which requires that all ARVs are stopped immediately with close monitoring or hospitalization of patients for acute care. Mortality is observed in up to 50% of cases. Patients on d4T, ddI and AZT as well as women who are obese, are particularly at risk.

Symptoms and Diagnosis:

- Hyperlactataemia presents with vague symptoms such as weight loss, nausea, vomiting, abdominal pain, shortness of breath, malaise and fever.
- Symptoms may also rapidly progress with tachycardia, tachypnea, jaundice, muscular weakness, mental status changes and respiratory distress, pancreatitis and organ failure.
- Laboratory findings may include: increases in lactate (often > 5 mmol/L), anion gap, AST, ALT, PT, and bilirubin.

Treatment:

Lactate level >5:

- Admit for supportive inpatient care including, oxygen and IV fluids
- Stop all ART
- Once clinically stable and lactate is below 2, re-initiate with appropriate ART. Discuss with an HIV Specialist as necessary.

Lactate level = 2.5-4.9:

- Check respiratory rate (RR). If >20 breaths/minute admit for inpatient care as described above.
- If RR ≤20 breaths/minute, switch offending ARV and recheck lactate in 3 days. If symptoms grow worse, discuss with an HIV Specialist.
- Lactate level ≤2.5 with symptoms, discuss with an HIV Specialist

b) Managing Stevens-Johnson Syndrome

SJS usually obligates cessation of all ARVs to permit recovery.

- Patients seriously ill from overt SJS (e.g., high fever, desquamating rash, severe mucous membrane involvement, clinical prostration) may not be able to take any medications by mouth, and so all ART must be stopped simultaneously.

Certain clinical distinctions and strategies may preserve NNRTI treatment options after the SJS resolves:

- If AST/ALT elevations are not > 5 times the ULN, and if the patient has mild symptoms (i.e., no jaundice, fever or vomiting, and appears non-toxic), it may be possible to discontinue NVP while continuing the two N[t]RTIs for 7 days, to preserve EFV as a possible future treatment option after the hepatitis/SJS has resolved.

However, if one of the NRTIs is ABC, which is metabolized by the liver, then all ART must be stopped simultaneously.

c) Managing ARV-Related Hyperlipidemia

All classes of ARVs can cause elevated total cholesterol (TC) and triglycerides (TG), which, if not addressed, may lead to serious long term, cardiovascular and/or cerebrovascular disease. In addition, elevated TG can cause pancreatitis.

> ***Because patients are living longer on ART, lipid related mortality and morbidity due to ARV therapy must be addressed promptly, including modification of other vascular risk factors such as smoking, hypertension, diabetes and obesity.***

- Elevated lipids can appear within the first months of initiating ART.
- The most significant lipid abnormalities occur with d4T and PIs, including LPV/r. NNRTIs cause relatively minor increases in cholesterol.
- Before initiation of PI-based ART, determine the baseline TC and TG and, if elevated, manage appropriately with follow-up as necessary. Ask patients about previous family history of heart related disease.
- ***Patients on PI-based ART should be screened annually with either fasting or non-fasting TC and TG***. If TC is > 5mmol/L, then fasting LDL is necessary.

Clinically significant LDL thresholds/goals vary according to the presence of known vascular risk factors or disease as follows:

- Vascular disease or diabetes: LDL should be < 2.5 mmol/L
- 2 or more cardiac risk factors: LDL should be < 3.3 mmol/L
- No cardiovascular risk factors: LDL should be < 4.0 mmol/L

As a rule, TC should be < 4.5 mmol/L. Any increased LDL (per above) and/or TC > 4.5 mmol/L requires the following step wise approach:

- Ongoing patient education about the risks of elevated lipids
- Dietary intervention, including nutritionist referral for counseling, if available
- Exercise, as indicated by the patient's overall health and cardiovascular status
- *Aggressive management of associated vascular risk factors:* cigarette smoking, hypertension, obesity, diabetes, insulin resistance, stress

If the above interventions are not successful, prescribe medications:

- Atorvastatin 10mg PO QD
- Increased TG: bezafibrate 200mg BD
- Follow-up lipids every 3 months until normal, and thereafter annually

d) Efavirenz Contraindications:

Avoid EFV use in the following:

- Severe, acute or chronic psychiatric illnesses (e.g., psychosis, depression, bipolar disorder, schizophrenia), unless the potential benefits outweigh the risks.
- History of attempted suicide.
- Children under 3 years of age.
- Co-administration with carbamazepine (substitute with gabapentin or lamotrigine).

Chronic, controlled seizure disorder is not a contraindication to EFV use. However, exercise caution with co-administration of anti-epileptics.

(See Annex 5: ART Formulations & Dosing, page No. 164)

5.4 Goals of ART

The goals of ART are to restore immunologic function and quality of life, and to increase life expectancy by decreasing morbidity and mortality due to HIV infection.

For ART initiation in patients of all ages, initial treatment success or failure is determined by the viral load 6 months after ART initiation.

- For the vast majority of **adult** patients initiated on ART, viral load at 3 months post-initiation will be < 400 copies/µL. However, a minority of adults may require longer (up to 6 months) before viral load becomes fully suppressed.
- ***For the adult patient whose viral load at 3 months is not < 400 copies/µL, there must be careful evaluation and monitoring for treatment failure, especially with regards to non-adherence.***
- Pediatric patients may require longer than 3 months to fully suppress viral load, but should nonetheless have viral load < 400 copies/µL no later than 6 months after ART initiation.
- ***Pediatric and adolescent patients who do not achieve a viral load < 400 copies/µL by 6 months after ART initiation must be discussed with a pediatric HIV Specialist.***

5.5 Recommended Clinical and Laboratory Monitoring Patients on ART

Clinical Visit Schedule While on ART:

- During the first two years after ART initiation, every patient should be seen ***every 3 months***, or as often as clinically indicated.

- If after the first two years of ART an ***adult*** patient has remained clinically stable, (i.e., has not had any treatment failure, is adherent, and has not developed ARV toxicity or other HIV-related complications) routine follow-up visits may then be decreased to ***every 6 months***.
- Children and adolescent patients must continue to be followed every 3 months, until age 18 years.

Clinical evaluation while on ART must always include:

- Review of possible ART side effects, as well as any other patient signs and symptoms of OIs.
- Clinical screening for active TB infection (include TB contact with children)
- Family planning and sexual reproductive choices
- Screening Pap smear for sexually active women every 3-5 years
- Assessment of adherence and initiation of any interventions necessary to enhance adherence.
- Assessment of all psycho-social issues
- Counseling on safe sex, nutrition, and avoidance of smoking and ingested traditional medicines.
- Ongoing improvement of patient HIV literacy: *e.g., the patient/care-giver should eventually know the names and doses of the ARVs and other HIV-related medications.*
- For all pediatric patients: Assessment for growth and development, with graphing of weight and height, and head circumference measurements for patients under age 2 years of age.
- Reinforcement of the importance of remaining in care

Laboratory Monitoring of Patients on ART:

After obtaining baseline, pre-initiation laboratory tests (see Section 5.1.2), routine laboratory monitoring of patients initiated on ART must include:

- **Viral load:** 3 and 6 months post-initiation, then as follows:
    - Every 6 months for adults
    - Every 3 months for pediatric patients and adolescents

> ***On a case-by-case basis, practitioners have the discretion to decrease the frequency of pediatric and adolescent viral load testing to every 6 months, after every-three-month viral loads over the prior 24 months have been fully suppressed, and adherence and care-giver/family support are deemed excellent.***

- **CD4 cell count or %:** 3 and 6 months post-initiation, then every 6 months (all ages) if the CD4 cell count or % response at 12 months after ART initiation has increased > 25-50 cells/µL for adults and adolescents, or CD4% increase > 5 percentage points above baseline for pediatric patients.

  Once a patient's CD4 cell count or % has been > 300 cells/µL and > 30%,respectively, for one year (i.e., two consecutive six-month determinations), then CD4 cell counts/% should be monitored every 12 months.

CD4 cell count or % measurements should return to every three month frequency (or more often as clinically indicated) when:

- Any new WHO stage 3 or 4 clinical condition or symptom develops
- A suppressed viral load becomes detectable
- ART regimen is changed for treatment failure

- Non-adherence is suspected
- Viral load results are not available or delayed for more than one month

Once any of the above situations becomes stable for 6 months, then CD4 cell count or % determinations may return to every 12 months.

- **FBC:** AZT-based ART: at 4 and 12 weeks post-initiation, ***then annually only,*** and as clinically indicated

  If not on AZT-based ART: ***annually only,*** or as clinically indicated
- **AST/ALT:** NVP-based ART: 2, 4, and 12 weeks post-initiation, thereafter only as clinically indicated.

  EFV-based ART: 4 and 12 weeks post-initiation, thereafter only as clinically indicated
  PI-based ART: only as clinically indicated
- **Glucose and total cholesterol/triglycerides:** annually ***only if on PIs***
- **TDF-containing regimens** only: Creatinine and creatinine clearance (CrCl): 3 and 6 months post-initiation; once stable, every 6 months.
- **Chemistry**: after baseline, only as clinically indicated
- **RPR**: after baseline, only as clinically indicated

Do not "routinely" order FBC, AST/ALT, CD4 cell count or %, and viral load at every clinical visit rather follow the recommended schedule.

Table 5.2: Adult Laboratory Monitoring Schedule for 1st Line Regimens containing: TDF/FTC/EFV, TDF/FTC/NVP, CBV/EFV, CBV/NVP, ABC/3TC/EFV, ABC/3TC/NVP and LPV/r*

	Baseline	2 wks	1 month	3 months	6 months	12 months	Thereafter
CD4 Count	if none in the past 3 months			x	x		q6 months
Viral Load	None						q6 months
FBC			x CBV or AZT	x CBV or AZT			q12 months
Chemistry							As indicated
AST/ALT		x NVP	x NVP	x NVP			As indicated
Creatinine & Cr CL	TDF			TDF	TDF	TDF	q6 months
RPR							As indicated

** For LPV/r containing 1st line regimens add: glucose, cholesterol and triglycerides at baseline and annually or as clinically indicated*

Criteria for Priority Laboratory Monitoring

- CD4 and VL for all patients < 20 years of age
- Confirmation of virologic failure
- ***Priority Viral Load (PVL)*** prior to switching from an adult or pediatric regimen containing d4T and/or ddI, when there has been no VL performed within the previous 3 months
- Follow-up 6 week VL after switching/restarting/continuing ART, and after any interventions for treatment failure due to non-adherence, toxicities, vaccinations, drug interactions, inappropriate ARV dose, and gastroenteritis
- ***CD4 cell count for any pregnant woman who is not yet on ART, in order to determine her eligibility for ART.***

If the 6 week viral load remains < 400 copies µL, then resume normal viral load monitoring. CD4 cell count or % monitoring can remain at every 6 month intervals.

NOTE: Whenever DNA PCR tests, resistance assays, CD4 cell counts, and viral loads are delayed, determine from the referral laboratory an estimated time for return of these results. Do not automatically repeat pending tests, since such repeat determinations will only increase laboratory burden, thereby further delaying return of results.

6.0 TB/HIV CO-INFECTION

Tuberculosis is a WHO Stage 3 or 4 condition and therefore people living with HIV and TB are eligible to begin ART regardless of CD4 count.

Co-infection with TB and HIV markedly increases the mortality and morbidity of both diseases, and represents an ongoing public health crisis in Botswana. In 2010, 68% of TB patients in Botswana were co-infected with HIV. Patients with both infections are more likely to have extrapulmonary TB and so the diagnosis of TB is often more difficult, especially in the advanced stages of HIV. Important steps have been taken in Botswana to improve integration of TB and HIV services in order to increase access to ART for TB patients and improve TB patient outcomes for those already on ART.

Increasing clinical evidence shows that early ART initiation reduces the risk of death in TB/HIV patients and this is particularly important at low CD4 counts. ART should be started as soon as the patient is tolerating ATT and at least by 2-8 weeks of the initial phase of ATT in those who are ART naïve. Close monitoring for signs or symptoms of hepatitis and worsening of TB due to IRIS is essential.

Optimal management of dually infected patients will reduce mortality, improve patient outcomes and prevent adverse reactions. Therefore, all HIV-infected patients must receive a thorough and documented screening for signs and symptoms of active TB infection at every clinical visit

6.1 Interaction Between TB and HIV

HIV increases the rate of progression of TB infection to active disease and increases the risk of TB recurrence. People living with HIV have a 10% annual risk of reactivating latent TB infection, compared to a 10% lifetime risk in HIV negative individuals. Tuberculosis also increases HIV progression to AIDS by decreasing CD4 counts and increasing viral loads.

6.2 Strategies to Reduce the Burden of TB in HIV Patients

6.2.1 Intensified Case Finding (ICF)

People living with HIV must be screened for TB in all places where they receive medical care including: ARV clinics, hospital wards, PMTCT facilities and HIV Testing and Counselling Centres (HTC). All HIV patients must be routinely screened for TB at health facilities and this information must be documented at each and every patient encounter.

ICF involves screening for signs and symptoms of TB by asking patients about cough, fever, night sweats and weight loss. It is also important to examine patients for evidence of lymphadenopathy. No one symptom is diagnostic for TB. Therefore any duration of cough, fever, night sweats, weight loss or presence of enlarged lymph nodes in an HIV patient should prompt an evaluation for TB.

- Always complete a comprehensive physical examination of HIV patients during routine follow up visits in order to rule out TB.

In addition to the above symptoms, TB screening in children must include asking about decreased playfulness and failure to gain weight (as evidenced on the under 5 card). Most young children acquire TB from an adult with smear positive TB. Therefore, it is essential to ask about TB exposure in the household as part of the symptom screen.

> ***Remember: A detectable viral load in a previously suppressed patient may be the first sign of TB disease. After assessing other causes of ARV treatment failure such as adherence, all failing patients must be carefully screened for TB.***

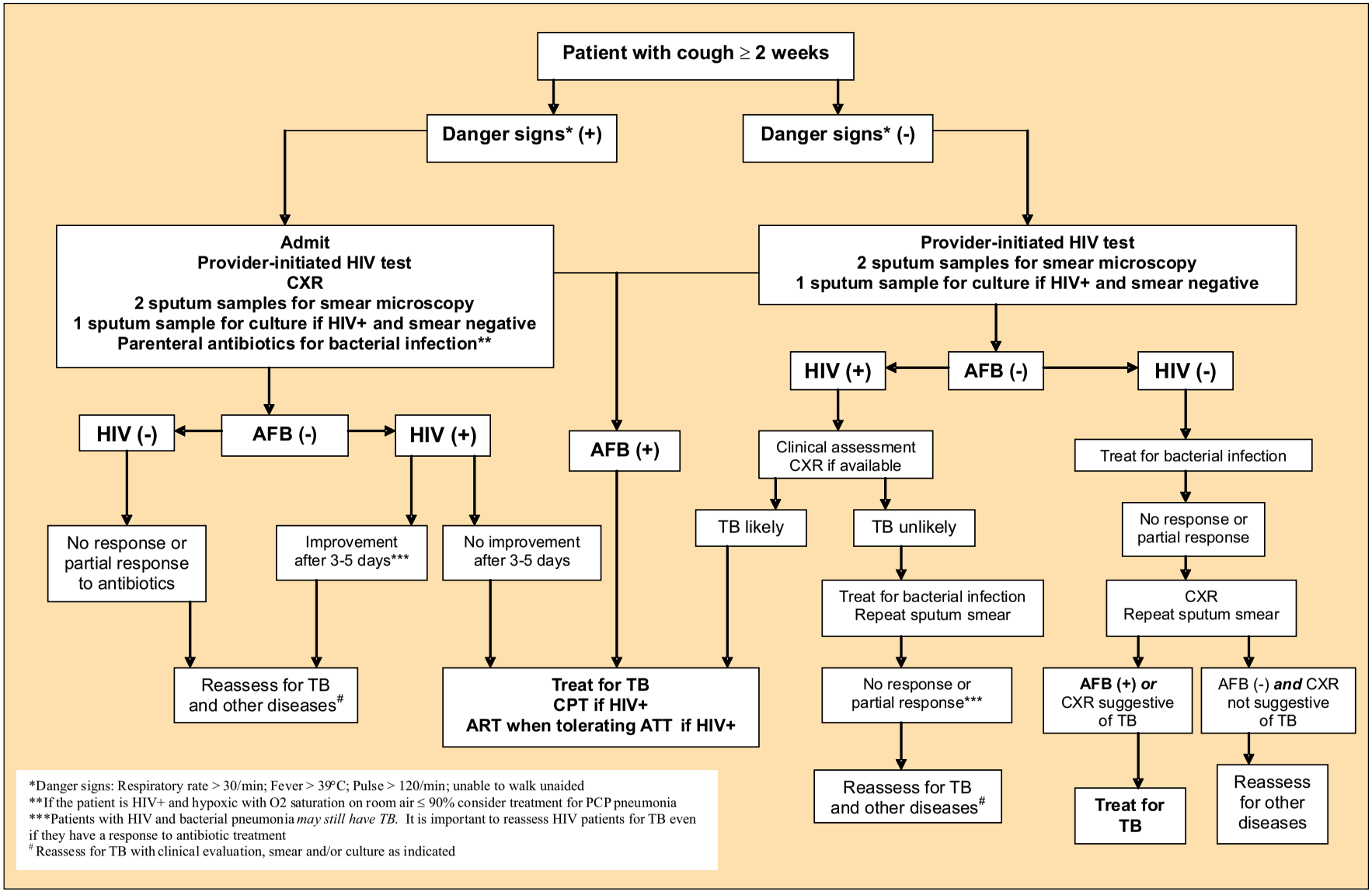
Screening Signs and Symptoms:

- Cough, fever, night sweats, weight loss, and lymphadenopathy, of any duration
- In children also include: decreased playfulness, failure to gain weight, and TB exposure in the household.
- All patients on ARV treatment with a detectable viral load must also be closely evaluated for TB co-infection.

A positive response or finding to any one of these signs and symptoms requires further evaluation for TB as follows:

(See Annex 6: Clinical Presentation of EPTB, page No. 169)

Figure 6.1 Diagnostic Algorithm for PTB in Adults



It is more challenging to diagnose TB in patients with HIV infection, especially in those with advanced immune suppression. Sputum smear microscopy and CXR may be normal in these patients, even in the presence of TB disease. For all HIV-infected TB suspects, culture should be requested if two smear microscopy results are negative.

Sputum culture is the most sensitive test for TB and detects more cases than smear microscopy. Culture is also more costly and time-consuming than microscopy and requires specialized media and skilled laboratory personnel. Therefore culture is not routinely recommended for all patients. However, culture is essential for certain patient groups in who the risk of drug-resistance is high or the sensitivity of sputum microscopy is low.

Drug susceptibility testing is performed on all positive cultures for isoniazid (H), rifampicin (R), ethambutol (E) and streptomycin (S). Results are available up to 40 days after the date the culture is positive. If the National TB Reference Laboratory confirms MDR-TB, the specimen is sent to a regional reference laboratory in South Africa for second-line DST. Due to the high mortality from TB, it is essential to detect drug-resistance early in patients with HIV.

(See Annex 7: Instructions on Sputum Collection, page No. 170)

6.2.1a Indications for Culture and DST:

- HIV-infected patients with 2 negative sputum smear results
- New patients who are smear positive at month 3 of treatment
- All retreatment patients regardless of reason (failure, relapse, or default)
- Patients who have received ATT for >1 month in the past
- All children
- Patients who develop TB during or after IPT
- Symptomatic individuals at higher risk of MDR-TB: lab workers, MDR-TB contacts, HCW
- Investigation of fluids and tissues suspected to be infected by M. tuberculosis
- Patients with suspected cryptogenic TB should have blood taken for TB culture and sent to the NTRL. The blood specimen should be collected in special culture bottles available from the National Health Laboratory

At present the NTRL is the only public sector culture and DST lab in Botswana. Culture may be positive in 7-14 days, but final results may take up to 8 weeks. If culture results do not arrive, they may be obtained directly from the NTRL (Gaborone – Tel: 3902368.)

Molecular Methods

Molecular tests detect M. tuberculosis DNA from a sample of sputum, body fluid or tissue. These tests are more sensitive than sputum smear microscopy. Currently the NTRL is building capacity for molecular tests which may be available by 2013. GeneXpert is one molecular test that can diagnose both TB and resistance to rifampicin from a sputum sample. GeneXpert is now recommended by the WHO to improve TB diagnosis in resource-limited countries and Botswana will be introducing GeneXpert at district and facility level over the next several years. When GeneXpert becomes widely available *(See Annex 8: Algorithm for the Diagnosis of PTB Using Xpert, page No. 171)* Until then smear microscopy remains the cornerstone of TB diagnosis in Botswana.

6.2.2 Isoniazid Preventive Therapy (IPT) (Pediatric & Adult)

Isoniazid preventive therapy (IPT) is an intervention to prevent people infected with TB from developing active TB disease, and involves a single 6-month course of daily isoniazid and pyridoxine.

It is important to note that anyone, regardless of age, who is asymptomatic but has been identified as an MDR-TB contact should not receive IPT

Pediatrics

All children ≤ 5 years, ***regardless of HIV status***, who are in contact with a smear positive individual, should be fully assessed for HIV and TB infection. Those children who are not clinically symptomatic for TB should receive IPT for 6 months.

All HIV-infected children > 5 years and ≤ 12 years, who are in contact with a smear positive individual, should be fully assessed for TB infection. Those HIV-infected children and adolescents who are not clinically symptomatic for TB should receive IPT for 6 months.

Adults

The Botswana IPT Programme is currently being re-structured and will be piloted at selected sites with a revised clinical protocol during 2012. Questions regarding IPT in healthcare facilities should be directed to the DHAPC.

(See Annex 9: Instructions on The Tuberculin Skin Test TST, page No. 172)

6.2.3 Infection Control

People living with HIV are at particular risk of TB transmission within health care settings. Infection control measures must be implemented at all times in all facilities where HIV infected patients receive care.

The most critical infection control measures are administrative and environmental controls which include:

- Rapid diagnosis of TB suspects and initiation of ATT as soon as possible
- Triage of coughing patients to separate waiting areas and hospital wards
- Sputum collection outside or in well-ventilated spaces only
- Patient education about proper cough hygiene
- Discharge of TB patients as soon as stable after initiating ATT
- Open windows and doors to improve ventilation

(For more information about TB infection control refer to Chapter 2, 7th Edition, 2011 National Tuberculosis Guidelines and the 2009 National TB Infection Control Guidelines. 1st Edition)

6.3 Strategies to Reduce the Burden of HIV in TB Patients

6.3.1 HIV Testing in TB Patients and Suspects

Tuberculosis is often the first indication that a person has underlying HIV infection. HIV testing must be offered to all patients who present with signs or symptoms suggestive of TB, regardless of age. Knowledge of HIV status is also important to facilitate access to key interventions such as CTX and early enrolment in ARV Care and Support.

- All TB patients and suspects must be screened and tested for HIV infection.
- All TB/HIV co-infected patients must receive prompt referral and timely follow-up in HIV care facilities, including counseling, social support and home-based care as necessary.

6.4 ART and ATT Co-Administration

(See Annex 10: ATT Fixed Dose Combinations Children and Adults, page No. 174)

6.4.1 Adult & Adolescent Patients Already on ART Who Develop TB

6.4.1a First-line ART patients who develop TB

Patients on first-line ART who develop TB should continue first-line ART while ATT is initiated, with close monitoring for any potential drug-drug interactions (e.g., rifampicin and LPV/r), additive toxicities (e.g., hepatitis), and TB-related IRIS.

- Stable patients receiving NVP should remain on NVP.
- First line regimens which are EFV and NVP based, do not require dose modification with ATT. The standard EFV dose of 600 mg Q nocte should be used.

6.4.1b Adult Second-line ART patients who develop TB

Patients on second-line ART containing a PI require dose modification as the effect of rifampicin on PI levels is significant. Therefore, PIs cannot be used in standard doses with rifampicin.

Preferred option:

- Double dosing of LPV/r to 800 mg/200mg BD (i.e., 4 LPV/r tablets BD)

Alternative options:

- Continue standard LPV/r dose 400 mg/100mg BD and add extra RTV boosting 300 mg BD (i.e., 1:1 ratio of LPV and RTV)

- RTV 400 mg / SQV 400 mg BD can be substituted for LPV/r. However, this combination may be associated with the risk of hepatotoxicity if TB treatment is started first (consult an TB/HIV specialist prior to use)

Remember, after completing a rifampicin-based ATT regimen, LPV/r must be changed back to standard doses.

6.4.2 ART Naïve Patients Who Develop TB

All HIV patients with TB are eligible to begin ART regardless of CD4 cell count.

TB treatment should be started first, followed by ART as soon as possible and within the first 8 weeks of beginning ATT

- Patients with CD4 count ≤100 cells/µl: start ART as soon as the patient is tolerating ATT
- Patients with CD4 count >100 cells/µl: start ART within 8 weeks and at least by the end of the initial phase of ATT

For patients with CD4 counts ≤50 cell/µL, ART should be started as soon as possible. However, caution is advised in severely immunosuppressed patients with suspected neurological involvement or deranged LFTs. Great care must be taken to monitor these patients for hepatitis and worsening of TB due to IRIS (seek advice from TB/HIV specialist if necessary).

6.4.3 ART Regimens in Treatment Naïve TB/HIV Co-infected Patients

6.4.3a Adults

- The standard first-line regimen is the same for TB/HIV co-infected adult patients: TDF+ FTC or 3TC + EFV (Atripla). Nevirapine may be used in cases of EFV intolerance.
- The standard second-line regimen is AZT + 3TC and double dosed LPV/r.

Table 6.1 ART Regimens for Treatment Naive Adults taking ATT

Line of Therapy	Drug Regimen
Naïve First-line adult and adolescent	**TDF + FTC or 3TC + EFV (Atripla)**
Alternative first-line	TDF + FTC or 3TC + NVP (TRU+NVP)
Second-line	**AZT+3TC+Double-dose LPV/r* (Aluvia)**
Alternative second-line	AZT+3TC+LPV/r + 300 mg Ritonavir BD
Pregnant women	TDF + FTC or 3TC + EFV (Atripla)**

* The dose of LPV/r should be 800 mg/200mg twice daily.
** See chapter 7 for details for ART during pregnancy.

Contact TB/HIV specialist in cases of salvage or unusual regimens.

6.4.3b Pediatrics

- In those ≤ 3 years: The standard first-line regimen is AZT/ 3TC and NVP.
- In those > 3 years: The standard first-line regiment is AZT/3TC, and EFV.
- The standard second line pediatric treatment regimen is ABC /3TC, and either double-dosed LPV/r or a standard dose of EFV or NVP depending on the original first line regimen and the age of the child.

NOTE: In both adult and pediatrics, treatment experienced or naïve patients:

- Atazanavir should not be used with Rifampicin due to drug/drug interactions. Therefore, LPV/r will continue to be the PI of choice for all TB/HIV co-infected patients taking Rifampicin. For questions consult a TB/HIV specialist.

6.5 Management of Severe Adverse Effects

If a severe adverse event occurs during TB treatment and ATT is the most likely cause, stop all drugs. The only exception is hearing loss or severe dizziness due to streptomycin. In this case, only streptomycin may be stopped and an alternative drug such as levofloxacin, may be substituted.

6.5.1 Management of Renal Failure

Renal failure complicates TB treatment because some anti-TB drugs are excreted by the kidneys. Ethambutol and streptomycin are cleared by the kidneys, while isoniazid and rifampicin are metabolized by the liver. Pyrazinamide is primarily metabolized by the liver but metabolites of the drug are cleared by the kidney and can accumulate in renal failure. The dosing frequency, rather than the drug dose, is adjusted in renal failure.

If the creatinine clearance is < 30 µL/min

- Ethambutol, pyrazinamide and streptomycin should be given at full doses every other day.
- Streptomycin should be avoided in renal failure if possible, due to the increased risk of hearing loss.
- Levofloxacin 750 mg every other day may be substituted for streptomycin for patients with renal failure in the first 2 months of a retreatment regimen

6.5.2 Management of ATT/ART-Induced Hepatitis

Regardless of ART regimen:

- AST/ALT should be monitored monthly for the first 3 months of ATT, or more frequently as indicated.
- There must also be patient/caregiver education about the signs and symptoms of hepatitis, with instructions to return immediately if any occur.

The development of hepatotoxicity (transaminases >3 ULN with symptoms - nausea, vomiting, jaundice, abdominal pain, etc.) or >5X ULN without symptoms, is a potentially life threatening complication of early initiation of ART during the first 2-3 months of ATT.

If ATT/ART-Induced Hepatitis Occurs:

- All medications with any potential to cause hepatotoxicity must be immediately discontinued, including ART, ATT, and CTX
- However, for those taking EFV or NVP, a one week "tail" of the two N[t]RTIs (but not ABC) should be given to prevent development of NNRTI resistance and preserve the use of EFV or NVP as a future treatment option, after the hepatitis has resolved
- AST/ALT must be monitored at least weekly until a significant downward trajectory has been established
- If significant nausea and vomiting develop, hospitalization may be necessary for IV fluids and closer clinical monitoring.
- Consult a TB/HIV specialist for alternative ATT or ARV regimens in severe cases.

Additional supportive measures include:

- Adequate rest and nutrition (with vitamins)
- Avoidance of alcohol, traditional medicines, and over-the counter medications, e.g., paracetamol.

Most patients with ATT drug-induced hepatitis will tolerate re-introduction of all first-line drugs. Once AST/ALT have dropped below 2 x the ULN and the patient's clinical condition has improved, then gradually re-introduce ATT. Introduce drugs one at a time gradually increasing the doses as outlined in Table 6.2 below. Rifampicin should be started first, because of its critical importance in the treatment regimen and because it is less likely to cause hepatitis than isoniazid or pyrazinamide. Ethambutol is not hepatotoxic so it should be started on Day 1 at full dose.

Table 6.2 Reintroduction Schedule of ATT Drugs after Drug-Induced Hepatitis

Day	Drug and dose
1	R 150 mg + E 1200 mg*
2	R 300 mg + E 1200 mg
3	R 450 mg + E 1200 mg
4	R 600 mg + E 1200 mg
5	R 600 mg + E 1200 mg *Check LFTs, if stable proceed*
6	R 600 mg + E 1200 mg + INH 100 mg
7	R 600 mg + E 1200 mg + INH 200 mg
8	R 600 mg + E 1200 mg + INH 300 mg
9	R 600 mg + E 1200 mg + INH 300 mg *Check LFTs, if stable proceed*
10	R 600 mg + E 1200 mg + INH 300 mg + Z 500 mg
11	R 600 mg + E 1200 mg + INH 300 mg + Z 1000 mg
12	R 600 mg + E 1200 mg + INH 300 mg + Z 1500 mg
13	R 600 mg + E 1200 mg + INH 300 mg + Z 2000 mg
14	R 600 mg + E 1200 mg + INH 300 mg + Z 2000 mg *Check LFTs*

*All doses are weight-dependent and the highest dose might not be indicated for low-weight patients or children.
Adapted from American Thoracic Society Guidelines

If symptoms recur or liver function tests increase >2 times normal, stop the last drug added. Consult a specialist if hepatitis recurs, or a patient is unable to tolerate the full reintroduction. A drug-related adverse event form should be completed and submitted to the Drug Regulatory Unit.

Patients with TB/HIV who are taking both ATT and ART have a higher risk of hepatitis. Check baseline ALT before starting ATT in these patients.

- Monitor ALT on a monthly basis for the first 3 months on ATT.
- If the ALT >3 times normal, consider an alternative regimen or consult a TB/HIV Specialist.

Patients with severe TB should be treated with streptomycin, ethambutol and levofloxacin until they are well enough to attempt re-introduction.

If clinical and laboratory parameters remain stable for 1 month after ATT:

- Restart ART.
- Replace NVP with either EFV or LPV/r depending upon the clinical and laboratory severity of the patient's hepatitis.
- Restart cotrimoxazole.

If severe hepatitis recurs, all medications must again be stopped, and the patient discussed with a TB/HIV Specialist.

(See Annex 11: Overlapping and Additive Toxicities of ART and ATT, page No. 176)

(See Annex 12: Symptom-based Approach to Management of Common Side Effects, page No. 177)

6.6 TB Immune Reconstitution Inflammatory Syndrome (TB-IRIS)

Immune Reconstitution Inflammatory Syndrome is an important complication of ART and ATT and can present as a paradoxical worsening of the patient's clinical status, often due to a previously sub-clinical and unrecognized opportunistic infection. In Botswana IRIS is most commonly due to underlying TB disease. TB-IRIS may also develop in a patient who does not have any obvious signs or symptoms of TB disease at ART initiation.

Most cases of TB-IRIS develop within 3 months of ART initiation and are more common with an initial low CD4 cell count and high viral load, a shorter time interval between the start of ATT and ART, and with disseminated or EPTB. The syndrome may present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress or exacerbation of inflammatory changes at other sites. It is relatively common in mild to moderate forms but is rare in its severe forms.

> ***Patients with advanced HIV may show clinical deterioration for a number of other reasons including other opportunistic infections or failure of ATT due to poor adherence, malabsorption, drug-interactions and toxicities, or drug resistance.*** **The diagnosis of TB-IRIS can only be made after other reasons for clinical deterioration have been excluded.**

The management of TB-IRIS includes non-steroidal anti-inflammatory drugs (NSAIDs) in mild disease and corticosteroids in moderate or severe disease. TB-IRIS is rarely life-threatening and most patients can be treated without interruption of ART.

Do not stop ATT in a patient with TB-IRIS. Management of cases of moderate-severe TB-IRIS should be made in consultation with a TB/HIV specialist.

Recommended Prednisone dosages for TB-IRIS:

- 60 mg QD x 5 days, followed by 40 mg QD x 5 days, followed by 30 mg QD x 5 days. (Questions regarding corticosteroid use can be discussed with a TB/HIV specialist).

6.7 Monitoring and Tracking of TB and HIV Co-Infected Patients

- Ensure that all TB patients referred for ART are carefully tracked into care.
- Ensure that all HIV patients receiving ART are promptly referred to TB facilities for initiation on ATT, if it is not available in the HIV clinic.
- Both TB and HIV healthcare facilities should make every effort to document their TB/HIV co-infection prevalence and incidence.

(See Annex 13: Mycobacteriology Request and Report Form MH2011, page No. 178)

7.0 CLINICAL CARE OF HIV-INFECTED WOMEN, HIV-EXPOSED INFANTS, AND HIV-INFECTED INFANTS

Since 1999, Botswana has remained an international leader in the successful implementation of its PMTCT programme. With support of both strong research and development partners, many of the most important PMTCT clinical trials have taken place in Botswana over the past ten years. As a result, the Botswana National PMTCT Programme has continued to progress - with the regular revisions to guidelines and improved methods to safe guard the lives of HIV-infected pregnant mothers and their children. In 2009, Triple ART Prophylaxis was initiated for all HIV positive pregnant women. As a result, it is expected that the MTCT rate in Botswana will fall below 2% - an admirable achievement in any country in the world.

However, as the programme continues to move forward many challenges lie ahead. One centers on how to integrate a full spectrum of sexual reproductive health options into care for HIV-infected and serodiscordant couples. Introducing safe contraceptive methods into the routine care of all HIV-infected patients in addition to the use of condoms, is therefore essential to ensure that the best and safest reproductive choices are made.

Expanding HIV testing also remains a critical factor for improvement of PMTCT services before, during and after pregnancy -- especially during late pregnancy, postpartum and throughout breastfeeding in those mothers who choose to do so. Additionally, recommending the best ART regimen for women taking TAP as well as those already on ART through pregnancy will require improved counselling for women and their partners to fully understand the risks and benefits associated with different ART options.

Finally, and most importantly, recommending which infant feeding method will best protect infants and children from acquisition of HIV post delivery while protecting the lives of children and their mothers long-term remains to be fully determined by on-going clinical trials. Therefore, in the interim, helping patients understand the risks and benefits of all infant feeding methods will demand improvements in patient counselling from all cadres of healthcare workers now and in the years ahead.

7.1 General Clinical Care of All HIV-Infected Women

The unique challenges facing HIV-infected women – childcare demands, disclosure issues, stigma, domestic violence, and social ostracism require that special considerations must be given by healthcare providers to ensure that HIV-infected women receive comprehensive and holistic care. These include:

- Baseline screening for cervical cancer with Pap smears with appropriate gynecologic follow-up for any detected abnormalities. *(See Cancer/HIV Chapter 10 Section 10.3)*
- Routine screening for TB at every clinical encounter
- Evaluation and treatment of any detected STIs, using a syndromic approach *(See Annex 2)*
- Use of cotrimoxazole prophylaxis if eligible regardless of pregnancy status
- Discussions on sexual and reproductive health
- Encouragement of HIV testing for children and sexual partners
- If domestic violence or abuse is suspected, ensuring women and their children are referred to appropriate social services for protection.
- Additional referrals to other appropriate health care personnel or social services, as needed.

7.2 Sexual and Reproductive Health and HIV Infection

The sexual and reproductive health of women and men affects not only their own health and well being, but also influences the health and well being of their children. Discussions about SRH with HIV-infected women and couples must be comprehensive and should entail more than inquiries about whether condoms are being used. Therefore, healthcare providers must provide comprehensive SRH counselling, including:

- Discussion of safe sex practices
- Determination of preferred contraceptive methods
- Ensuring that appropriate contraception is being used (e.g., depo-medroxyprogesterone) if pregnancy is not desired.
- Assistance with ***careful planning of all pregnancies before becoming pregnant*** to ensure safe conception, pregnancy and delivery of HIV-negative children
- Counseling on all available ART regimen options before, during and after pregnancy
- Encouragement to involve male partners in sexual and reproductive health decisions.

7.2.1 Contraceptive Options for HIV-Infected Women

Providing safe and effective contraception and family planning services reduce unintended pregnancies. By reducing family size, HIV-infected women and their families may improve their health, their level of education and their economic status, thereby benefiting themselves and their communities. Individuals and couples should therefore be encouraged to plan the spacing and size of their families according to their ability to care for them.

In order to educate patients correctly so that they can make informed decisions regarding their choice of birth control, health care providers should familiarize themselves with various levels of contraceptive effectiveness, their indications and side effects

Women who do not use effective methods of family planning have a risk of pregnancy as high as 85% over a period of one year. Although HIV-infected women may have lower fertility rates than non-infected women, the likelihood of unwanted pregnancies is inevitable without appropriate contraception. Remember, if a woman does not want to become pregnant, condom use alone, is not adequate to protect against conception.

7.2.2 Use of Hormonal Contraceptives

While some published research suggests that some hormonal contraceptive methods may increase the risk of HIV transmission, other studies have shown no increased risk, and the association between hormonal contraception and HIV transmission risk remains uncertain. Studies have also documented interactions between oral contraceptives and ART such that contraceptive effectiveness is reduced. For example, NNRTIs and PIs (especially ritonavir) can reduce contraceptive hormonal levels by as much as 20% and 40%, respectively. According to a recently published technical statement by the WHO, “an expert group reviewed all the available evidence

and agreed that the data were not sufficiently conclusive to change current guidance."*(Hormonal Contraception and HIV - Technical Statement 2012, WHO)*

Therefore, always recommend dual protection for both HIV transmission and contraception.

- For effective contraception with NNRTI use, exercise caution with hormonal contraceptives by adding an additional barrier method
- For effective contraception with LPV/r use, Depomedroxyprogestrone (DMPA) is the most effective.
- In cases of TB/HIV co-infection with rifampicin-containing ATT regimens, use of oral contraceptives or hormonal implants is contraindicated. In these cases, alternate birth control methods as well as education on correct condom usage are essential.
- IUCD can be used by HIV-infected women who are on ART and clinically well with no evidence of STIs or PID. IUCD is not recommended for HIV-infected women at high risk for STIs, especially those with more than one sexual partner or whose primary partner has more than one sexual partner.
- Combined oral contraceptives (COC) can be safely used as long as HIV-infected women are not breastfeeding or heavy smokers.
- Progestin-only pills (POPs or "minipills") are a good choice for breastfeeding women because they do not reduce the mother's milk supply. POPs can be used from six weeks postpartum and by HIV-infected women who cannot use methods with estrogen.
- Emergency contraceptive pills are safe for use in HIV-infected women and should be made available for women who have been sexually assaulted

Recommending the correct contraceptive method requires careful clinical evaluation and consideration of preference for HIV-infected women and their partners.

Special Considerations with Hormonal Contraception Use

Exercise caution when recommending hormonal contraception with current clinical or previous history of:

- Migraine headaches, especially with focal neurologic signs
- Cigarette smoking or obesity in women > 35 years
- Tuberculosis on ATT
- Breast cancer
- Breastfeeding
- Thromboembolic disease
- Hypertension with vascular disease in women >35 years
- Systemic lupus erythematosus with vascular disease, nephritis or antiphospholipid antibodies
- Less than 3 weeks postpartum
- Hypertriglyceridemia
- Ischemic or valvular heart disease
- Congestive heart failure
- Cerebrovascular disease

7.2.4 Special Considerations: Sterilization

For HIV-infected women and their partners who have completed their reproductive desires, sterilization – tubal ligation for women or vasectomy for men – remains a viable permanent contraceptive option.

For comprehensive information on contraceptive use see recommendations of the 2009 SRH – Family Planning Manual

7.3 Reproductive Rights of HIV Positive Women and Men

As stated in the National SRH Policy Guidelines and Service Standards (2004), reproductive rights are derived from fundamental human rights which are protected by the Constitution of Botswana. Therefore, women and men living with HIV have the same reproductive rights as individuals without HIV infection. In addition to the SRH Policy Guidelines, the Botswana Human Rights Charter also supports the expression of reproductive health rights for persons living with HIV.

In 2006, WHO recognized reproductive health as a priority and stated that: "HIV-infected individuals should have a satisfying, responsible and safe sex life. They should be able to reproduce and freely decide whether, when and how often to do so." By promoting a "right-based" approach to family planning services, healthcare providers will be better equipped to meet the special sexual reproductive needs of HIV-infected women and men alike. Providing family planning services to all individuals regardless of their HIV status will also ensure that HIV-infected women and their partners are empowered to make the best reproductive choices for themselves and their families.

7.3.1 Recommendations for HIV-Infected Women and Couples Who Desire Children

HIV-infected couples, both discordant and concordant, may wish to have children. If after discussing the possibility of adoption, couples continue to desire their own biological child, HIV infected women and their partners should be assisted to understand that ***pregnancy in the setting of HIV infection is not risk free***. Furthermore, increasing evidence points to higher incidence of teratogenicity with the use of ART in pregnancy, ***regardless of ART regimen***.

It is therefore critical that would-be mothers and their partners plan their pregnancies cautiously with the assistance of healthcare providers in order to fully understand the complexities involved in their decision to give birth (e.g., possible exposure and infection with HIV, fetal demise, maternal and infant death, congenital mal-formations).

During counselling for pregnancy, carefully explain the potential risks of unprotected intercourse to both partners, especially to the HIV-negative partner.

Advise as follows:

- Refrain from having sex when either partner has any signs of STI, especially genital ulcer disease

- Confine unprotected intercourse only to the woman's fertile period by using fertility awareness methods (for both calendar methods and symptom-based methods refer to the 2009 SRH-Family Planning Manual for details on the use of both methods).
- Provide adequate counseling time for serodiscordant couples who wish to conceive so that advice can be tailored to their specific needs, which may vary from couple to couple

In order to minimize the risk of a negative outcome in pregnancy, HIV-Infected women recommend that the following conditions should be met prior to pregnancy:

- Viral load suppression to: <400 copies/µL
- CD4 count > 200 cells/µL
- Stable on ART for no less than 2 years
- A stable partner for assistance
- Repeat/repeated pregnancies highly discouraged
- Ability to maintain good nutritional status throughout pregnancy

Additionally, healthcare providers should take a holistic approach while counselling HIV infected women regarding pregnancy which includes an evaluation of their current state of health.

Advise that the following medical conditions may be worsened or exacerbated by pregnancy, thus posing increased risk to mother and child:

- Hypertension
- Anemia
- Cardiac Disease
- Diabetes
- Asthma
- Renal Disease
- TB
- Liver Disease
- Epilepsy
- Cancer
- Malaria
- STI's

7.3.2 Clinical Care of HIV-Infected Women Already on ART Who Desire Children:

Women who are clinically and virologically stable on any of the following regimens can remain on those regimens throughout pregnancy and delivery:

- CBV/NVP, CBV/ALU, CBV/ATV, CBV/SQR/r
- ABC/3TC/NVP, ABC/3TC/ALU, ABC/3TC/ATV
- ***For all of the above regimens, during labour give supplemental AZT 300 mg every three hours not to exceed 1,500 mg***

Women found on d4T containing regimens should be switched to alternative regimens after confirmation of viral suppression. However, in cases of previous complicated treatment history, discuss alternate regimens with an HIV specialist before making regimen switches.

7.3.3 Pregnancy Considerations for HIV-Infected Women Taking Efavirenz

To date, the results of clinical trials determining the risk of teratogenicity of efavirenz use during the first trimester of pregnancy remain unclear. Simultaneously, the significant advantages of single dose TDF+ FTC or 3TC+ EFV (Atripla) as a first line ART for women as well as men cannot be ignored. Determining the risk/benefit ratio for the most appropriate ART options for women of reproductive potential requires careful consideration of patients as well as the healthcare workers who counsel them.

Deciding whether HIV infected women who are currently on EFV containing regimens and desire children should switch to NVP or LPV/r (Aluvia) before becoming pregnant should be based on the following:

- Previous ART history, including intolerance or side effects to any ART
- Viral load suppression to <400 copies/µL within the last 3 months
- CD4 count >200 cells/µL
- Previous history of adherence issues or defaulting on treatment
- Patient preference

Women who were placed on EFV containing regimens due to previous intolerance or side effects should be discussed with an HIV specialist before treatment switch from their currently stable EFV based regimen.

Women who were placed on EFV who are not virally suppressed must be clinically evaluated to determine the causes of viral rebound.

Virologically failing women should be advised to postpone pregnancy until they have been successfully placed on a suppressive regimen. Contact HIV Specialist, if necessary.

For those women who have any history of previous adherence issues or defaulting, the decision whether to switch from a stable one pill once a day regimen to a more complicated regimen must be made with caution. In these instances it is often better to keep women on TDF + FTC or 3TC + EFV (Atripla) rather than to risk another episode of virologic failure as the risk of EFV use and abnormal fetal outcome is very low.

7.3.4 ART Recommendations for Women who Prefer to be Switched From Efavirenz (before pregnancy or ≤ 14 weeks gestation)

- ***Do not change the NRTI backbone***
- If CD4 counts ≤250 cells/µL switch EFV to NVP
- If CD4 counts >250 cells/µL switch EFV to ALU

With all ART regimen switches, baseline laboratories: AST/ALT, chemistries, CD4 and PVL must be documented to be stable within the last 3 months before proceeding. If laboratories are older than 3 months, repeat before regimen change.

For women who are switched to LPV/r (Aluvia) containing regimens for their pregnancy, switch back to their original regimen after confirmation of virologic suppression post partum.

7.4 ART Recommendations for Treatment Naïve Pregnant Women Found to be Eligible for Life-Long ART and Triple ART Prophylaxis (TAP)

7.4.1 Treatment Naïve Pregnant Women Eligible for Lifelong ART

ART Eligibility for pregnant HIV-infected women is the same as that for all other adults: CD4 ≤ 350 cells µL or WHO stage 3 or stage 4 conditions. ***Pregnant women who are eligible for ART must be given priority scheduling for ART initiation, without exception.***

The principles of ART in HIV pregnant women, including dosages, laboratory monitoring, and criteria for treatment success or failure, are unchanged from other adults (see Chapter 5). ***Even late in pregnancy, ART should be started if the patient is eligible. Unless active labour has started, there is no stage of pregnancy that is too late to begin ART.***

- All HIV positive women who do not meet the criteria for life-long ART should be initiated on TAP.

7.4.2 Regimen Selection for Pregnant Women (Lifelong ART or TAP) Based on Gestational Age

Before 14 weeks gestation and after checking appropriate baseline labs:

- If CD4 counts ≤250 cells/µL: **TRU/NVP**
- If CD4 counts >250 cells/µL: **TRU/ALU**
- After delivery, if clinically and virologically stable make no changes to regimen for those placed on NVP containing regimens
- ***At labour, give supplemental AZT 300 mg every three hours, not to exceed 1,500 mg.***

If renal insufficiency and no anemia,	CD4 ≤250 begin CBV/NVP CD4 >250 begin CBV/ALU
If renal insufficiency with ANEMIA,	CD4 ≤250 begin ABC/3TC/NVP CD4 >250 begin ABC/3TC/ALU

Remember: Women initiated on LPV/r (Aluvia) containing regimens (due to CD4 > 250 cells/µL) should be switched back to Atripla after confirmation of virologic suppression post partum.

Starting at 14 weeks gestation and after checking appropriate baseline labs:

- **Initiate TDF+FTC or 3TC+EFV (Atripla)**

  If renal insufficiency and no anemia: CBV+EFV
  If renal insufficiency with ANEMIA: ABC+3TC+EFV

- For women on Atripla, who are clinically and virologically stable after delivery, make no treatment changes.
- For women on ABC containing regimens, if clinically and virologically stable, once renal insufficiency has resolved switch to Atripla.
- ***For women on either Atripla or ABC at labour, give supplemental AZT 300 mg every three hours, not to exceed 1,500 mg.***

After 28 Weeks gestation (who received ≤ 4 weeks prophylaxis):

It is critical that late presenting HIV-infected pregnant women are placed on appropriate ART as soon as possible. In cases where women appear clinically stable every effort should be made to initiate ART immediately.

In order to do this:

- Expedite all baseline laboratories so that they are received as a priority at the laboratory with results returned no later than 2 weeks.

- Ask women to return to the clinic as soon as possible (no longer than 3 days) with an adherence partner for ART counseling and initiation processes.
- For those women accompanied by an adherence partner, start Atripla immediately if the patient appears clinically stable.
- Make any necessary regimen adjustments within one week of receiving the results from the baseline labs.
- ***At onset of labour, give supplemental AZT 300 mg every three hours, not to exceed 1,500 mg and sdNVP.***
- If patient appears clinically unstable discuss clinical management with an HIV Specialist.

Late ANC Presenters (seen at onset of labour):

- Give supplemental AZT 300 mg every three hours, not to exceed 1500 mg
- Give sdNVP 200 mg one time only
- Evaluate immediately post partum for ART eligibility

> *If at onset of labour the patient and her medical records are uncertain or unclear about whether or not she received AZT for at least 4 weeks, administer sdNVP, as well as AZT as described above.*

7.4.3 Special Considerations With sdNVP Use

- Evaluate carefully between true and false labour as the dose of NVP should only be given one time.
- Any woman who received 4 weeks of AZT or more of prior to labour, should not receive sdNVP.
- When after pregnancy a woman who received sdNVP within the prior 6 months becomes eligible for ART, use LPV/r as there is a risk of virologic failure with NNRTI-based ART.

7.4.4 Intolerance to Oral AZT

- Give IV AZT: 2 mg/kg IV loading dose over 1 hour, followed by infusion of 1 mg /kg every hour until delivery

7.5 Other Special Considerations for HIV-Infected Pregnant Women

- Evaluate and treat all sexually transmitted infections. Routine syphilis serology must be monitored, and positive results addressed. *(See Annex 2):*

- There must be counseling at every visit on the importance of using condoms during the pregnancy.
- Treat any episode of genital **HSV** aggressively with acyclovir.

  Dosage: *Acyclovir 800 mg PO TDS until lesions are contained. If necessary, obtain HIV Specialist approval for use of acyclovir for this indication.*

- **Anemia** may complicate the use of AZT containing regimens during pregnancy:
  - For viability of the pregnancy and to allow the use of AZT regimens or during delivery, consider transfusion when Hb is <7g/dl.
  - If transfusion is not possible or effective, use or switch to TDF or ABC containing regimen, with approval of an HIV specialist

- **Tuberculosis**: All first-line ATT drugs are safe in pregnancy, except streptomycin which can cause hearing loss in the fetus. Do not give streptomycin in pregnancy and refer to a TB Specialist if the pregnant woman requires a retreatment regimen.

- **Malaria** prevention chemoprophylaxis should be administered to HIV positive pregnant women as follows:
  - Southern Botswana: Not recommended
  - Northern Botswana: Proquanil (200 mg daily) and Choloroquine 300 mg weekly, EXCEPT in those receiving CTX which provides effective protection from Malaria used alone.

Diagnosis of malaria should be confirmed by laboratory. However treat for malaria if there is high degree of suspicion, as follows:

  - 1st Trimester: oral quinine
  - 2nd and 3rd Trimesters: Artemether-lumefantrine (AL)

    (all types: P. vivax, malariae, ovale and faciparum)

- **Elective caesarean section** has been shown to reduce MTCT when maternal viral load is > 1000 copies/µL. However, this intervention, which can be associated with morbidity and mortality, is currently unavailable under the government program. C-section may be considered in the private sector, in selected cases and where feasible.

  There may arise in the public sector instances where elective C-section may be medically indicated for the health of an HIV-infected woman and/or her baby (e.g., known placenta previa, abnormal fetal position). When intravenous AZT is not available for administration during the procedure, AZT 600 mg PO should be given 3 hours before the elective C-section.

<u>Quality Assurance: In all cases, regardless of ART regimen:</u>

- Carefully note which ART was received in the antenatal and maternity registers as well as the patient's own obstetric record.
- Address nausea and vomiting promptly to minimize non-adherence and decreased absorption of ART prophylaxis or life-long ART.

7.6 At Completion of Triple ART Prophylaxis

7.6.1 Stopping TAP in a Non-breastfeeding Woman

- Continue ART in women receiving TAP for a minimum of six weeks post delivery.

- Discontinuation of TAP should only be made if the patient has remained clinically stable on ART throughout pregnancy without complications.

- If there were any pregnancy or postpartum complications, discuss whether or not to stop or continue TAP with an HIV Specialist.
- Any woman who develops WHO stage 3 or stage 4 conditions during pregnancy should continue ART.

An NRTI "Tail" of TDF + FTC (TRU) or AZT + 3TC (CBV) when stopping an NNRTI containing regimen is needed to reduce the risk of emergence of NNRTI drug resistance (due to the long half-life of NNRTI's and its low resistance threshold).

For Women on Atripla or TRU containing TAP, at six weeks:

- Continue Truvada (TRU) for one additional week before stopping all ART.

For Women on CBV containing TAP, at six weeks:

- Continue Combivir (CBV) for one additional week before stopping all ART.

7.6.2 Stopping TAP in Women Who Choose Breastfeeding:

- Continue TAP for a minimum of six weeks after the complete cessation of breastfeeding and baby is completely weaned.
- Discontinuation of TAP should only be made if the patient has remained clinically stable on TAP throughout the breastfeeding period without complications.
- If there were any HIV related complications during the breastfeeding period, discuss whether or not to stop or continue TAP with an HIV Specialist.
- Any woman who develops a WHO stage 3 or stage 4 conditions during the breastfeeding period should continue ART.
- TAP will be provided for the first 6 months post delivery.
- Continue TAP in those women who will continue breastfeeding up to 12 months, if the formula feeding still does not meet the AFASS requirements.

For Women on Atripla or TRU containing TAP, at six weeks:

- Continue Truvada (TRU) for one additional week before stopping all ART.

For Women on CBV containing TAP, at six weeks:

- Continue Combivir (CBV) for one additional week before stopping all ART.

7.7 Non-ART Interventions for PMTCT

Obstetric measures to reduce MTCT:

- Avoidance of artificial rupture of membranes
- Avoidance of routine episiotomies
- When assisted vaginal delivery is indicated, use of non-traumatizing suction cups on vacuum extractors, where possible
- Avoidance of fetal scalp puncture
- Consideration of labor induction beyond 4 hours after rupture of membranes

(See Annex 14: PMTCT Prophylaxis/Treatment Algorithm, page No. 179)

7.8 Neonatal ARV Interventions for PMTCT

7.8.1 Four Week Short Course of AZT and sdNVP to the Infant

Regardless of whether or not the mother received any ARVs during pregnancy or delivery, short-course ARVs to the HIV-exposed infant must be administered as soon as possible after delivery within 72 hours, in order to maximize PMTCT:

- AZT 4mg/kg po every 12 hours for 4 weeks.
- Preterm or low birth weight, give AZT dose is 2mg/kg po every 12 hours for the first 2 weeks, then increase to 2mg/kg dose po every 8 hours (TDS) for the final 2 weeks.
- NVP syrup 6 mg orally as a single dose
- Preterm or low birth weight, give NVP syrup 2 mg/kg orally
- HIV-exposed infants brought in > 72 hours after birth should not receive AZT prophylaxis but rather should be referred to an HIV Specialist or ARV clinic.

7.9 Recommendations for Infant Feeding:

All women regardless of the HIV status should be provided with infant feeding information and counselling during ANC to ensure that they are supported in making the best decision for their situation, whether that decision is to formula feed or to breastfeed. Infant formula is provided at SR healthcare facilities until the infant is 12 months of age.

To achieve the goals of Vision 2016 for an AIDS-free generation, the Government of Botswana recommends that:

- **HIV infected women for whom formula feeding** is acceptable, feasible, affordable, sustainable and safe(AFASS) should exclusively formula feed for the first 6 months of life and continue formula feeding until 12 months of age, introducing complementary foods beginning at age 6 months.
- **HIV infected women for whom formula feeding** is NOT AFASS should exclusively breastfeed for the first 6 months of life ***only if they are placed on TAP or ART***. At six months, assess the mother's situation using AFASS criteria:
    - If formula feeding **is still not AFASS**, breastfeeding until 12 months of age (or until formula feeding becomes AFASS) **only with administration of TAP**. Complementary foods should be started at six months of age.
    - If formula feeding is **AFASS**, gradual weaning (over a period of one month) with introduction of formula feeding. Complementary foods should be introduced at six months of age.

Women who continue TAP through breastfeeding must continue to receive ART until 6 weeks after complete cessation of breastfeeding.

When formula feeding is AFASS, HIV infected women should be provided with adequate counselling, education and support to completely avoid breastfeeding.

Table 7.1 Botswana's Infant and Young Child Feeding Recommendations

Client Situation At time of birth	Feeding recommended from 0-6 months	Feeding recommended from 6-24 months
HIV negative women	Exclusive breastfeeding (no added foods or liquids, not even plain water)	Breastfeeding until at least two years of age plus introduction of complementary foods at six months of age
Women of unknown HIV status[1]	Depending on HIV test outcome, either EFF or EBF	Complete HIV test as a matter of priority
HIV infected women for whom formula feeding is AFASS[2]	Exclusive formula feeding (no added foods or liquids, not even plain water)	Formula feeding until 6 months of age plus introduction of complementary foods at six months of age From 12-24 months of age, offer animal milk and/or other milk products (yoghurt, cheese and madila) plus complementary foods.
HIV infected women for whom formula feeding is not AFASS [2]	Exclusive breastfeeding (no added foods or liquids, not even plain water)	At six months, assess the mother's situation using AFASS criteria: ● **If formula feeding is still not AFASS, breastfeeding until 12 months of age (or until formula feeding becomes AFASS [2,3])** ● If formula feeding is AFASS, gradual weaning (over a period of one month) with introduction of formula feeding **Introduce complementary foods when baby is six months of age;** from 12-24 months of age, offer animal milk and/or other milk products (yoghurt, cheese and madila) plus complementary foods.

1 *Women of unknown HIV status should be counseled and tested for HIV.*

2 *AFASS = acceptable, feasible, affordable, sustainable and safe*

3 *Early cessation is not recommended if the infant is HIV infected or if formula feeding is not AFASS.*

- **Acceptable**: The mother perceives no significant barrier(s) to choosing a feeding option for cultural or social reasons or for fear of stigma and discrimination.
- **Feasible**: The mother (or other family member) has adequate time, knowledge, skills, and other resources to obtain formula regularly, prepare feeds, and to feed the infant as well as the support to cope with family, community, and social pressures.
- **Affordable**: The mother and family, with available community and/or health system support, can pay for the costs of the formula feeds—including formula, fuel, transportation and clean water—without compromising the family's health and nutrition spending. The formula is provided by the Government, but women must have fuel to sterilize cups and utensils and boil water for every feed.
- **Sustainable**: The mother has access to a continuous and uninterrupted supply of infant formula until the infant is 12 months old.
- **Safe**: Formula is correctly and hygienically stored, prepared and fed in nutritionally adequate quantities; infants are fed with clean hands using clean utensils, preferably cups.

(See Annex 15: How to Stop Breastfeeding Early, page No. 180)

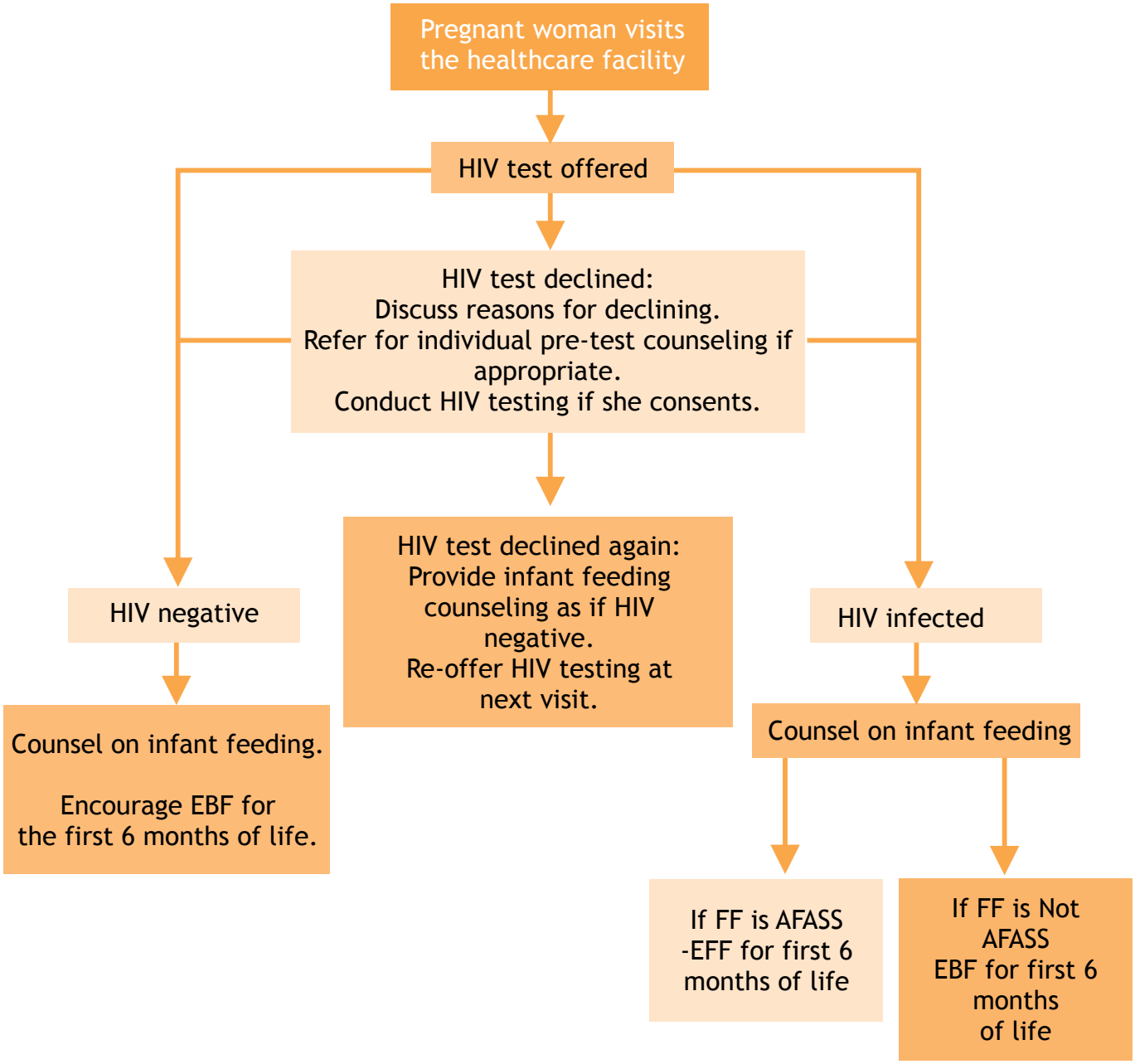
Counseling on Infant Feeding Choices

All women and their partners, regardless of HIV status, should be provided with infant and young child feeding counselling during antenatal care according to the infant and young child feeding recommendations (see Table 7.1, above) Figure 7.1 below summarizes the timing and primary message of infant feeding education, counselling and support.

For women who request ART in order to safely breastfeed but who did not receive TAP or ART during their pregnancy, complete comprehensive HIV counselling, education, and evaluation for ART eligibility.

- Ensure that these HIV-infected mothers understand the risks of HIV transmission that have already taken place by their not having undergone TAP or ART during their pregnancy and delivery.

Figure 7.1: Overview of infant feeding counselling in ANC



EBF = exclusive breastfeeding
FF- formula feeding
AFASS = acceptable, feasible, affordable, sustainable and safe.
EFF- Exclusive formula feeding

8.0 CHILDREN & ADOLESCENTS

This new chapter highlights diagnostic and treatment considerations for children and adolescents and summarizes key pediatric issues in order to improve the standard of pediatric HIV clinical care in Botswana.

8.1 Screening and Testing Children:

Pediatric and adolescent CD4 and clinical screening follows the same general principles as for adults. History, physical examination and laboratory investigations determine the appropriate WHO staging. However, preventive and supportive care of pediatric patients must focus on both the child and the care-giver(s) and other family members.

> In particular, HIV-infected adolescents (age 10 to 19 years) should not be treated as "small adults," but should be provided with preventive and supportive care sensitive to the psychosocial aspects unique to this special population of HIV-infected patients.

8.1.1 HIV Diagnosis in Children

Always consider the best interests of the child when deciding to test for HIV. However, ***in those instances where parents are reluctant to test their children due to fear or stigma, healthcare providers should make every effort to encourage testing***.

- In cases where the child is clearly sick and likely suffering from HIV, explain to parents that full medical investigations for all possible causes must be taken and complete the HIV test.

8.1.2 HIV Diagnosis in Adolescents

Adolescents

The Attorney General advises that the Botswana Family Planning General Policy Guidelines and Service Standards guide the testing of minors. This policy states that: "…teenagers are to be provided with appropriate family planning methods on request after adequate counselling." In other words, if the counsellor is satisfied that a young person is mature enough to fully understand his or her behavior and the consequence of that behavior, parental consent is not necessary in order to receive services.

- Adolescents, including pregnant adolescents, do not need parental consent to be tested for HIV or join the PMTCT programme, and parents do not have to be present during counseling.
- The 2009 Children's Act puts age of consent for sexual reproductive services at 16 years including HIV testing and counselling
- Adolescents may choose to have a parent or another adult with them to provide the necessary support during HIV testing and this option should be discussed with the adolescent and encouraged.
- It is important for the family members who will be assisting the adolescent with the baby to be included.

- Always disclose HIV positive results to adolescents in a supportive and safe environment.

8.1.3 Addressing Sexuality with Adolescents:

- Parents and clinicians must initiate frank discussions about sex with adolescents, including non judgmental discussion of safe sex methods to satisfy sexual needs.
- Parents and clinicians should ensure that adolescents understand that condoms will provide some protection against HIV transmission ***but not necessarily provide adequate contraception***.
- All children and adolescents who are victims of defilement or rape should be immediately taken to a healthcare facility to receive PEP and counseling services.

8.2 Disclosure of HIV status to children and adolescents:

Disclosure of HIV status is a difficult issue in the field of pediatric HIV, in every setting. Caregiver reluctance to disclose HIV status to a child or an adolescent is often related to fear of stigmatization and discrimination. Disclosure, however, is important for HIV-infected children and adolescents, and is associated with elevated self-esteem, willingness to accept treatment, and improved adherence to ART. It is recommended that health care professionals assist caregivers with a stepwise approach to disclosure from an early age, using age-appropriate language and concepts.

> Disclosure of HIV status to children should be considered a process rather than a one-time event. Providing children and adolescents with age-appropriate information about their illness is an essential part of HIV care, and, in coordination with the family and other clinic staff, is the responsibility of the treating practitioner.

Observe the following recommendations:

Truth Telling:

- Never tell lies to children about their medical care. Always encourage families to be truthful with children when discussing their medical situation.
- Do not tell children beginning ART that they are taking ARVs for transient conditions such as coughs or rashes. Instead, tell children that the medications will help them become and remain strong and healthy.
- If the child reveals that he already is aware of his HIV status, the medical team is obligated to support the child in this knowledge, and help the child develop a positive outlook regarding HIV infection.

Simplification of messages for children:

- Counsel families regarding age-appropriate ways to communicate with children about their illness.
- Do not use “adult words” such as “HIV” and “ARVs” with very young children. Instead, help

them to learn early on the names of their medications that will help to make them strong and healthy, ***and that it is important never to miss medication doses***.

- Add further medical details about HIV infection as the child ages, and as the family becomes more ready for full disclosure.

Positive messages:

- HIV-infected children have the potential to be healthy and productive adult members of society. Counter false and negative messages regarding HIV-infected people.
- Continuously validate and encourage HIV infected children. Always provide positive reinforcement for HIV-related knowledge and clinical improvement achieved by pediatric patients.
- At each visit for follow-up care, teach children facts about their health, including positive messages.

Age Specific Interventions for Children:

Young Children:

- Assist caretakers to teach young children how their medicines are taken (e.g., what time, how much).
- Teach children that their medicines will help them stay healthy by making their CD4 cells ("soldiers of the body") remain strong and numerous.

School Age Children:

- Teach children to remind their caregivers when it is time to take medicines, and ensure that the appropriate doses are given (although adult supervision is still required and the adult remains ultimately responsible for adherence).
- Teach children and their caretakers the names of the medicines.
- Explain to children that as long as they continue to take their medicines correctly, they can achieve all that they want in life.

Older Children:

- Use "adult" terminology when discussing health issues.
- Respect that older children and adolescents will likely be more sensitive to stigma and discrimination among their peers and address these issues directly.
- Continuously reinforce positive messages and assess understanding at all childhood and adolescent visits.

For families who elect not to disclose their children's HIV status to them:

- Use metaphor and story telling to help children understand. A helpful technique that children tend to relate to well is the paradigm of "soldiers" of the body (CD4 cells) and "bad guys"(HIV). Tell children that there are "soldiers" inside of them that should be strong, but become weak when the "bad guy" attacks them. The medicines (ART) keep the "bad guy" sleeping.

8.3 Special Considerations for Adolescents :

Intensified, Clinic-Based Psychosocial Support:

Most HIV-infected adolescents have special psychosocial issues which can often lead to adherence problems:

- Denial and fear related to HIV diagnosis
- Misunderstandings related to diagnosis and health needs
- Lack of belief in the efficacy of ART
- Distrust of family, practitioners, and the healthcare system
- Low self-esteem and unstructured, chaotic lifestyles
- Limited familial and social support

Data suggests that adolescents may be less likely to maintain effective responses to ART than younger children; this is generally related to problems with non-adherence to ART and psychosocial concerns, particularly depression. Hence, the most critical aspect of providing appropriate care to HIV-infected adolescents is closely monitoring their psychosocial health. All ART clinics should identify staff with interest in adolescent care who can provide continuity of care to HIV-infected adolescents. These designated staff members can form a "therapeutic alliance" with adolescents, to help them handle challenges to their wellbeing. These "continuity-of-care" providers should explore with the adolescent issues of sexuality, safe sex, substance abuse, barriers to adherence, and community support.

Although adolescents are often knowledgeable regarding their health care, and are capable of coming to medical appointments alone and taking medications independently, ***responsible adults should still remain involved in their care***.

- To ensure continuous adherence to medications, an adult adherence partner should directly observe ingestion of all doses, even when the adolescent has a history of good adherence.
- Peer support is also an important aspect of adolescent care. Clinics that have several HIV-positive teenagers should form peer support networks, such as teen clubs, where the HIV-positive teens can meet and support each other.
- Such teen clubs have been pioneered in Botswana and have been internationally recognized as key interventions for HIV-infected adolescents. Teen clubs are well described at the following link:
  AIDSTAR-One Promising Practices Database: *(http://www.aidstar-one.com promising practices database/g3ps/teen club peer support group hiv positive adolescents)*

Discontinuation of therapy due to non-adherence:

After every effort has been made to correct poor adherence, it may become necessary to temporarily discontinue ART in pediatric and adolescent patients who are unable to take their medications reliably. However, ***it is not recommended to discontinue ART, even temporarily, in children or adolescents with severe immunosuppression***. For non-immunosuppressed patients for whom this step is taken, this should be a temporary measure that is closely monitored and done only in order

to preserve future treatment options. (Whenever possible, the long half lives of NNRTIs should be taken into account and dual NRTIs can be given for a period of one week).

However, ***discontinuation of ART should never be considered a punitive measure, nor should it ever be presented to the patient and family as such.***

- Carefully and sympathetically explain to the patient and family the reasons for ***temporary treatment discontinuation.***
- At the same time as the temporary treatment discontinuation, formulate and implement a plan for preparing the patient to safely restart therapy.
- Evaluate all factors leading to non-adherence prior to temporary treatment discontinuation
- ***Start CTX prophylaxis and a multivitamin in all patients who discontinue ART*** regardless of immunologic and clinical status. This will help preserve the patient's health, and help to re-establish the habit of good adherence to medications.

8.4 Cotrimoxazole (CTX) Prophylaxis in Children:

CTX prophylaxis must be given OD, for all ages, in order to provide protection against diarrheal and respiratory pathogens.

In addition to the CTX criteria listed below, the following children should also receive CTX prophylaxis:

- Children of any age who qualify for ART, but who are not currently receiving ART for any reason.
- Restart CTX in all HIV-infected children on ART who develop virologic failure until the viral load has re-suppressed and there are no other indications for CTX prophylaxis.

8.4.1 Cotrimoxazole Eligibility in Children: (For infants see Chapter 3, Section 3.3.1)

Start and/or continue CTX prophylaxis in all HIV-infected children with active, current WHO clinical stage 2, 3, or 4 diseases, ***until the clinical condition has resolved or been stable for at least 6 months***.

Ages: 1-5 years:

- **CD4 % <25%.**
- WHO clinical stage 2, 3, or 4 disease

>5 years:

- CD4% <15% or absolute CD4 cell count ≤ 200 cells/μL
- WHO clinical stage 2, 3, or 4 disease

8.4.2 Cotrimoxazole Prophylaxis Pediatric Dosing:

- The standard pediatric dosing of CTX is 2.5-5.0 mg trimethoprim (TMP)/kg, to a maximum of 160mg/dose.
- For sulfa allergy: Dapsone 2 mg/kg OD to a maximum of 100mg OD.

Recommended simplified CTX dosing (as per WHO guidelines) overleaf:

Table 8.1: Dosing Recommendations for Cotrimoxazole in Infants and Children

Dosing Recommendation for Cotrimoxazole for infants and Children		
Age Range	Suspension 40 mg TMP/200mg SMZ per 5 ml	Single Strength Tablet 80 mg TMP/400 mg SMZ
< 6 months	2.5 ml daily	¼ tablet Daily
6 months to 5 years	5 ml daily	½ tablet Daily
5-14 years	10 ml daily	1 tablet daily
>14 years		2 single strength or 1 Double strength daily

8.5 Indications for ART Initiation in Infants and Children

All HIV-infected infants under age 24 months require prompt initiation of ART, regardless of immune and/or clinical status.

- Immediately refer all infants whose first DNA PCR is positive for ART initiation, without waiting for the confirmatory DNA PCR.
- Discuss any HIV-exposed baby who has a WHO stage 3 and 4 clinical condition ***and for whom the DNA-PCR is not available***, with an HIV Specialist for possible initiation of ART, pending return of the DNA PCR, since such babies are at high risk for morbidity and mortality from HIV infection.
- ***Follow babies without WHO stage 3, and 4 clinical conditions, and for whom the DNA PCR is pending, on a monthly basis, completing WHO staging at each visit, since HIV-infected babies are at high risk for clinical deterioration.***

All HIV-infected children >24 months and <5 years of age with either one of the following two conditions require immediate initiation of ART:

- "Advanced" or "severe" symptoms (i.e., WHO clinical stage 3 or 4)
- CD4 counts ≤750 cells/µL and CD4 ≤25%

>5 years:

- Absolute CD4 cell count ≤350 cells/µL; if <15% consult HIV specialist
- WHO clinical stage 3 or 4 disease

The simplified chart below, modified from WHO definitions, summaries the clinical criteria for ART eligibility based on immune suppression in children over 24 months of age based on CD4% and/or CD4 count and is adjusted for patient age.

Table 8.2 WHO Definition of Immune Suppression in Children

WHO Immune Stage	12-35 Months	36-59 Months	5 Years
Mild	25-30%	20-25%	350-499 cells/µl
Advanced	20-24%	15-19%	200-349 cells/µl
Severe	<20% or <750 cells/µl	<15% or <350 cells/µl	<15% or <200 cells/µl

Table 8.3 Clinical Criteria for Commencement of ART in Children

Age	Infants and Children <24 months of age[a,b]	24 to 59 months of age	Five years of age or older
%CD4+	All[c]	≤25	NA
Adsolute CD4	All[c]	≤750 cells/mm³	≤350 cells/mm³ (As in adults)

8.6 Baseline Evaluation and Preparation for ART Initiation (Pediatric and Adolescent Patients)

1) Complete a full physical examination and review of systems to identify any acute OIs or other serious medical conditions which require treatment before ART initiation.

> ***Always include careful TB screening for children and adolescents at each and every clinical encounter.***

Special attention should focus on signs or symptoms of:

- **Meningitis:** neck stiffness, confusion, headache, fever
- **TB (pulmonary and extrapulmonary):** cough, respiratory difficulty, enlarged lymph nodes, fever, decreased playfulness, weight loss, night sweats
- **KS:** lesions, anemia, weight loss, fatigue
- **Wasting:** significant weight loss, intermittent or continuous diarrhea, weakness, fever
- **PID:** vaginal discharge, pain, fever, menstrual difficulties

2) Encourage all caregivers of an HIV-infected child to share the child's HIV status with whomever in the family will be involved and prepared to actively participate in the ongoing care and treatment of the child.

- Adherence problems often occur when only a single caregiver is aware of the child's medical needs, including the importance of strict adherence.

3) Assess the following prior to initiation of ART in a pediatric patient:

- Who will be primarily responsible for administering medications and supervising adherence?
- If there are multiple caregivers, how will coordination between these caregivers be achieved?
- What is the caregiver's knowledge of the medical regimen?
- Who will ensure medication adherence if the usual caregiver(s) is absent?
- What age-appropriate role will the child play in ART adherence?
- What is the child's understanding of the medications and his HIV status?
- If the child is able to appropriately dose medications, what adult will be responsible for supervising the child?

- Prior to commencement of ART, establish the nature of the family, who cares for the child at various times, and who would be available to ensure appropriate care of the child if the primary caregiver is unavailable.
- Ensure that within the family there is adequate support and understanding to ensure excellent adherence.

Although other clinic staff should be involved in these evaluations, it is the primary responsibility of the treating clinician to make the above determinations.

4) Carefully evaluate children for previous history of sdNVP during PMTCT.

5) Complete all baseline laboratory evaluations.

Document all baseline medical information and findings clearly on the medical record.

8.7 Baseline Laboratory Tests for ART Initiation (within the last 3 months):

- CD4 cell count or %

If any previous CD4 count or % has made the patient eligible for ART, do not repeat for eligibility purposes, unless clinically indicated.

- FBC and chemistry, to include ALT/AST, urea, creatinine, glucose, electrolytes
- RPR (adolescents)
- Baseline Pap smears for sexually active adolescents
- **For TDF-containing ART:** calculation of CrCl (see Chapter 5, Section 5.3.1)
- **Chest X-ray** is not required unless the patient has symptoms suggestive of respiratory disease in which case every effort must be made to obtain the Chest X-ray promptly so that ART is not unduly delayed. ***However, do not delay ART in critically ill children (i.e., suspected TB patients with advanced AIDS).*** Consult an HIV Specialist for assistance, if necessary.

8.8 Recommended First and Second Line Pediatric Regimens

8.8.1 Infants and Children:

Before initiating ART, it is essential to determine whether or not the patient received sdNVP at birth or the mother was taking NNRTI-containing ART while the infant was in utero, since NNRTI resistance arising from NNRTI exposure can cause treatment failure with NNRTI-based ART. A history of maternal participation in PMTCT is a sufficient indicator of neonatal sdNVP exposure.

8.8.1a Standard First Line Regimen in Treatment-Naïve Infants and Children:

- **AZT + 3TC + (NVP or EFV)**

  If <3 years of age, use NVP
  If > 3 years of age use EFV

With baseline anemia (Hgb ≤ 7.00 gms/dL or AZT-induced anemia, or if the patient has symptoms attributable to anemia of any degree) substitute AZT with ABC.

All children under 3 years of age exposed to sdNVP should be started on PI-based regimen

- If the infant received sdNVP at birth:

  If ≤ 1 month, consult an HIV Pediatric Specialist

  If >1 month and ≤ 3 years of age: **AZT + 3TC + LPV/r.**

- If > 3years of age and exposed to sdNVP:

  AZT + 3TC + EFV.

8.8.1b Standard Second Line Regimen for Pediatric Patients who fail the first line regimen of AZT + 3TC + NNRTI or ABC + 3TC + NNRTI:

From AZT+3TC+NNRTI switch to **ABC + 3TC + LPV/r**

- If d4T had been used for first line regimen use **AZT + 3TC + LPV/r**
- If AZT cannot be used because of persistent anemia, consult an HIV Specialist

From ABC + 3TC+ NNRTI **depending on the level of development** switch to **CBV + LPV/r or TRU + LPV/r**

- If patient is unable to tolerate AZT and is too young from TDF, consult an HIV Specialist

Note: Pediatric FDCs should be used whenever available to allow for easy dosing and to improve adherence (*See Annex 16: Pediatric Fixed Dose Combination Formulations, page 183*)**. In rare cases requiring single dose formulations, refer to Annex 18 to determine appropriate dose calculations.**

Whenever available dispersable FDC tablets can be given to infants and children of all ages by mixing them in a small amount of water which may improve the quality of care.

8.8.1c Standard First and Second Line Regimens for Adolescent Patients

ARV regimen and dosing for adolescent clients depends on physical maturity, as determined by the Tanner scale (*See Annex 17: Sexual Maturity Rating: Tanner Staging, page 184*). The Tanner scales define physical measurements of development based on external primary and secondary sexual characteristics.

- Adolescents who are Tanner stages I, II and III are pre-pubertal; regimens and dosages should be guided by the pediatric dosing guidelines. These clients require close clinical monitoring as adolescence is a time of hormonal changes and rapid growth.

- Adolescents who are Tanner stages IV and V are post-pubertal and should be treated according to the adult ARV guidelines.

Pre-Pubertal

For adolescents (Tanner scale I, II or III), first line ART regimens contain NVP or EFV plus 2 NRTIs.

Table 8.4 Regimens for Children and Pre-Pubertal Adolescents (Tanner scale I, II or III)

Regimen	ART	
	NRTI backbone	NNRTI component
Preferred 1st line	AZT + 3TC +	NVP or EFV[1]
Alternative 1st line[2]	ABC + 3TC +	NVP or EFV[1]
Preferred Second line	ABC + 3TC +	LPV/r[4]

1 The preferred regimen for adolescents with tuberculosis is EFV + the 2 NRTI backbone.
2 Use the alternative 1st line regimen only if there are contraindications to AZT (for example, severe anaemia, <7 g/dl; or neutropenia, <500 cells/mm^3).

Dosing in pre-pubertal adolescents is usually based on either weight or body surface area. As these change with growth, drug doses must be adjusted at each visit to avoid the risk of under-dosing. For additional information on dosing and regimens for specific scenarios (for example, patients with hepatitis, *(See Annex 18: Pediatric Antiretroviral Dosing Dosage, BIPAI Tables, page 185)*

Post-Pubertal Adolescents

For post-pubertal adolescents (Tanner scale IV and V), the 2012 first line ART regimens include a TDF + FTC "backbone". TDF + FTC + EFV (Atripla) is now the preferred first line regimen due to easy dosing, long-term potency, favourable mutation pathway, and lower incidence of anaemia. See Table 8.4 above for preferred and alternative first and second line regimens.

Table 8.5: Regimens for Post-Pubertal Adolescents (Tanner scale IV and V)

Regimen	ART	
	NRTI backbone	NNRTI component
Preferred 1st line	TDF + FTC +	NVP or EFV(Atripla)
Alternative 1st line	ABC + 3TC +	NVP or EFV
Preferred 2nd line	AZT + 3TC +	LPV/r

8.8.1d Virologic Failure in LPV/r First Line regimens:

When infants and children who were placed on LPV/r first line regimens due to a prior history of sdNVP develop virologic failure, after an intensive adherence intervention, a genotypic resistance assay must be performed. Promptly discuss such cases with an HIV Specialist, since it is unclear whether NNRTI-based second line regimens will be effective. However, do not wait for the assay to return before discussing the case with an HIV Specialist.

8.8.1e Switching Pediatric Patients from d4T:

Switch all pediatric patients who are currently on d4T containing regimens (both 1st and 2nd line), and are documented as virologically suppressed within the last three months to the following:

d4T in First Line:

- d4T + 3TC + NVP or EFV switch to **ABC + 3TC + NVP or EFV**

  Complete follow-up priority viral load in 6 weeks.

d4T in Second Line:

- d4T + 3TC + LPV/r switch to **ABC + 3TC + LPV/r**

  Complete follow-up priority viral load in 6 weeks.

8.9 Goals of ART:

The goals of ART are to restore immunologic function and quality of life, and to increase life expectancy by decreasing morbidity and mortality due to HIV infection. ***For ART initiation in patients of all ages, initial treatment success or failure is determined by the viral load 6 months after ART initiation:***

- The virologic goal of ART initiation is achievement of viral load ≤ 400 copies/μL by no later than 6 months after starting ART.
- Pediatric patients may require longer than 3 months to fully suppress viral load, but should nonetheless have viral load ≤ 400 copies/μL no later than 6 months after ART initiation.
- Pediatric and adolescent patients who do not achieve a viral load ≤ 400 copies/μL by 6 months after ART initiation must be discussed with a Pediatric HIV Specialist.

8.10 Recommended Clinical and Laboratory Monitoring:

Clinical Visit Schedule While on ART:

Evaluation by a doctor and/or pediatric-trained ***ART nurse at least every 3 months, more frequently (at least monthly)*** if the child becomes ill or is not improving.

- ***Measure and plot growth*** at every visit (height and weight for all children; head circumference for children <2 years of age)
- Carefully review the growth curves to determine if growth failure is occurring
- Complete a review of systems, with special attention to possible ART side effects that may be more subtle in a child (e.g., declining school performance as a primary manifestation of neuropsychiatric side effects of EFV)

- Assess developmental milestones. Loss of milestones must prompt neurological examination and review of causes of clinical failure.
- Always screen for TB and any TB contacts.
- Complete a physical examination, with attention to areas likely to reveal HIV related pathology, e.g., the mouth and skin, the lungs, digits for clubbing and lymph nodes.
- Assess adherence, including both qualitative (e.g., questioning the patient and caregiver) and quantitative (e.g., pill counts) measures.
- ***At a minimum, pediatric and adolescent patients must continue to be followed every 3 months until age 18 years. When possible, follow adolescent patients more frequently given their high rates of failure. Where feasible they should be seen every 6 weeks for clinical assessment and adherence checks.***

Laboratory Monitoring of Pediatric & Adolescent Patients on ART: After obtaining baseline, pre-initiation laboratory tests *(refer to Section 5.1)*, routine laboratory monitoring of patients initiated on ART must include:

- Viral load: Every 3 months

> ***On a case-by-case basis, practitioners have the discretion to decrease the frequency of pediatric viral load testing to every 6 months, if quarterly viral loads over the prior 24 months have been fully suppressed, and adherence and care-giver/family support are deemed excellent. However, this is not recommended for adolescent patients.***

- CD4 cell count or %: 3 and 6 months post-initiation, then every 6 months (all ages) if the CD4 cell count or % response at 12 months after ART initiation has increased > 25-50 cells/µL for adults and adolescents, or CD4% increase > 5 % above baseline for pediatric patients.

Once a patient's CD4 cell count or % has been > 300 cells/µL and > 30%, respectively, for one year (i.e., two consecutive six-month determinations), then CD4 cell counts/% should be monitored every 12 months.

CD4 cell count or % measurements should return to every three month frequency (or more often if clinically indicated) when:

- Any new WHO stage 3 or 4 clinical condition or symptom develops
- A suppressed viral load becomes detectable
- ART regimen is changed for treatment failure
- Non-adherence is suspected
- Viral load results are not available or are delayed for >1 month

Once any of the above situations becomes stable for 6 months, then CD4 cell count or % determinations may return to every 12 months.

- FBC: AZT-based ART : At 4 weeks and 12 weeks post-initiation, ***then annually*** and as clinically indicated.

  If not on AZT-based ART: ***Annually only,*** and as clinically indicated

- AST/ALT: ***NVP-based ART***: 2, 4, and 12 weeks post-initiation, then only as clinically indicated.

  EFV-based ART: 4 and 12 weeks post-initiation, then only as clinically indicated

  PI-based ART: Baseline and then annually or as indicted below:

Table 8.6 Recommendations for Lipid Monitoring in Children Taking PIs

	Total Cholesterol	LDL Cholesterol	Triglycerides	Monitor Labs	Intervention
Acceptable (75th percentile)	⩽4.4	⩽2.9	<2.2	Baseline (start of PI) then annually	None
Borderline 75th-95th	4.4-5.2	2.9-3.4	2.2-5.5		
High (>95th percentile)	⩾5.2	>3.4	>5.5	Baseline (starting PI) then 6 mo until normal. Then follow as above	1) Refer to Dietician if reported on more than two occasions 2) Obtain Fasting Measurement including glucose 3) Provide Advice on Diet and Physical Activity 4) Achieve/maintain healthy body mass (using BMI chart) 5) Aged > 10 yrs and LDL-C⩾4.9 mMol/L or LDL-C > 4.1 with family history or > 2 additional CVD risk factors consider pharmacological intervention (e.g. statin) or nutritional intervention (e.g. omega-3 fatty acids)

- Glucose and total cholesterol/triglycerides annually only if on PIs
- TDF based regimens only: Creatinine and CrCl: 3 and 6 months post-initiation; once stable, every 6 months
- Chemistry: After baseline, only as clinically indicated
- RPR (Adolescents): After baseline, only as clinically indicated

Table 8.7: Pediatric Laboratory Monitoring

Pediatric Laboratory Monitoring for the Following 1st Line ART Regimens:
AZT+3TC+ NVP or EFV or LPV/r, ABC+3TC+ NVP or EFV or LPV/r, TDF+3TC+ NVP or EFV or LPV/r

	Baseline	2 wks	1 month	3 months	6 months	9 months	12 months	Thereafter
CD4 count or %	X			X	X		X	q6 months
Viral Load	**NONE**			X	X	X	X	q3 months
FBC	X		**AZT only**	X			X	q12 months
Chemistry	X							As indicated
AST/ALT	X	**NVP only**	**NVP/EFV** only	**NVP/EFV** only				As indicated
Glucose, TC/ TG	**LPV/r only**						**LPV/r only**	q12 months
Growth and development	X		**weight only**	X	X	X	X	q3 months

Pediatric Laboratory Monitoring for 2nd Line ART Regimens:

	At Switch	6 wks	3 month	6 months	9 months	12months	Thereafter
CD4 count or %	X If not done in prior 6 months		X	X		X	q6 months
Viral Load	If not done in prior 3 months	X	X	X	X	X	q3 months
FBC	If not done in prior yr	If switch to **AZT only**	X **AZT only**			X **AZT only**	q12 months
Chemistry	If not done in prior yr						As indicated
AST/ALT	If not done in prior yr	If switch to **NVP only**	**NVP/EFV** only				As indicated
Glucose, TC/ TG	**LPV/r only**					**LPV/r only**	q12 months
Growth and development	X	**Weight only**	X	X	X	X	q3 months

Criteria for Priority Laboratory Monitoring:

- CD4 and VL for all patients ≤ 20 years of age
- Confirmation of virologic failure
- Follow-up VL 6 weeks after switching/restarting/continuing ART, after interventions for treatment failure due to non-adherence, toxicities, vaccinations, drug interactions, inappropriate ARV dose, and gastroenteritis
- VL prior to switching from a pediatric regimen containing d4T and/or ddI, when no VL has been performed within the previous 3 months

If the 6 week viral load remains ≤ 400 copies/µL, then resume normal viral load monitoring. CD4 cell count or % monitoring can remain at 6 month intervals.

8.10A Special Considerations: TB in Pediatric Patients

Intensified case finding for TB involves screening for signs and symptoms of TB by asking patients about cough, fever, night sweats and weight loss. It is also important to examine patients for evidence of lymphadenopathy. No single symptom is diagnostic for TB. Therefore any duration of cough, fever, night sweats, weight loss or presence of enlarged lymph nodes of any duration in an HIV patient should prompt an evaluation for TB.

In addition to the above symptoms, TB screening in children must include asking about decreased playfulness and failure to gain weight (as evidenced on the under 5 card). Most young children acquire TB from an adult with smear positive TB. Therefore, it is essential to ask about TB exposure in the household as part of the symptom screen.

Remember: A detectable viral load in a previously suppressed patient may the first sign of TB disease. After assessing other causes ARV treatment failure such as adherence, all failing patients must be carefully screened for TB.

Risk Factors for Pediatric TB

The risk of developing TB disease following HIV infection is mainly determined by these factors:

- ***History of a recent TB contact***: Adult or adolescent with PTB
- ***Age:*** Risk of developing active TB is highest in very young children (< 3 years)
- ***Time since exposure/infection:*** The majority of children who develop TB disease do so within the first year after HIV infection
- ***Immune status:*** Conditions that suppress the immune system make disease more likely; these include HIV infection, severe malnutrition, and immune suppressive therapy such as corticosteroids

Diagnosis

Microbiologic confirmation is challenging, as sputum samples are difficult to obtain, especially in young children. However, a thorough clinical evaluation will detect the majority of pediatric TB cases.

Signs and Symptoms

Pulmonary TB is the most frequent form of TB in children. However, extrapulmonary TB is more common in children than it is in HIV negative adults. No one symptom is diagnostic for TB. Symptoms that are commonly associated with TB in children include:

- Weight loss or failure to thrive (no weight gain over 3 months)
- Enlarged lymph nodes (more than 1 x 1 cm)
- Cough for > 2 weeks
- Fever for > 2 weeks

- Fatigue/reduced playfulness ≥ 2 weeks
- Profuse night sweats ≥ 2 weeks

Symptoms associated with TB disease are often non-specific and may overlap with other chronic diseases, especially HIV. Clear symptom definitions (as defined above) are essential to improve diagnostic accuracy.

Hypersensitivity Phenomena

These phenomena represent early clinical evidence of the immune system response to M. tuberculosis infection. The following may occur 8-12 weeks after a child is infected:

Common:

- TST conversion

Less common:

- Erythema nodosum: painful nodules usually on the shins
- Phlyctenular conjunctivitis: red nodule on the eye with conjunctival injection
- Polyarthritis

(See Annex 19: Diagnostic Algorithm for Pulmonary TB in Children ≤ 12 years, page No. 189)

ART Regimens in Pediatric Treatment Naïve TB/HIV Co-infected

Initiation of ART is a priority in HIV - infected children with suspected or confirmed TB.

- In those ≤3 years **not exposed to sdNVP**: The standard first-line regimen is AZT + 3TC and NVP.
- In those ≤3 years **exposed** to sdNVP: The standard first-line regimen is AZT + 3TC, double dose LPV/r.
- In those >**3 years**: The standard first-line regiment is AZT + 3TC and EFV.
- The standard second line pediatric treatment regimen is ABC + 3TC, and either double dosed LPV/r or a standard dose of EFV or NVP depending on the original first line regimen and the age of the child.

Table 8.8: HIV Treatment Regimens for Pediatric TB/HIV patients while taking ATT

Line of Therapy	Drug Regimen	Not exposed to sdNVP		Exposed to sdNVP
		< 3yrs	> 3yrs	
First-line	AZT**+3TC+	Line of Therapy	EFV	Double dose LPV/r
Second-line	ABC+ 3TC+ double dose LPV/r*	In patients exposed to LPV/r as first line contact TB or HIV specialist		

** The dose of LPV/r should be doubled*

*** If there is severe anaemia use ABC in place of AZT. (If ABC is used in the first line regimen then use AZT in the second line regimen (if the anaemia has resolved))*

Contact TB/HIV specialist in cases of salvage or unusual regimens

NOTE: Atazanavir and darunavir should not be used with rifampicin due to drug/drug interactions. Therefore, LPV/r will continue to be the PI of choice for all TB/HIV co-infected patients taking rifampicin. For questions consult TB/HIV specialist.

8.10B Special Considerations: Isoniazid Preventive Therapy in Pediatric Patients

Isoniazid preventive therapy (IPT) is an intervention to prevent people infected with TB from developing active TB disease, and involves a single 6-month course of daily isoniazid and pyridoxine.

It is important to note that anyone, regardless of age, who is asymptomatic but has been identified as an MDR-TB contact should not receive IPT.

Pediatrics

- All children ≤ 5 years, ***regardless of HIV status***, who are in contact with a smear positive individual should be fully assessed for HIV and TB infection. Those children who are not clinically symptomatic for TB should receive IPT for 6 months.
- All children > 5 years and ≤ 12 years, ***who are HIV positive***, who are in contact with a smear positive individual should be fully assessed for TB infection. Those HIV positive children and adolescents who are not clinically symptomatic for TB should receive IPT for 6 months.

In both of the above instances, IPT can be given regardless of the child's TST status.

8.10C Special Considerations: Pediatric Immunizations:

Immunization is a crucial component of preventive health care in all children, particularly those living with HIV. Healthy HIV-exposed babies should receive all vaccinations which are currently recommended for HIV-negative children. However, live vaccines (e.g., OPV, Rotavirus, BCG & measles) should be avoided whenever possible in severely immune-suppressed children. Children with severe immune suppression also may not be able to mount protective immune responses to immunization, and protection against disease can be improved by vaccinating family members and close contacts.

Table 8.9: Botswana Childhood Immunization Schedule

Contact	Age of Child	New Schedule
1.	At birth	BCG and HBV 0
2.	2 months	Pentavalent: (DPT/HBV/Hib),OPV1 Rotavirus Pneumococcal
3.	3 months	Pentavalent: (DPT/HBV/Hib), OPV2 Rotavirus Pneumococcal
4.	4 months	Pentavalent: (DPT/HBV/Hib), OPV3 Pneumococcal

8.10D Special Considerations: Nutrition

Nutritional assessment and dietary support must be an integral part of initial and continuing assessment of all HIV-infected children on or off ART. This is very important because long-term ART use is associated with metabolic complications which must be recognized early and managed effectively. Remain mindful that:

- HIV-infected children have greater energy needs than the non-infected.
- Micronutrient deficiencies are common among HIV-infected children. Micronutrient supplements are therefore recommended.
- Optimal nutrition of HIV infected mothers during pregnancy and lactation increases weight gain, and improves pregnancy and birth outcomes.
- Growth faltering in children often precedes HIV symptoms. This is because HIV infection impairs the growth of children early in life.
- Poor growth correlates positively with increased risk of child mortality in HIV-infected children.
- Improving dietary intake helps HIV-infected children regain lost weight after opportunistic infections.

8.10E Special Considerations: Fluid Management

The maintenance of fluid volume will often need to be adjusted for all sick children. In non-dehydrated children, consider using 2/3 maintenance levels in sick children, especially those with pneumonia and meningitis.

Table 8.10: Pediatric Fluids Management

Fluids	Uses
Normal saline	Initial boluses, Replacement of deficit, Replacement of losses
½ Normal saline with glucose	Maintenance (consider in low potassium loss [e.g., emesis without diarrhea, poor intake, fever, etc].)
½ DD	Maintenance (consider in high potassium loss [e.g., diarrhea])

Premade solutions with potassium chloride 20 ml/L may be used unless the serum potassium is elevated; there is anuria or renal failure.

Current formula; Maintenance:

Weight: Where weight is not available or impractical to measure, ideal body weight can be estimated by **Wt= [age in years +4] x 2**

4 ml/kg/hr for the first 10 kg (=100 ml/kg/24 hours)

Adding 2 ml/kg/hr for the second 10 kg (=50 ml/kg/24hrs)

And 1 ml/kg/hr for each kg over 20 kg (=25 ml/kg/24hrs)

Example:

For a 22 kg child calculate 4 ml/kg for the first 10 kg, and then add 2 ml/kg for the next 10 kg, and finally add 1 ml/kg for the remaining weight. This gives us a total of 62 ml/hr.

One may hydrate at 1.5-2 x maintenance levels (usually for chemo and other pre-hydration protocols). However, this tends to be less accurate and can overestimate fluids. Therefore, whenever possible, use the surface area calculation which is more accurate:

Approx BSA (Mosteller Method): BSA (m2) = ([Height (cm) x Weight (kg)]/3600) ½

Maintenance fluid (ml/day) = 1600 mL* BSA

Where there are deficits please follow the WHO rehydration guidelines.

9.0 ART TREATMENT FAILURE AND ITS MANAGEMENT

(Adult, Adolescent and Children)

After 10 years, the strength of Botswana's anti-retroviral treatment programme is most evident from its documented adult first line virologic failure rate of < 5%. This success is largely due to the programme's ability - since its inception - to closely monitor viral loads. Additionally, requiring that every patient initiated on ART is accompanied by an adherence partner has proved to be an important key to reducing personal stigma and improving adherence for patient's long term success.

Although Botswana has continued to expand treatment access while maintaining excellent treatment outcomes, its ability to maintain long-term financial sustainability now centers on continuing to keep first line failure rates at a minimum. This will be achieved through the efforts of healthcare professionals to improve adherence interventions as well as their skills at early detection and management of ARV treatment failure and resistance surveillance.

Viral load monitoring remains the gold standard for determining adherence and ART effectiveness. It is therefore critical that all healthcare professionals diligently utilize viral load test results by:

1. Acting quickly upon all out-of-range viral loads;
2. Assisting stable patients to continue to maintain virologic suppression long-term;
3. Improving patient literacy regarding the importance of continued viral load suppression and strict adherence.

9.1 Definition of Treatment Failure (all ages)

9.1.1. Virologic Failure

- Viral load > 400 copies/µL after 6 months post initiation or
- Viral load rebound to > 400 copies/µL after documented full suppression

However, pediatric patients may require longer than 6 months to achieve full virologic suppression. ***When viral load in a pediatric patient is not < 400 copies/µL by 6 months after ART initiation, a pediatric HIV Specialist must be consulted.***

In Botswana, over 85% of adult patients achieve full viral load suppression (viral load < 400 copies/µL), three months after initiating ART. However, for those who do not, special care should be taken to closely monitor their progress on treatment, conduct intensified adherence counselling, and make appropriate treatment switches as required.

Closely track, monitor and intervene in all patients who:

- Do not fully suppress their viral load to < 400 copies/µL by 3 months to ensure treatment success by 6 months. Complete intensified adherence counseling and investigate all possible non-resistance causes of treatment failure. *(See Section 9.2.2 below)*

- Received sdNVP as part of PMTCT (both infants and mothers) and do not fully suppress their viral load to < 400 copies/µL at 3 months after being initiated on NNRTI based regimens.

Promptly identify these patients who remain at high risk for NNRTI resistance and conduct intensified adherence counseling and investigate other non-resistance causes of treatment failure.

Remember: A detectable viral load while on ART should always be repeated as a "priority viral load" to confirm the presence of virologic failure. While awaiting the confirmatory viral load, begin treatment failure evaluation.

9.1.2 Immunologic Failure:

The current consensus on what clinical and laboratory parameters define immunologic failure remain unclear. Generally, it can be classified as those cases which fail to achieve and maintain an "adequate CD4 response" in spite of full virologic suppression. Adequate CD4 response has been correlated to CD4 levels at baseline; the higher the CD4 count at ART initiation, the more likely a patient will achieve and maintain higher CD4 counts on treatment.

Poor CD4 count response after initiation of ART or during long-term follow up has been associated with increased risk of AIDS and non-AIDS-related mortality and morbidity. However, there is no clear evidence that, in the presence of viral suppression, treatment switches (particularly switching from NNRTI to PI) significantly improves CD4 count levels.

Immunologic failure in the presence of full virologic suppression and clinical improvement does not merit a treatment change (consult an HIV Specialist, as needed).

However, all clinicians should:

- Closely monitor patients whose CD4 counts do not improve on ART, fall below their nadir, or remain < 200 after one year of treatment. Schedule routine follow up visits for these patients at least 4 times a year.
- Conscientiously complete all routine laboratory tests as recommended.
- Be diligent with all screening protocols (i.e., Pap smear, TB, etc.) and thoroughly investigate the source of any detected anemia.
- Improve patient literacy by helping patients understand their immune status in order for them to be alert to the development of any illness and promptly seek medical attention whenever needed.

9.1.3 Clinical Failure:

"Clinical Failure" is a term used to describe adult, adolescent or pediatric patients who, although virologically suppressed, do not make good clinical progress; this may also refer to patients who after making good clinical progress, go on to develop new opportunistic infections.

For pediatric patients, clinical failure may be considered when one of the following situations arises:

- Recurrence or persistence of AIDS-defining conditions or serious infections, excluding IRIS.
- Progressive neurodevelopmental deterioration or failure to reach expected neurodevelopmental milestones.

- Growth failure, i.e., a persistent decline in weight-growth velocity despite adequate nutrition and without other explanation.

For adolescent and adult patients, consider clinical failure when a new AIDS-defining illness develops after initiation of ART (i.e., a new WHO stage 3 or 4 condition), excluding IRIS. Clinical failure in the presence of full virologic suppression may or may not justify a change in ART; consult an HIV Specialist as needed.

9.2 Causes of Virologic (Treatment) Failure:

In our setting, the term "treatment failure" refers to "virologic failure" (i.e., two documented out-of-range viral loads). The causes of virologic/treatment failure can be separated into:

- Resistance causes
- Non-resistance causes

Remember: Virologic failure does not necessarily mean that HIV drug resistance has developed. However, if non-resistance causes of virologic failure are not promptly addressed, and if ongoing viremia persists in the presence of ART, resistance will inevitably develop.

9.2.1 Types of HIV Drug Resistance (HIV-DR):

- **Primary or Transmitted Resistance:** Initial infection with an HIV resistant strain.
- **Secondary or Acquired Resistance:** Drug resistance that occurs when HIV continues to replicate in the presence of suboptimal ART levels. It is the most common type of HIV-DR among patients.

9.2.2 Causes of Non-Resistance Treatment Failure :

- Co-morbidities, such as the presence of other infections (e.g., TB or sub-clinical malignancies)
- Non-adherence or poor adherence (the most common cause)
- Incorrect dose of ART (e.g., pediatric dose determinations)
- Adverse drug-drug interactions (e.g., rifampicin and LPV/r)
- Tolerability of medications (e.g., persistent nausea or vomiting)
- Variable absorption (e.g., wasting, gastroenteritis)
- Lack of regimen potency and/or durability (e.g., mono/dual therapy)

9.3 Clinical Approach to Treatment Failure:

Ensuring complete viral suppression is a primary goal of HIV medicine. It is therefore the responsibility of HIV healthcare providers to review viral load results and identify any clinical signs or symptoms of treatment failure at each and every clinical visit as follows:

1) **Review all relevant clinical and laboratory information:**

- Promptly identify the presence of treatment failure by ***reviewing viral load results on a timely basis - as soon as the results arrive at the clinic from the laboratory.***
- ***Immediately act upon all viral loads that are not fully suppressed to < 400 copies/µL:***
  - Contact patients to return to clinic for confirmatory priority viral load (PVL) and re-send the specimen as soon as possible.
- Monitor CD4 cell count or % in comparison to nadir and previous values, especially in those instances where viral load results are missing, outdated or delayed.
- Monitor clinical condition for any sign or symptoms of new HIV-related disease(s) or other co-morbidities.

> ***Pay particular attention to weight loss and thoroughly investigate its source. Rarely should a healthy HIV positive patient lose weight while taking ART. Always be alert to weight loss and rule out the possibility of sub-clinical TB, malignancies or other co-morbidities.***

If a patient's clinical condition is unstable (i.e., new onset HIV related disease or other illness) and is continuing to worsen, and there are no recent viral load results available to confirm treatment failure, contact an HIV Specialist.

2) **Determine and rectify any non-resistance causes of treatment failure:**

- Identify and address all non-resistance causes *(see Section 9.2.2 above).*
  - In cases of ***medication intolerance*** in the presence of viremia, change the complete regimen. Discuss with an HIV Specialist, as needed.
  - In cases of a suspected ***drug/drug interaction***, attempt to substitute alternative medications other than ART (i.e., using gabapentin instead of carbamazepine).
  - In cases of ***sub-optimal adherence***, complete an intensive adherence intervention *(as outlined in Section 9.5).*

> ***After successfully addressing the cause of suspected treatment failure and/or changing or continuing ART, repeat priority viral load within 4-6 weeks. if the viral load is not significantly trending down or fully suppressed to < 400 copies/µL, then assume resistance has developed.***

9.4 Switching ART due to Treatment Failure:

Switching ART in a non-adherent patient will very likely result in continued treatment failure, as non-adherence typically continues to subsequent ART regimens, with resulting resistance over time. Therefore make every effort to ensure adherence issues are identified and corrected at the first sign of treatment failure.

- Never change the regimen for a patient with complete viral suppression and immunologic and/or clinical failure without first consulting an HIV Specialist.

- Always obtain a repeat priority viral load to confirm viremia; never change a regimen on the basis of one viral load measurement alone.

- While awaiting results of the confirmatory viral load, complete intensive adherence counseling and evaluation for other non-resistance causes of treatment failure.
- Avoid judgmental attitudes toward patients during adherence counseling; rather kindly assist them to overcome their barriers to better adherence.
- If viral load is trending down, you may continue to monitor patient's viral load every 4-6 weeks until full suppression is achieved.
- Never stop a patient on a failing regimen while awaiting confirmatory results unless clinically indicated due to adverse drug reaction or intolerance. *Remember, a failing regimen is **usually** better than no regimen at all. Consult an HIV Specialist as necessary.*

If the priority viral load does not return within 2 weeks, contact the laboratory in order to track the specimen and expedite confirmatory results. If after one month, no results have returned and the patient's clinical condition continues to worsen, consider a full empiric treatment regimen switch in consultation with an HIV Specialist.

9.4.1 First Line Regimen Failure:

If confirmatory viral load remains elevated at the same level or higher, ask the patient to immediately return to the clinic ***with an adherence partner*** to be changed to the appropriate second-line regimen.

- At the second line initiation visit, complete intensive adherence counseling in the presence of the patient's adherence partner.
- After counseling, initiate appropriate second line regimen.

However, if confirmatory viral load has dropped at least one log, continue the patient on the same regimen with follow up and repeat PVL in 4-6 weeks. Continue this schedule of follow up until the patient has achieved full viral suppression or until the viral load plateaus.

- Once the viral load plateaus at the same log scale above 400, initiate a second line regimen, as described above.

HIV Specialist consultation is not required for permission on straightforward switching to second line regimen for first line failures, unless there are unusual clinical circumstances.

9.4.2 Second Line Regimen Failure:

In addition to the steps followed above for first line failure, and after non-resistance causes have been ruled out and intensive adherence intervention completed:

- Send a blood sample for genotypic resistance testing using Genotypic Resistance Testing Request Form. *(See Annex 20: Genotypic Resistance Testing Request Form, page No. 190)* Specimens should be drawn and sent to the laboratory in two purple top tubes. A***s the laboratory will complete a viral load test on the resistance sample, there is no need to send additional blood for viral load.***

- ***Specimens will not be accepted without the Resistance Testing Request Form which includes the patient's full clinical history.***

- ***However, if the clinical status of the patient is worsening, do not wait for more than 8 weeks for the resistance assay to return before changing to an empiric third line regimen, <u>under Specialist guidance and approval only</u>, pending eventual return of the resistance assay.***

9.4.3 Monitoring After Treatment Switch for 1st and 2nd Line Failure:

- Any change in ART for treatment failure requires 4-6 week follow-up viral load and CD4 cell count or % measurements to document viral suppression.
- Continue new regimens as long as the viral load is trending downwards by at least one log. Ask the patient to return every 4-6 weeks until full viral load suppression is achieved.
- After documented suppression, repeat viral loads at 3 and 6 months after initiation of the new regimen. If at 6 months the viral load is < 400 copies/µL, then return to viral load monitoring at 6 month intervals for adults; continue every 3 month monitoring for pediatric/adolescent patients.
- CD4 or % monitoring can also return to every 6 months for all ages.

9.5 Managing Sub-Optimal Adherence:

Non-adherence is the most common causes of treatment failure. Whereas patient self-reports of good adherence can be unreliable, patient self-report of poor adherence is a strong predictor of non-adherence, and must always be taken seriously. Pill counts, pharmacy refill data, and patient disclosure of HIV status are also important indicators of adherence. Clinician assessment of adherence is a poor predictor, as are patient educational level, sex, and socioeconomic status.

Barriers to adherence in children are often complex and must be promptly addressed *(See Chapter 8, Section 8.3 for discussion of pediatric and adolescent adherence).*

- Once non-adherence is suspected or confirmed, request that the patient bring back their adherence partner for further support.
- Complete intensive adherence counseling to identify adherence challenges and complete further investigations or make appropriate referrals as necessary.
- Maintain patients with poor adherence on their current regimen, while the non-adherence issues are being addressed.
- Continue the current regimen and repeat follow up priority viral load 4-6 weeks if after adherence intervention psycho-social or other medical issues have been identified and resolved.
- If after intensive adherence intervention full viral suppression (VL= <400 copies/µL) has been achieved within 4-6 weeks, then complete follow-up viral load in 3 months. If viral load remains < 400 copies/µL, then, return to every 6 month viral load monitoring for adults, and every 3 month viral load monitoring for pediatric and adolescent patients.
- If the viral load 4-6 weeks after adherence intervention is not <400 copies/µL, and all correctable causes have been acted upon, assume that resistance has developed and change the regimen accordingly (as instructed in Section 9.4 above).

9.5.1 Defaulting Patients and Lost to Follow Up

- Patients who have either defaulted from therapy or have been lost to follow-up are at very high risk for subsequent treatment failure once ART is restarted.
- Before restarting ART make sure that the reasons for the defaulting and/or missing clinic appointments have been adequately identified and addressed.

- Restart these patients on their last treatment regimen and complete the first routine follow up visit between 4-6 weeks, following the same visit and monitoring schedule as above.
- ***Patients that were previously on NVP-based regimens and are restarting NVP should be started on OD dosing if the time off NVP has been >2 weeks or more***.

9.6 Special Considerations in Treatment Failure:

9.6.1 Discontinuation of ART:

- Whenever NNRTI-based ART is discontinued (e.g., for toxicity, side effects, intolerance, or severe gastroenteritis) the long half-lives of NNRTIs should be addressed, if possible, by continuing the 2 N[t]RTIs beyond cessation of the NNRTI.
- The recommended length for an N[t]RTI "tail" is 7 days in non-life threatening situations. However, in cases of severe NVP-induced toxicities, a 3-5 day tail may be necessary.
- Treatment failure due to severe gastroenteritis (e.g., protracted vomiting and/or frequent voluminous diarrhea, not controlled by standard therapy) may require regimen discontinuation while the gastroenteritis is being treated. Management and follow-up of with a priority viral load 4-6 weeks after resolution of the gastroenteritis is otherwise the same as with non-adherence, as above. However, ***as a rule, ART should not be stopped - especially in severely immunocompromised patients without first consulting an HIV Specialist***.
- For treatment failure due to non-adherence, decisions about continuation or discontinuation of the current regimen must be made carefully.

9.6.2 Transient viremia secondary to intercurrent infections and immunizations:

- Any acute, intercurrent infection (e.g., viral upper respiratory infection, HSV, TB, malaria) can elevate a previously suppressed viral load, as can immunizations (e.g., the "flu shot," measles vaccine, yellow fever vaccine).
- Once the infection or vaccination effects resolve, viral load should return to <400 copies/µL.
- Defer routine viral load measurements whenever there is an intercurrent infection or recent vaccination.

9.6.3 Viral blips:

- A "viral blip" is a transient increase in viral load from ≤400 copies/µL to no more than 1000 copies/µL, with follow-up viral load returning to ≤400 copies/µL.
- The causes of "blips"are unknown.
- Sustained viremia (more than one viral load measurement >400 copies/µL) does not constitute a "viral blip" and should always be considered treatment failure.

9.6.4 Recognition and Management of Treatment Failure When Viral Load and CD4 Results Are Not Available:

In the absence of both a recent viral load and CD4 cell count or %, evaluate for treatment failure solely on clinical parameters, as above: i.e., any new or recurrent WHO stage 2, 3, or 4 condition which occurs more than six months after initiation of ART. Diagnosing treatment failure within the first 3-6 months of ART initiation on the basis of clinical deterioration must exclude the possibility of IRIS, which does not denote treatment failure. Clinical and/or immunological parameters should be carefully evaluated to determine whether or not treatment failure is likely. In all such cases, it is essential to discuss the case with an HIV Specialist.

- The following clinical scenarios are highly suggestive of treatment failure:
  - Any new or recurrent WHO stage 2, 3, or 4 condition, which occurs more than 6 months after ART initiation.
  - Any drop in CD4 cell count or % to below nadir value, or a 50% decline in CD4 cell count or % from the highest on-treatment value.
  - The likelihood of treatment failure is increased when both clinical and immunologic deterioration are present simultaneously.

9.7 HIV Specialist Panel HIV

Adult and General HIV/AIDS and TB care:

Dr. T. Gaolathe *	72111501	tgaolathe@bhp.org.bw/gaolathet@gmail.com
Dr. A. Avalos *	72116222	avaavalos@gmail.com
Dr. Mukendi Kazadi	72105517	jhmukendi@bhp.org.bw
Dr. M. Letebele	72339858	mletebele@yahoo.com
Dr. K. Mwantembe	72108076	kmwantembe@bhp.org.bw
Dr. M. Haverkamp *	76516520	haverkamp.bup@gmail.com

Pediatric and Adolescent HIV/AIDS and TB care :

Dr. H. Jibril	71838264	hjibril@gov.bw/jibril.harunababa@gmail.com
Dr. M. Mazhani	71677145	loeto.mazhani@mopipi.ub.bw
Dr. M. Matshaba *	71814939	matshaba@bcm.edu
Dr. A. Steenhoff	72126505	steenhoff@email.chop.edu

MDR-TB / BNTP:

Dr. C. Modongo**	71861294	ntungwana@yahoo.co.uk
Dr. Basore**	74510849	tesfayeabicho@gmail.com
Dr. R. Ncube	72415212	rncube@gmail.com

PMTCT and Women's Health:

Dr. D. Ramogala-Masire	72687480	doreen.masire@gmail.com
Ms. K. Keapoletswe	71458658	kokeapoletswe@gov.com

Cancer/HIV Registry

Dr. M. Pusoentsi	72306355	mpusoentsi@gmail.com
Dr. A. Agrawal (Peds)	72259379	anua@bcm.edu

Laboratory Issues:

Dr. M. Mine	71307122	mmine@bhp.org.bw
Ms. K. Makhaola	72682425	kmakhaola@bhp.org.bw
Mr. G. Sebetso	71718939	gsebetso@bhp.org.bw
Ms. T. Nkoane	72104373	tnkoane@bhp.org.bw

*** Denotes HIV Resistance Specialists**
**** Denotes TB Resistance Specialists**
Toll-Free Line: 0800 600 691
This list will be updated as needed: refer to ***www.moh.gov.bw.***

Doctors and other healthcare workers should contact members of the HIV Specialist Panel, above, whenever difficult questions of patient management arise. ***Specific instances requiring such consultation include, but are not limited to those outlined in the Table 9.1:***

Table 9.1: Indications for Specialist Referrals

	Pediatric HIV Specialist Required	Adult HIV Specialist Required	Resistance Specialist Required
Infants whose DNA PCR results are pending, with WHO stage 2,3, or 4 conditions	X		
Special indications for ART, e.g. severe WHO 2 stage, inappropriately low CD4% (<15%) with CD4 >350 (adult & Peds)	X	X	
Viral Load >400 copies/ml after 6 months of ART	X	X	X
Post delivery decisions regarding continuing or stopping TAP in women w CD4 >350		X	
Second line regimen failure and all subsequent regimen failures			X
Ordering of genotypic and phenotypic resistance testing	X	X	
Interpretation of genotypic and phenotypic resistance assays			X
Immunologic and/or clinical failure with full viral suppression	X	X	
Evaluation of treatment failure in the absence of monitoring lab results	X	X	X
Difficult decision regarding PEP initiation	X	X	
Approval for Raltegravir, Darunavir, or Atazanavir and other HIV related drugs not included in routine first and second line ART regimens			X

9.8 Failure Management Teams & Clinics:

Plans are underway to build the necessary local capacity in Botswana to decentralize HIV specialist care to a number of districts in the upcoming years. Implementation of these plans will see additional HIV and TB specialists trained and deployed around the country to provide specialist care to complicated HIV patients and those identified with HIV drug resistance. The close monitoring of HIV-DR will be an integral part of this process with resistance databases deployed in HIV/TB Centers of Excellence to keep accurate records of resistance surveillance trends.

Management of treatment failure is a "team effort," both for direct patient intervention and for discussion of treatment strategies and options. Accordingly, every ART clinic must establish a Failure Management Team and hold a Failure Management Clinic to address failure management in a comprehensive, methodical manner. The recommended team composition should include the following:

- The director of the ART clinic and/or the most experienced HIV doctor/medical officer in the clinic.
- Clinic doctors and nurses who are interested in failure management
- The clinic's focal ART nurse
- Clinic pharmacist(s) or pharmacy technician(s)
- If available, clinic staff who perform counseling responsibilities: adherence educator(s), clinic social worker(s), lay counselors

9.8.1 Responsibilities of the Failure Management Team:

The Failure Management Team should have regularly scheduled meetings to discuss all patients currently failing therapy as well as those who were recently switched to 2nd line or salvage regimens to review and/or plan individual interventions. Patients failing first line regimens can be switched to second line without prior discussion with FMT, however, all treatment switch cases should be presented during the subsequent meeting. Team members with the greatest HIV/AIDS clinical experience should lead the discussion.

- Maintain a Failure Management Registry for the clinic, which includes all copies of the Genotypic Resistance Request Form **including clinical history.**
- Any difficult cases for which there is no team consensus should be discussed with an HIV Specialist, with the consultation reviewed at subsequent meetings.
- Report to an HIV Specialist any of the following:
  - Any consistent pattern of specific causes of treatment failure
  - The association of certain ART regimens and/or ARVs with an increased incidence of treatment failure, adverse side effects/toxicity, and/or non-adherence

Patients to be reviewed by the Failure Management Team:

- Patients with virologic, immunologic, and/or clinical failure
- Patients who do not suppress viral load to < 400 copies/µL at 3 months post-initiation of ART
- Patients who experience severe, potentially life-threatening treatment toxicity, and who require a new ARV regimen

Completing Failure Management Forms:

- It is the responsibility of ART clinic staff to ensure the timely and accurate updating of patient information on Failure Management and Resistance Request Forms on a regular basis (at a minimum every 6 months). Fill out all forms completely and legibly.
- Copies of the forms should be kept in: 1) Individual patient file; 2) Failure Management Registry for the clinic.
- When requesting resistance testing, a copy of this form will sent in a sealed envelope with all resistance samples sent for processing to the Reference Laboratory in Gaborone.
- ***Remember: Resistance testing samples without full clinical information will not be processed.***

9.8.2 Clinical Review of Detectable Viral Loads:

As baseline viral loads are no longer performed, every viral load result represents a patient on ART, and thus must be < 400 copies/µL.

- It is the responsibility of the ART clinical team to ensure that the review of viral load results take place within 48 hours after they arrive from the reference laboratory, and to act upon any abnormal results promptly.
- All efforts must be made to recall patients with out of range viral loads, since delay in addressing treatment failure will eventually lead to the accumulation of resistance mutations, which could limit future treatment options.
- A patient must not be maintained on a failing regimen longer than absolutely necessary. Therefore, waiting to review monitoring lab results until the patient returns for the follow-up 3 or 6 month appointment is not advised.

9.8.3 Assessment for Virologic Failure/ Intensive Adherence Intervention

The Failure Management Team/Clinic should follow a standardized protocol for assessment/adherence intervention of treatment failure, which includes a review of the following:

- Patient motivation and understanding of the importance of adherence
- Involvement of adherence partner and/or care-giver(s)
- Review of any side effects which might interfere with adherence
- Inconvenience of regimen
- Presence of depression or other mental illness
- Substance abuse or alcohol abuse
- Problems with stigma or disclosure
- Presence of any illness or intercurrent infections
- Review of potential drug-drug interactions
- Any medical conditions interfering with oral intake or ARV absorption

Clinical management of treatment failure should be done according to the principles and guidelines in this chapter. As a rule, during the initial evaluation of treatment failure, patients may require more frequent clinic visits (e.g., every 1-2 weeks), and should not be automatically relegated to the standard every three-month schedule of visits.

9.9 Special Use of Raltegravir, Darunavir & Atazanavir

Raltegravir (RAL) is an integrase inhibitor which is effective in highly ART experienced patients. **Darunavir** (DAR) is a potent protease inhibitor which his active against HIV with multiple PI resistance mutations. Both are used in combination for patients requiring "salvage" regimens.

- Use of DAR/RAL requires documented resistance test displaying multiple NNRTI, NRTI and PI resistance mutations.
- **Adult Dosing:** **DAR** (300 mg tablets) 600 mg PO BD with RTV 100 mg BD.
  RAL (400 mg tablets) 400 mg PO BD
  plus optimized background therapy
- **Pediatric Dosing:** **DAR** *(FDA approved for > 3 years):*
  DAR 11-19 mg/dose BD + **RTV** 1.5-2.5mg/kg/dose BD
  >40kg use adult dosing
  RAL *(FDA approved for >2 years):*
  RAL 6mg/kg/dose BD
  ≥12 years use adult dosing
- Special order forms authorized by HIV Resistance Specialists are required to initiate use of RAL and DAR, all cases should be discussed.
- Carefully screen all salvage patients for sub-clinical TB or MDR-TB before initiating RAL and DAR.
- Do not use DAR in cases of treatment for TB with ATT. Discuss with an HIV Specialist for an alternative regimen selection.

Atazanavir (ATA) is a protease inhibitor that does not cause derangement of lipids or significant GI disturbance. For patients who remain refractory to statins to decrease cholesterol, or those who are experiencing intolerance to LPV/r due to GI disturbance, Atazanavir may be substituted. Discuss cases with an HIV Specialist for the necessary authorization and special order approvals.

- Adult Dosing: Atazanavir 300 mg OD with RTV 100 mg OD + optimized background therapy
- Pediatric Dosing *(FDA approved for >6 years):*
  15 - 25kg: **ATA** 150mg + **RTV** 80 mg OD
  25 - 32kg: **ATA** 200mg + **RTV** 100mg OD
  32 - 39kg: **ATA** 250mg + **RTV** 100mg OD
  ≥ 40kg use adult dosing
- Do not use ATA in cases of treatment for TB with ATT. Discuss such cases with an HIV Specialist for an alternative regimen selection.
- Some patients may develop jaundice with ATA use, discuss such cases with an HIV Specialist for alternative regimen selection.

CHAPTER 10: HIV AND CANCERS

Since the initiation of active cancer surveillance in 1998, Botswana has seen a steady increase in cancer incidence. The major contributing factor to this rise is the HIV epidemic which is closely associated with the development of several AIDS-defining cancers. Furthermore, with increased survival due to the implementation of ART, more non-AIDS related cancers are developing in the later stages of HIV infection.

In almost all cases, ART can be successfully co-administered during oncologic therapy and is associated with improved outcomes. However, some cancers such as AIDS-related lymphomas can continue to develop despite ART. Early screening, diagnosis and treatment are therefore essential to optimize survival and decrease morbidity due to malignancy in all HIV-infected patients.

Healthcare workers managing HIV patients must remain diligent during clinical visits to screen for all types of cancer, (i.e., AIDS-related and age-specific) and promptly complete appropriate investigations when warranted.

10.1 Concurrent Cancer and ART

The majority of malignancies in Botswana arise in HIV-infected patients receiving ART. The concurrent management of cancer and HIV treatment can be complex, with important drug-drug interactions and overlapping toxicities. Although current knowledge of these issues is limited, there is ongoing work in Botswana and elsewhere to fill these knowledge gaps. As we await further information to direct clinical practice, we must note observed interactions and follow several core principles:

Principles of Concurrent Treatment

In most cases HIV-infected patients diagnosed with cancer are managed by oncologists whenever possible. However, in some facilities medical officers do initiate chemotherapy.

- ***Coordination of care: HIV clinicians and oncologists should work in synergy.*** Advise patients to share their HIV medical records with oncologists and their oncology records (i.e., chemotherapy, radiation, etc.) with HIV clinicians. Carefully document history of ART and cancer treatments in each patient's medical record.
- ***Timing of ART in Adults:*** Immediately Start ART once cancer is diagnosed in an HIV-infected patient. In rare cases in which concurrent chemotherapy and ART cannot be given safely, ART may need to be deferred or interrupted. Discuss these cases with an HIV Specialist, whenever needed.
- ***Timing of ART in Children: Discuss timing of ART initiation and chemotherapy in pediatric patients with a pediatric oncologist.***
- ***Avoid AZT or CBV:*** Nearly all chemotherapy leads to lymphopenia and anemia, and co-administration of chemotherapy with AZT or CBV increases hematologic toxicity. Switch patients receiving AZT or CBV to ABC or TDF depending on renal function, planned chemotherapy and presence of adverse drug effects.
- ***Exercise caution with PIs:*** Toxicity from chemotherapy may be increased considerably due to inhibition of hepatic metabolism. Chemotherapy doses may need to be reduced, or patients

may need to be switched to alternative regimens during cancer treatment. Monitor patients receiving PIs and chemotherapy closely.

- ***Exercise caution with TDF:*** In addition to direct renal toxicity from several chemotherapy agents, the dehydration that frequently accompanies cancer therapy due to diarrhea, mucositis, or nausea can quickly lead to tenofovir-related renal failure. Monitor creatinine and creatinine clearance carefully. In cas***es of developing renal complications a switch to ABC should be considered***.

(See Annex 21: Chemotherapy and ART interactions, page No. 191)

10.2 Kaposi Sarcoma

Kaposi Sarcoma is the most common cancer affecting the HIV-infected population in Botswana. According to the National Cancer Registry, from 1998-2008, KS cases represented 21.7% of all malignancies. Of these cases, 92.1% were recorded to be HIV positive.

KS is a spindle-cell tumour thought to derive from endothelial cell lineage. This condition carries a variable clinical course ranging from minimal mucocutaneous disease to extensive organ involvement. KS can be primarily categorized into four types: epidemic of AIDS-related, immunocompromised, classic or sporadic, and endemic (African).

Human herpesvirus 8 (HHV-8) genomic sequences have been identified by polymerase chain reaction in more than 90% of all types of KS lesions (including epidemic and endemic forms) suggesting a causative role.

10.2.1 Clinical Presentation of Adult KS:

- ***Multiple skin lesions*** – most often papular (less commonly plaque-like) occur in virtually all patients. Lesions can appear in colors ranging from hues of pink, red, purple and brown.
- ***Tumour-associated lymphedema*** - typically manifest as lower extremity or facial involvement and is thought to occur secondary to obstruction of lymphatic channels.
- ***Pain*** – is usually associated with ambulation due to lesions involving the soles of the feet.
- Systemic involvement is found in less than 10% of cases and usually indicates a more advanced HIV/AIDS disease presentation. These may include:
    - Gastrointestinal lesions can occur anywhere within the gastrointestinal tract. Lesions are often asymptomatic and clinically indolent. Symptoms can include:
        - Odynophagia, dysphagia
        - Nausea, vomiting, abdominal pain
        - Hematemesis, hematochezia, melena
        - Bowel obstruction

- Pulmonary involvement is difficult to distinguish from opportunistic infections and may be an asymptomatic radiographic finding. Pleural effusions, which are often exudative and bloody, may occur. Additional ***symptoms include:***
  - Cough
  - Dyspnea
  - Hemoptysis
  - Chest pain
- Lymphadenopathy may require a lymph node biopsy and may lead to significant lymphedema.

10.2.2 Diagnosis of KS

Diagnosis should be based upon histology. However, in patients with a high clinical suspicion or those with systemic disease, chemotherapy should not be delayed while awaiting biopsy results. In cases of clinical certainty, histological confirmation should still be sent. Imaging is not necessarily warranted and should instead be made on a case-by-case basis.

- Referral for biopsy for histologic confirmation of KS will depend upon facility resources.
- ***Experienced medical officers can complete FNA and biopsy, if needed.***

10.2.3 Laboratory Investigations for KS

All patients with lesions which are suspicious for KS should be tested for HIV and CD4 count.

Other laboratory investigations include:

- ***FBC, urea, creatinine, electrolytes and LFTs***

10.2.4 Disease Classification of KS

After diagnosis and before treatment, classify all KS patients as follows:

- ***Localized disease:*** Disease involving skin only.
- ***Disseminated disease:*** Disease with lymph node involvement or lymphedema.
- ***Systemic disease:*** Disease affecting internal organs.

10.2.5 Disease Staging and Prognosis of KS (Adults):

Stage all patients upon initial presentation. The staging of disease is both important as a survival predictor and to inform treatment choice.

Table 10.1: Disease Staging and Prognosis of KS

	Good Risk (all of the following)	Poor Risk (any of the following)
Tumour	Confined to skin and/or lymph nodes Minimal oral disease (non- nodular KS confined to palate)	Tumour-associated oedema or ulceration Extensive oral or GI tract involvement KS in other non-nodal viscera
Immune system	Cd4 cell count ⩾200 cells/µl	Cd4 cell count <200 cells/µl
Systemic illness	No history of opportunistic infection. No B symptoms Karnofsky performance status ⩾ 70	History of opportunistic infection B symptoms present Karnofsky performance status <70 Other HIV related illness

10.2.6 Treatment for Adult KS

The goals of KS treatment are as follows:

- ***Palliation of symptoms:*** Shrinkage of tumour to alleviate edema, organ compromise and psychological stress.
- ***Prevention of disease progression***
- ***Cure***

10.2.7 Treatment Options Available for Adult KS

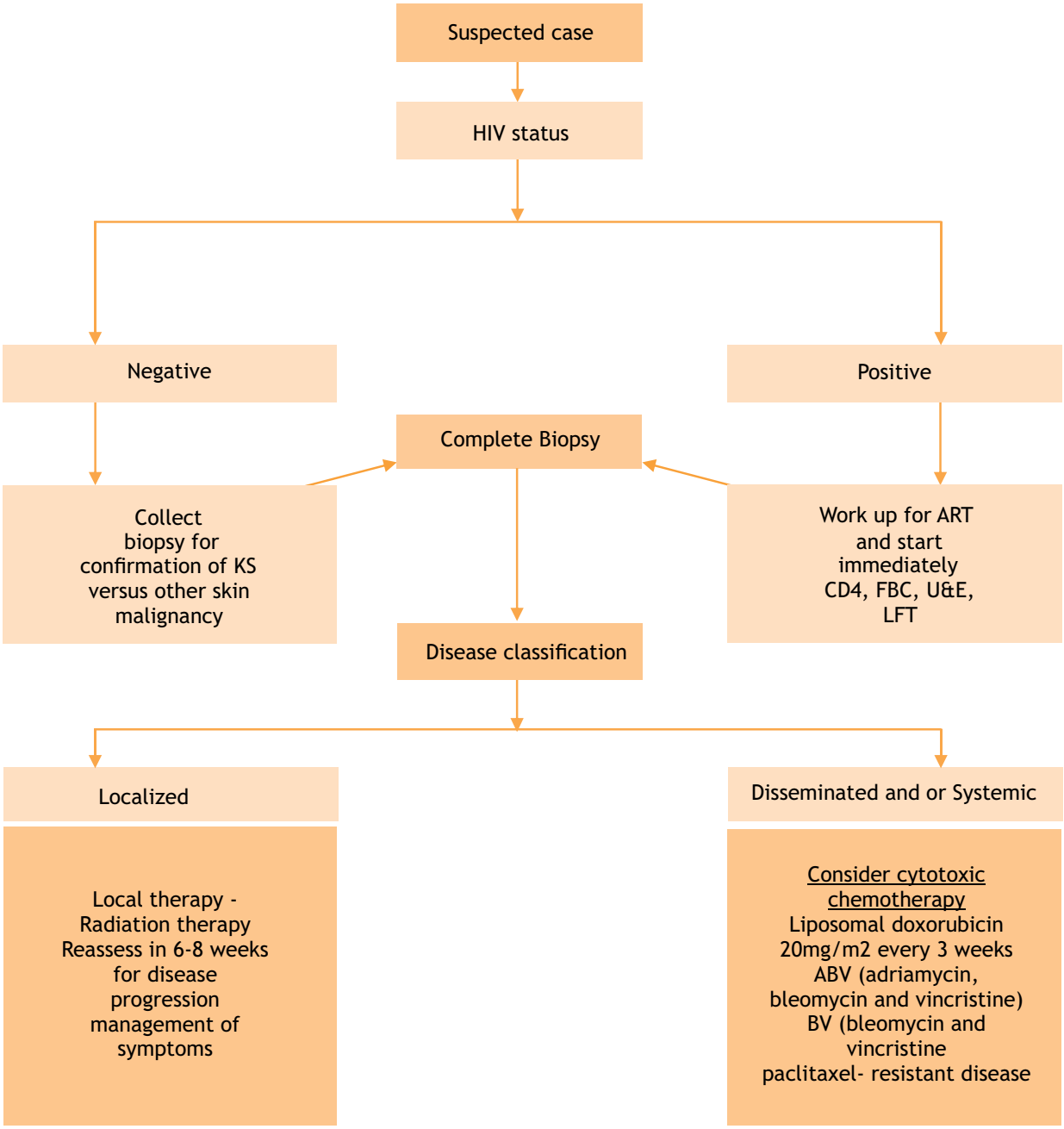
- ***ART:*** Immediately start ART in all adult patients diagnosed with KS once baseline laboratories have been completed. Often this may be the only treatment required.
- ***Local therapy:*** Radiotherapy and intralesional chemotherapy are very effective for cosmetic control of skin lesions and palliation of painful lesions on the soles of the feet, genitalia, oral cavity and conjunctiva.
- ***Cytotoxic chemotherapy:*** Reserved for patients with more advanced and or rapidly progressive disease.

10.2.8 Clinical Monitoring of Adult KS

Monitor KS patients closely to determine disease progression and response to treatment. Special attention should be paid to the development of anemia, neutropenia, and renal insufficiency. It should be noted that although systemic disease is usually asymptomatic, KS can also present at an advanced stage.

> ***Always carefully document chemotherapy and ART history on patient's clinical cards and HIV clinical charts at the IDCC.***

Figure 10.1: Flow Chart for Kaposi Sarcoma Management (Adults)



10.2.9 Kaposi's Sacoma in Children:

Clinical presentation and outcome of KS in children may be quite different from what is seen in adults. Therefore, questions remain about proper staging and treatment of pediatric KS, which up to now has been based on experience with adult patients.

10.2.9A Clinical Presentation of Pediatric KS:

- Cutaneous lesions occur in virtually all patients.
- A distinct presentation with lymphadenopathic KS in younger children at higher CD4 counts may be seen. Lymph nodes are often quite hard, non-mobile, and tender. If there is extremity involvement, there may be associated lymphedema.
- Response rate, especially in younger children without systemic disease, is likely favorable.

10.2.9B Staging in Pediatric KS

No uniform pediatric staging criteria or treatment regimen has been prospectively studied in the literature. In general, those children with local disease (limited to the skin) do well with ART initiation +/- chemotherapy (see below recommendations). Those with dissemination to lymph nodes or lymph channels represented by lymphadenopathy or lymphoedema respectively have an intermediate prognosis, and those with systemic disease represented by visceral involvement usually do poorly.

10.2.9C Diagnosis of Pediatric KS

Histologic proof of KS is preferred. This can usually be done with skin biopsy although lymph node biopsy may be required. Treatment (i.e., ART and/or chemotherapy; see below) can be started while awaiting the biopsy results based on level of clinical suspicion and health of the patient. If the patient is clinically well, the practitioner may wait for the biopsy results prior to commencing any therapy; if the patient is sick, chemotherapy and/or ART may be initiated while the biopsy results are pending.

10.2.9D Baseline Investigations with Pediatric KS

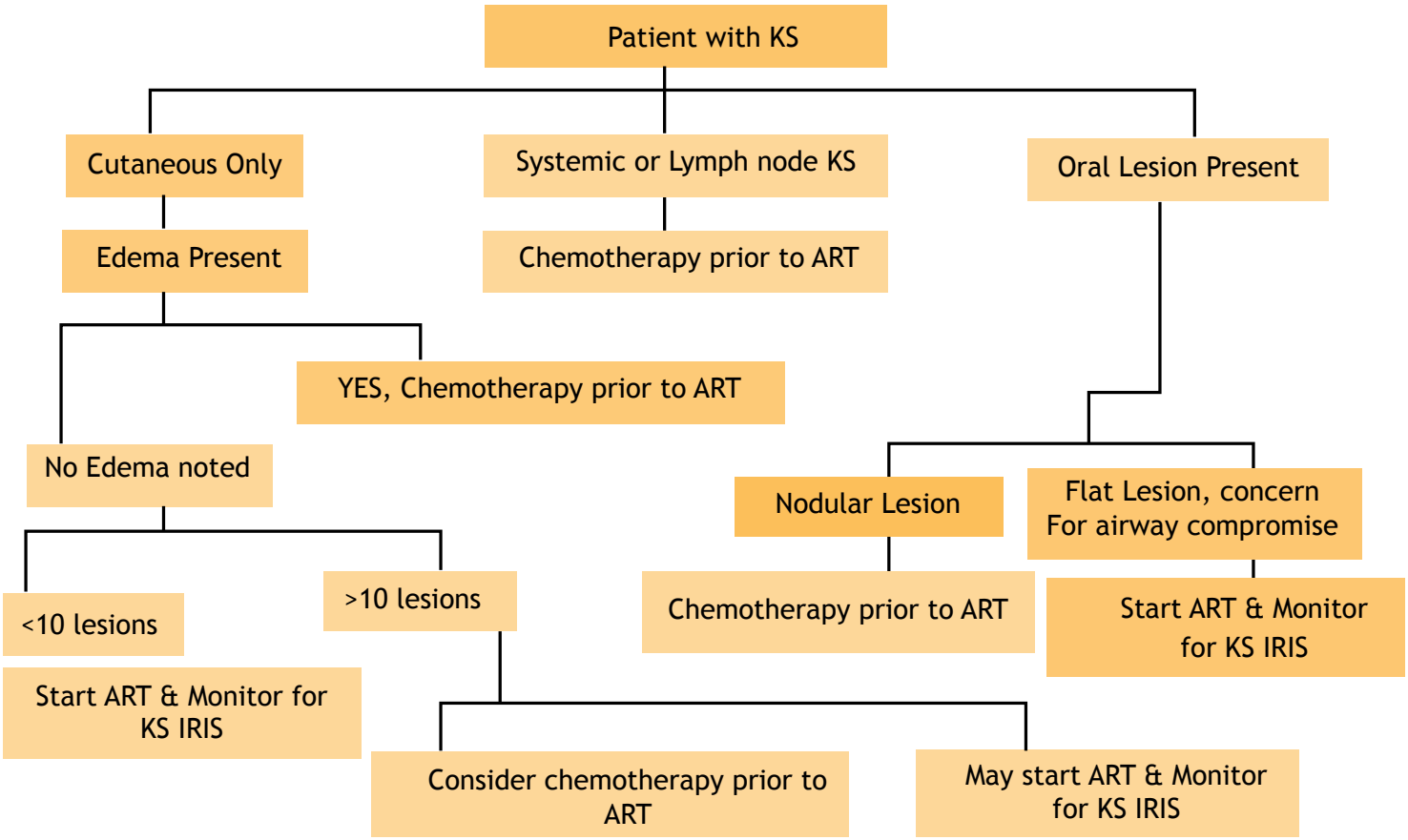
For those children with ≤10 skin lesions likely to improve with ART alone, it is not necessary to do further laboratory investigation as chemotherapy will not likely be utilized. Further studies to prove that the patient does not have disseminated or systemic disease should be strongly considered based on clinical presentation. These studies should include a CXR and abdominal ultrasound if there are any concerning symptoms.

10.2.9E Treatment of Pediatric KS

- Treat all patients with ≤10 skin lesions with ART alone.
- Closely monitor those that do not show improvement in the skin lesions or have progressive KS for subsequent chemotherapy.
- Treat adolescents as per adult guidelines and initiate on ART prior to or concomitantly with chemotherapy.

- Younger children, especially those with a high absolute CD4/CD4%, and extensive disease (e.g., 10 skin lesions or disseminated/systemic disease), should receive chemotherapy prior to ART due to the risk of the development of KS-IRIS. Such cases should be discussed with a pediatric specialist whenever possible (see Decision to Treat flowchart).

Figure:10.2 Pediatric KS Decision to Treat



10.2.9F Treatment Options for Paediatric KS

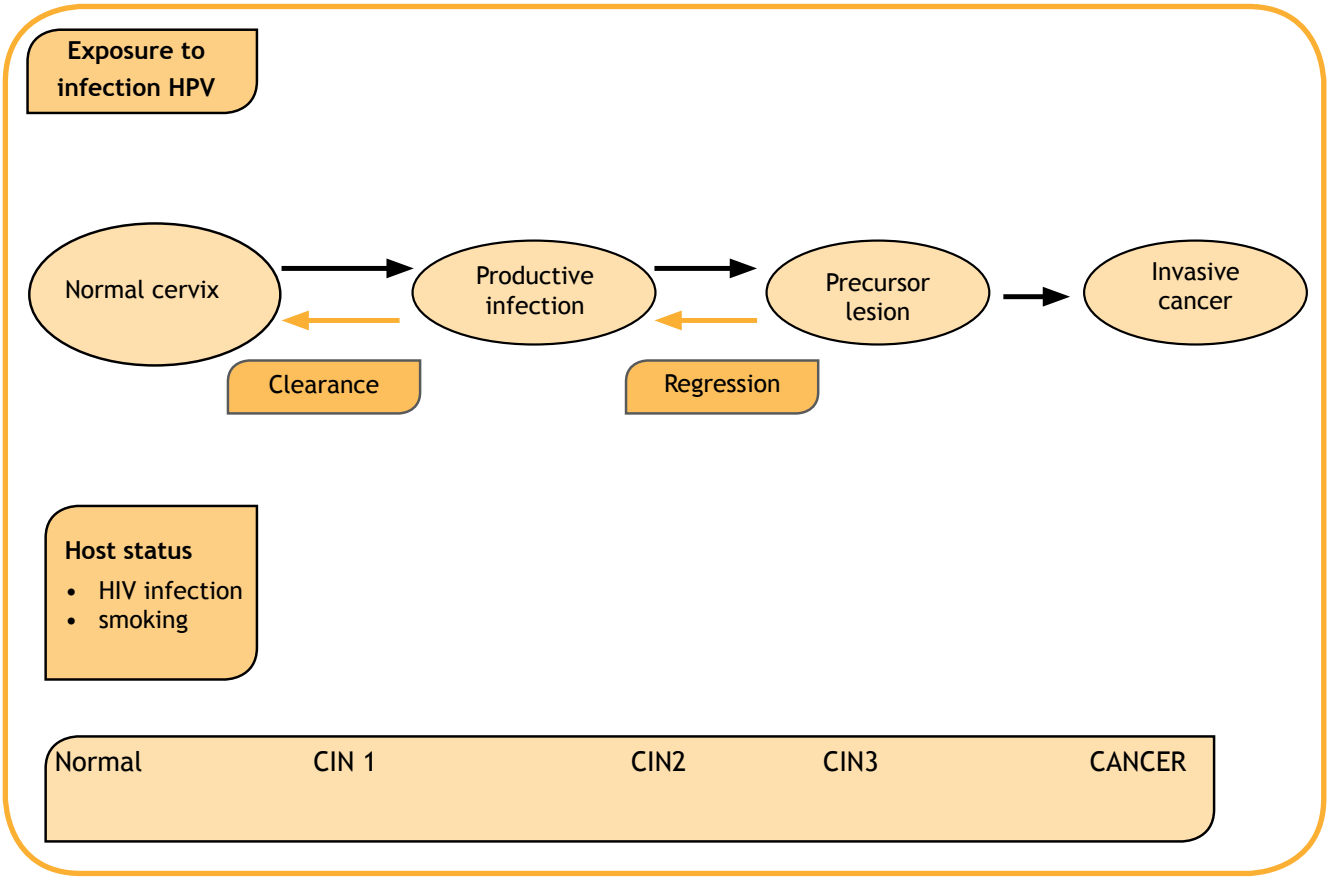
Multiple potentially viable treatment options are available to treat paediatric KS. Both ABV (doxorubicin [adriamycin], bleomycin, and vincristine) and BV (bleomycin and vincristine) are options. In general, ABV is the preferred regimen and should be given as 4-6 cycles, with each cycle lasting 21 days. However, due to the myelosuppression caused by doxorubicin, the BV regimen should be initially substituted for ABV in the patient with KS bone marrow involvement, represented by cytopenias including at least two lineages (i.e., anemia, thrombocytopaenia, and/or neutropenia). Once the bone marrow involvement has improved with BV, ABV can be started. Patients should not receive more than 300 mg/m2 of doxorubicin or 250 mg/m2 of bleomycin. Note that vincristine can cause peripheral neuropathy which may be exacerbated by the concomitant usage of d4T as part of the ART regimen and/or isoniazid as part of anti-TB treatment.

10.3 Cervical Cancer and HIV-Infected Women

Cervical cancer is the leading cause of cancer among all women in Botswana, accounting for 24% of female malignancies. Worldwide, cervical cancer is the second most common malignancy in women after breast cancer and remains the leading cause of cancer related death in developing countries. HIV infection has been widely linked with cancer of the cervix and in 1993, the WHO classified cervical cancer as a stage 4, AIDS defining disease.

Cancer of the cervix starts in the cells on the surface of the cervix and is linked to genital infection with human papillomavirus (HPV) which is the most common sexually transmitted virus. Although most HPV infections clear spontaneously, some may persist and progress through precancerous stages, into invasive disease.

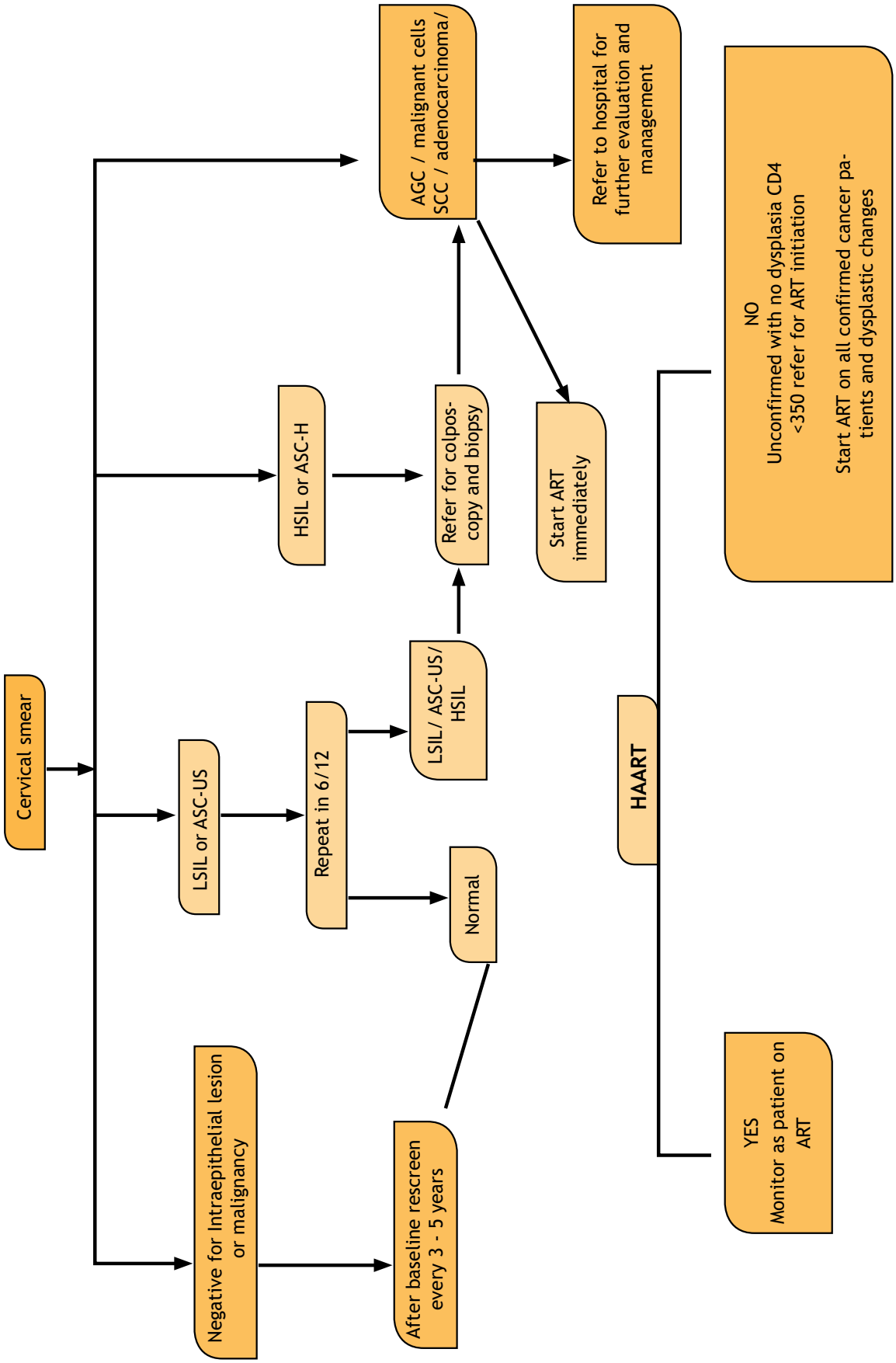
Figure 10.3: Progression of Cervical Cancer



Cervical cancer poses a serious threat to the long-term wellbeing of HIV-infected women, who are commonly diagnosed 10 years earlier than the general population. Reasons for this include:

- Higher prevalence of persistent HPV infection.
- High prevalence of multiple high risk HPV types.
- Higher risk of pre-cancerous lesions resulting from a higher degree of immunosupression.
- More frequent presentation of advance disease with poor prognosis.

Figure 10.4: Pap Smear Flow Chart



10.3.1 Screening Recommendations for Cervical Cancer

Currently the Botswana cervical cancer screening recommendations for HIV-infected women are being revised. In the interim, all sexually active HIV-infected women should complete a screening baseline Pap smear. If the baseline Pap smear is normal, then follow-up screening should take place every 3-5 years. For those HIV-infected women who display abnormal cervical changes, follow up should be based upon the recommendation of their treating physician or gynaecologist.

- All women with a positive screening test (atypical changes) should be referred to gynecology for further management at the discretion of the treating physician.
- Visual Inspection with Acetic acid (VIA) is to be considered only for pre-menopausal women.

Women with recorded abnormal Pap smears must be closely monitored and tracked in order to ensure that adequate follow-up was completed.

Table 10.2: Histological Classification Chart

Cytological classification used for screening		Histological classification used for diagnosis	
Pap	**Bethesda system**	**CIN**	**WHO descriptive classification**
Class I	Normal	Normal	Normal
Class II	ASC-US, ASC-H	Atypia	Atypia
Class III	LSIL	CIN 1	Koilocytosis
Class III	HSIL	CIN2	Moderate dysplasia
Class III	HSIL	CIN3	Severe dysplasia
Class IV	HSIL	CIN 3	Carcinoma in situ
Class V	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

CIN Cervical Intraepithelial neoplasia; LSIL Low grade squamous intraepithelial lesion; HSIL High grade intraepithelial lesion; ASC-US atypical squamous cell of undetermined significance; ASC-H atypical squamous cell cannot exclude high grade squamous epithelial lesion

10.3.2: Clinical Presentation and Diagnosis of Cervical Cancer

Table 10.3: Symptoms and Signs of Cervical Cancer

Early	Late	Very late
* Irregular bleeding * Post coital bleeding * Post menopausal bleeding * Persistent vaginal discharge not responsive to standard STI syndromic management	* Urinary frequency * Backache * Lower abdominal pains	* Severe back pain * Weight loss * Decreased urine output * Leakage of urine or faeces through the vagina * Swelling of lower limbs * Breathlessness

10.3.3 Diagnostic Investigations for Cervical Cancer

- Vaginal speculum and rectal examination
- Women with lesions that are suspicious for cervical cancer require an urgent referral for gynecological evaluation.

10.3.3.1 Laboratory & Radiographic Investigations for Cervical Cancer

All patients with signs or symptoms which are suspicious for cervical cancer should be tested for HIV with CD4 count.

Other investigations include:

- ***Laboratory:*** FBC, urea, creatinine, electrolytes and LFTs
- ***Imaging:*** Chest X-ray, abdominal and pelvic ultrasound

10.3.3.2 Staging of Cervical Cancer

Disease staging is determined using the FIGO classification.

10.3.4 Treatment of Cervical Cancer

The gold standard treatment for cervical cancer remains surgery and/or radiotherapy. Chemotherapy with radiotherapy is the standard of care for locally advanced cervical cancer. Relapse patients may receive chemotherapy only. Curative surgery in cervical cancer aims to remove the primary tumour with all extensions in one single operation. The choice of operation procedure is determined by the disease stage.

10.4 AIDS Related Lymphoma / Non-Hodgkin's Lymphoma

Cancer involving the lymph nodes is the 3rd most common cancer affecting HIV-infected patients in Botswana. The etiology of ARL is largely unknown. However, several factors play an important role in development of the disease. These include infections with viruses (notably, Epstein-Barr virus [EBV] and human herpesvirus 8 [HHV-8]) continuous B-cell stimulation, and immunodeficiency.

Different clinicopathologic categories of AIDS-related lymphomas arise from distinct B-cell subtypes and multiple factors interact in varying proportions to give rise to different varieties. ARL can be divided into 3 types on the basis of areas of involvement:

- Systemic NHL
- Primary central nervous system lymphoma (PCNSL)
- Primary effusion lymphomas ("body cavity lymphoma")

The risk for developing AIDS-related lymphoma is highest among those with advanced HIV disease. However, it can occur at any CD4 count.

10.4.1 Clinical Presentation of ARL:

The presenting symptoms and signs of AIDS-related lymphomas depend on the site of involvement and the stage of the disease. Frequently, symptoms of lymphoma are initially mistaken for tuberculosis.

Systemic NHL

- Peripheral adenopathy is the common presenting symptom.
- Symptoms may be organ specific or nonspecific. Lymphoma may involve the lungs, bone marrow, gastrointestinal tract and liver.
- Non-specific symptoms include: bloating, early satiety, or abdominal pain/fullness due to enlargement of the spleen.
- The majority of patients have constitutional ("B") symptoms at the time of presentation.

"B" Symptoms include:

- Unexplained fever (>38 degrees Celsius)
- Night sweats
- > 10% involuntary weight loss

Primary Central Nervous System Lymphoma (PCNSL)

- Common signs and symptoms include: headache, blurred vision, muscular weakness, sensory deficits, personality changes, depression, apathy, confusion, memory impairment, and cranial neuropathies.
- These findings may also occur with leptomeningeal involvement

10.4.2 Diagnostic Investigations for ARL:

The diagnosis of ARL should be based on a tissue sample rather than a cytologic sample.

- ***Laboratory:*** FBC, urea, uric acid, electrolytes, creatinine, and LFTs.
  - ***LDH:*** not a diagnostic criterion, but useful for disease burden and prognosis
- ***Imaging:*** CXR, abdominal CT scan for staging. (When CT is not available use ultrasound at the sites of adenopathy).
- Other important tests: Bone marrow aspiration (to rule out marrow involvement) and lumbar puncture (to rule out CNS involvement)

10.4.3 Staging and Prognosis of NHL

Table 10.4: The Ann Arbor Staging System

Stage	Definition
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III_1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III_2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III_1
IV	Involvement of extranodal site(s) beyond that designated as "E" More than one extranodal deposit at any location Any involvement of liver, bone marrow or cerebrospinal fluid
A	No symptoms
B	Unexplained weight loss of >10% body weight during the 6 months before staging investigation Unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month Recurrent drenching night sweats during the previous month
E	Localized, solitary involvement of extra lymphatic tissue, excluding liver and bone marrow

10.4.4. Treatment for Non-Hodgkin Lymphoma (NHL)

ART

Concurrent chemotherapy plus ART is generally safe. ***All patients with HIV should commence ART before commencing chemotherapy.*** *(See Annex 21: Chemotherapy and ART Interactions)*

Chemotherapy

The mainstay of treatment for patients with systemic AIDS-related NHL is chemotherapy. Due to the high likelihood of tumour dissemination, AIDS patients who develop NHL must be assumed to have widespread disease at presentation and should be treated with systemic chemotherapy, even if tumour dissemination is not confirmed on routine staging evaluation.

Before initiating chemotherapy discuss drug selection with a highly qualified physician or oncologist. Some of the commonly used regimens designed for AIDS-related NHL are listed on the next page in Table 10.5.

Surgery

Because lymphoma is a systemic illness, surgical resection of sites of disease is used only in selected cases and is most commonly used to establish a diagnosis. Surgery may be particularly useful in GI lymphomas where disease is localized or where there is risk of perforation. Orchiectomy may be the initial treatment for patients with testicular lymphoma.

Growth factor and other support

The major dose-limiting toxic effect of multiagent chemotherapeutic regimens is myelosuppression. Co-administration of myeloid hematopoietic growth factors enhances patient tolerance of these regimens.

- Prophylaxis with trimethoprim/sulfamethoxazole and fluconazole can also reduce the risk of infection during intensive chemotherapy and rituximab.

Salvage chemotherapy

Patients in whom initial treatment fails or relapse occurs after initial remission rarely achieve a prolonged second remission. Refer these cases for palliation.

Radiation therapy

The role of radiotherapy in systemic lymphoma is limited to consolidation of the effects of chemotherapy. Treatment principles are similar to those used for aggressive NHL in the non-HIV setting and typically include the use of involved or extended fields only.

Table 10.5: Chemotherapy for AIDS Related NHL

Regimen	Drugs & Dosage	Cycle Length	CR rate (%)	Median Survival
R-EPOCH	Rituximab, 375 mg/m^2 IV day 1	Q3-4wk	79	53 mo+
	Etoposide, 200 mg/m^2/96 h IV			
	Prednisone, 60 mg PO on days 1-6			
	Vincristine, 1.6 mg/m^2/96 h IV			
	Cyclophosphamide, 187 mg/m^2 IV on day 5 (if CD4 count <100 cells/ml) or 375 mg/m2 IV on day 5 (if CD4 count $\geq$100 cells.ml)			
	Doxorubicin, 40 mg/m^2/96 h IV			
R-CHOP	Rituximab, 375 mg/m^2 IV day 1	Q21d	63	9 mo
	Cyclophosphamide, 750 mg/m^2 IV on day 1			
	Doxorubicin, 50 mg/m^2 IV on day 1			
	Vincristine, 1.4 mg/m^2 IV on day 1 (maximum, 2 mg)			
	Prednisone, 60 mg PO on days 1-5			
CDE	Cyclophosphamide, 800 mg/m^2/96 h IV	Q28d	46	8.2 mo
	Doxorubicin, 50 mg/m^2/96 h IV			
	Etoposide, 240 mg/m^2/96 h IV			

CNS prophylaxis with either intrathecal cytarabine (Ara-C; 50 mg) or intrathecal methotrexate (10–12 mg) every week for four treatments has been shown to be effective in reducing the incidence of CNS relapse.

Lymphomatous meningitis

For patients with lymphomatous meningitis and/or radiographically detectable cerebral deposits, "step-brain" irradiation (including the covering meninges) is administered along with intrathecal chemotherapy to control microscopic spinal disease. Focal radiation therapy may be required for known tumour deposits along the spine.

Patients who have lymphomatous meningitis have a poor prognosis and are best treated with palliative regimens and should be referred to specialist.

Primary CNS Lymphoma

An effective therapy for patients with AIDS-related CNS lymphoma has not yet been found, but palliative radiation should be considered.

Radiation therapy: The conventional standard treatment is step-brain irradiation, which can result in response rates of 50% and improved survival.

10.5 Other Cancers

ART is now recommended for all HIV-infected patients who are diagnosed with ANY cancer. Initiate ART as soon as possible regardless of the CD4 levels and before initiation of chemotherapy in all adults.

There is very limited data available on the effects of HIV infection on the incidence of other malignancies including melanoma, and cancers of the head and neck, urologic system, colon and breast. Therefore, these patients should be co-managed by oncologists and HIV specialists together according to standard guidelines for HIV-negative patients.

10.6 Complications of Cancer Treatments and HIV

10.6.1 Management of Bone Marrow Suppression:

Chemotherapy for HIV-related malignancies is associated with myelosuppression increasing the risk of infection. Bone marrow suppression is the major dose-limiting toxicity of cancer chemotherapy. However, wide field radiation therapy can also suppress the bone marrow, leading to:

- Pancytopenia
- Neutropenia: Usually occurring first, 7-10 days post chemotherapy. The risk of sepsis is related to the severity and duration of neutropenia.
- Thrombocytopenia: Usually develops by day 10-14 post chemotherapy
- Anemia: Usually develops by day 14-21 post chemotherapy

10.6.2 Neutropenic Fever:

Neutropenic fever is common and mainly due to infection; other causes include blood product transfusion, pyrogenic medications, central venous catheters and the underlying malignancy itself. Neutropenic fever is a medical emergency and should be treated promptly to avoid mortality which

can result quickly without immediate interventions. Therefore, antibiotics are given empirically after blood culture, sputum culture, urine MCS, chest x-ray and swabs from all central lines are taken. If necessary, consult a specialist physician on choosing broad spectrum antibiotics in these cases.

- Complete a detailed physical exam (including external perirectal space and venous lines), FBC, LFTs, chest x-ray, urinalysis and urine MCS, and blood cultures (if available).
- Initiate broad-spectrum antibiotics with a least one agent active against pseudomonas.
- Remove urinary catheters and consider removal of venous catheters.
- Failure to resolve fever within 5 days may indicate opportunistic infections.
- Initiate all HIV-infected cancer patients on appropriate prophylaxis.
- ***Once stable, refer any patient who develops fever and/or diarrhea to the physician who prescribed the chemotherapy.***

10.6.3 Thrombocytopenia

Thrombocytopenia is also common for patients receiving chemotherapy. Spontaneous bleeding is unlikely until platelet levels fall to < 20 x 10^9/L. However, the risk of traumatic bleeding is high when levels fall to < 40 x 10^9/L. Transfuse if levels fall to 10 x 10^9/L or in active bleeding if ≤ 20 x 10^9/L.

10.6.4 Anemia

Development of anemia is a very common side effect of chemotherapy. Its causes include: bleeding, chronic disease, malnutrition, chemotherapy and radiation.

- Both chemosensitivity and radiosensitivity are affected by anemia.
- Transfusion of one unit of blood will raise hemoglobin by approximately 1g/dl in a 60 kg patient.
- Use of erythropoietin is controversial and not recommended.
- Exercise caution with transfusion and thrombocytopenia.

10.7 B-Symptoms Associated with Cancer: Distinguishing from Active TB

The presence of "B" Symptoms with cancer is a prognostic indicator and in HIV patients can mimic symptoms of tuberculosis. In smear negative TB suspects who are refractory to ATT, consider the possibility of AIDS-related malignancy.

"B" Symptoms include:

- Unexplained fever (>38 degree Celsius)
- Night sweats
- >10% involuntary weight loss
- Diarrhea persisting more than 2 weeks

CHAPTER 11: MANAGEMENT OF OPPORTUNISTIC INFECTIONS AND OTHER AIDS-RELATED CONDITIONS

11.1 Cryptococcal Meningitis:

Cryptococcal meningitis remains a leading cause of HIV-related mortality in Botswana. Improving clinical care for patients with Cryptococcus is therefore critical to ensure successful outcomes. Providing lumbar puncture for diagnosis, managing increased intracranial pressures and prescribing appropriate antifungal therapy remain the cornerstones of treatment success.

Cryptococcal meningitis is caused by the fungus Cryptococcus neoformans in the majority of cases, although in some studies in Botswana, up to 30% of isolates have been found to be caused by Cryptococcus gattii. Although their management is the same, Cryptococcus gattii may be more likely to form CNS cryptococcomas and is associated with poorer outcomes.

11.1.1 Risk Factors and Clinical Manifestations of Cryptococcal Disease

Risk Factors:

- Immunosuppression: Cryptococcus rarely occurs in normal hosts
- CD4 <200 cells/µL: Most patients present with CD4 count <100 cells/µL

Clinical Manifestations:

Maintain a high degree of suspicion in patients who report any of the following: chronic headache, often initially of low-grade severity, deterioration of mental status, visual disturbances and/or unexplained fever, especially in patients with low CD4 counts (≤100 cells/µL or CD4% ≤15%). Disease onset is often subtle, with classic meningeal signs absent in up to 50% of cases. Signs and symptoms can include:

- ***CNS:*** Headache, fever, photophobia, altered mental status, focal neurologic signs such as cranial nerve palsies, seizures. Visual loss may occur from increased intracranial pressure or from optic nerve infection (endopthalmitis). Symptoms usually develop slowly over several weeks, but can occur over days. ***Neck stiffness is an unreliable sign.***
- Neurologic deficits such as hemiparesis are uncommon in cryptococcal meningitis patients and should prompt suspicion for other causes, (e.g., stroke (CVA), TB meningitis, CNS malignancies, etc.)
    - * Rarely, vasculitis can complicate cryptococcal meningitis and TB meningitis. ***Patients who present with the clinical picture of meningitis and possible CVA should be immediately referred to the hospital for further investigations.***
    - ***Pulmonary disease:*** Isolated nodules, cavitary disease, pleural effusions and hilar lymphadenopathy may be found on chest x-ray. The disease process may also present as chronic pneumonia mimicking TB or PCP.
    - ***Skin disease:*** Disseminated disease can resemble molluscum with largely umbilicated lesions. ***All individuals with cutaneous cryptococcosis should be evaluated for CNS involvement with a lumbar puncture.***

11.1.2 Diagnosis of Cryptococcocal Meningitis

Lumbar Puncture:

> ***A lumbar puncture should be considered an emergent, "opt-out", life-saving procedure that does not require explicit consent. Reassure reluctant patients and their families that the potential benefits of completing an LP far outweigh any risk of complications.***

- Complete a comprehensive physical exam (including a full neurological exam) and lumbar puncture in all HIV-infected patients with CD4 < 200 cells/μL suspected to have cryptococcal meningitis.
- In the majority of individuals, the risk of herniation while performing a lumbar puncture is extremely low even if a CNS mass lesion is present.

CT of the Head:

> If a CT of the head can be performed and reviewed within a few hours, it is reasonable to defer a lumbar puncture pending the CT head results for a patient who presents with hemiparesis and other focal neurologic signs. However, in all other situations, CT is not a requirement for a lumbar puncture.

CSF Investigations:

India ink smear and culture are the most sensitive CSF investigation available in the government sector. Up to 20% of cryptococcal meningitis cases will have normal CSF values for WBC, glucose and protein. In cases displaying lymphocytic meningitis and a negative India ink and culture, the most likely diagnosis is TB meningitis. Complete the following:

- ***India ink smear and cryptococcal culture.***
- ***AFB smear and culture.***
- Cell count, differential, MCS, and where available, protein and glucose.

Additional Investigations Prior to Initiation of Amphotericin:

- Send and monitor urea, creatinine, LFTs, glucose, chest X-ray and urine pregnancy test in women of childbearing age.
- Consider serum cryptococcal antigen in select cases when cryptococcal meningitis is strongly suspected but LP cannot be obtained. It is reasonable to send the serum antigen and initiate therapy pending results. However, ***every attempt should be made to perform a lumbar puncture to diagnose and manage increased intracranial pressure.***

11.1.3 Management of Increased Intracranial Pressure for Adults

Draining up to 30 mL has NOT been associated with adverse outcomes. For every mL of fluid drained, the pressure will decrease by approximately 1.25 cm H2O, i.e., for every 4 mL of CSF drained, the pressure will decrease by approximately 5 cm H2O.

- Normalize intracranial pressure (opening pressure to < 20 cm H2O).
- Measure both the opening and closing pressure. Drain enough CSF to achieve a closing pressure of 15-20 cm H2O.

- If no manometer is available, measure the pressure by marking intravenous fluid tubing every cm and connecting this to LP cannula to estimate pressure.
- Avoid corticosteroids, acetazolamide and mannitol for managing increased intracranial pressure as their use has been associated with increased mortality.
- Perform daily lumbar punctures until the opening pressure is 20 cm H2O or less and then decrease LPs to once every 48 hours. If the opening pressure is normal for two consecutive readings, perform subsequent lumbar punctures for fever, headache or other presenting signs of meningitis. ***Assess for worsening symptoms daily.***

11.1.4 Supportive Care

Adults

- Ensure a minimum of 3 liters of fluids per day, IV or oral
- With every liter of fluid add 40 mEq of potassium.
- Monitor potassium and creatinine at least twice per week. If you are unable to measure twice per week, measure as frequently as possible.
- If creatinine clearance falls between 50-75 µL/min, increase isotonic fluids (0.9% sodium chloride or ringers lactate) to 1000 µL with each dose of amphotericin.

Review other potential nephrotoxins (e.g., NSAIDS [ibuprofen, indomethacin]), B-lactam antibiotics, cotrimoxazole, TB drugs, aminoglycosides), and consider holding these medications. Review other causes for renal failure such as hypotension and dehydration, and correct any contributing factors. Make every effort to continue amphotericin given the compromised efficacy of fluconazole monotherapy.

- ***Amphotericin can be used with no dose adjustment in existing, stable renal failure patients. However, due to the nephrotoxic potential of the drug, reducing the dose or holding the drug in the setting of a rising serum creatinine may be warranted.***
- If creatinine clearance falls to less than 50 µL/min while on amphotericin, switch to fluconazole monotherapy with a dose of 600 mg daily. If creatinine clearance is ≤ 10 give 300 mg of Fluconazole. If the patient is receiving hemodialysis use Amphotericin and Fluconazole 800 mg after each dialysis. Repeat creatinine in 48 hours and if creatinine clearance has improved to >50 µL/min, restart amphotericin and increase fluconazole to 800 mg daily.

Table 11.1: Renal Adjustment of Fluconazole

Creatinine Clearance	Adjusted Dose
CrCl <50 ml/min	600 mg
CrCl < 10 ml/min	300 mg
On Hemodialysis	Full dose after each dialysis

- If potassium falls to < 4.0 mmol/L, begin potassium replacement with oral slow-K 600 mg potassium up to TDS or IV. Add 2 grams IV of magnesium per day.

Potassium cannot be given at a rate > 20 mmol/hr IV in order to avoid a risk of cardiac arrest. Never push potassium IV.

Fluid Resuscitation for Pediatric Patients:

Remember that the maintenance fluid volume will need to be adjusted for all sick children. In non-dehydrated children, consider using 2/3 maintenance in sick children, especially those with meningitis. (For fluid options in the dehydrated child see Chapter 8, Section: 8F)

11.1.5a Treatment: Antifungal therapy for Adults

First Line Therapy:

Induction:
- Amphotericin at 1 mg/kg + Fluconazole 800 mg daily for 2 weeks **followed by**:

Consolidation:
- Fluconazole 800 mg daily for 8 weeks **followed by:**

Maintenance:
- ***Fluconazole 200 mg daily until the CD4 count is >200 cells/µL for 6 months***

Observe the following precautions:

- In patients with renal failure (see section on "Supportive Care" above)
- Ensure that 500 cc of normal saline or Ringer's lactate is administered with each dose of amphotericin.

- Nevirapine levels are increased by nearly 100% with fluconazole administration. Consider NVP treatment switch with high dose fluconazole co-administration, and discuss such cases with an HIV specialist.

If Amphotericin is not available use:

- Fluconazole 1200 mg daily for 2 weeks (15 total doses) f***ollowed by***
- Fluconazole 800mg daily for 2 months (60 total doses) ***followed by***
- Fluconazole 200 mg daily until the CD4 count is >200 cells/µL for 6 months

Fluconazole should be avoided in the first trimester of pregnancy or during breastfeeding. Discuss cases of women who develop cryptococcal meningitis during their first trimester of pregnancy with a HIV specialist.

Treatment Failure:

- If patients do not show improvement or stabilization within 3 days, contact an HIV Specialist.

11.1.5b Antifungal Therapy for Children:

Cryptococcal meningitis is uncommon among children. Given the lack of data in children, current recommendations for the treatment of cryptococcal meningitis are extrapolated from adult studies. Combination anti-fungal treatment appears superior to single agent therapy for the management of acute cryptococcal meningitis. If available, Amphotericin B combined with 5FC is preferable, although the combination of amphotericin B and fluconazole appears to be an adequate alternative. Discuss all cases with a Paediatric HIV Specialist.

Induction: (2 weeks)

Amphotericin B: 1.0 mg /kg/day for 2 weeks
plus
Fluconazole: 6 mg /kg/day for 2 weeks **followed by***:*

Consolidation: (8 weeks)

- Fluconazole: 6 mg /kg/day for 8- 10 weeks **followed by***:*

Maintenance:

- Fluconazole: 3 mg/kg/day until CD4>200/15% (for greater than 6 months)

If no amphotericin available: Discuss with a Pediatric HIV specialist

Table 11.2: Antifungal Treatment for Cryptococcal Meningitis

	Adults	Pediatrics
Induction 2 weeks (15 doses)	*Amphotericin B: 1 mg/kg + Fluconazole 800 mg daily	Amphotericin B: 1 mg/kg + Fluconazole: 6 mg/kg daily
Consolidation 8 weeks (60 doses)	Fluconazole 800 mg daily	Fluconazole: 6 mg/kg daily
Maintenance Until CD4 count remains >200/15% for 6 months	Fluconazole 200 mg daily	Fluconazole 3 mg/kg/daily
*** If amphotericin is not available for adults, use:** Fluconazole 1200 mg daily for 2 weeks, followed by Fluconazole 800 mg daily for 60 days Until CD4 count remains > 200/15% for 6 months		

* If amphotericin is not available for adults, use:

Fluconazole 1200 mg daily for 2 weeks, followed by Fluconazole 800 mg daily for 60 days

Until CD4 count remains >200/15% for 6 months

Adjunctive Therapy for Adults and Children:

Cryptococcal meningitis is a WHO stage IV disease and therefore all patients infected with Cryptococcus must receive cotrimoxazole prophylaxis.

11.1.6 When to start ART in Treatment Naïve Patients with Cryptococcal meningitis:

The optimal timing for ART initiation remains unclear. The risk of dying from a delay in initiating antiretroviral therapy must be balanced against the risk of dying from immune reconstitution syndrome. Mortality of crypto-associated IRIS is approximately 20%.

- For patients who receive amphotericin + fluconazole: Initiate ART after completion of the induction phase (2 weeks) if CSF pressures have normalized. If pressures are still elevated, delay ART initiation until CSF pressures are < 20 cm H2O for 48 hours.
- Patients who receive fluconazole alone: If CSF pressures have normalized to at least < 20 cm H2O for 48 hours, initiate ART after completion of 4 weeks of fluconazole monotherapy.
- Discuss timing of ART initiation with an HIV Specialist for cases in which CSF pressures remain > 20 cm H2O after 4 weeks.

11.1. 7 Treatment Complications

- ***Renal failure:*** Potassium and magnesium wasting secondary to amphotericin (see section on "Supportive Care" above)
- ***Drug-induced Hepatitis:*** Discuss cases related to high dose fluconazole therapy with an HIV Specialist.
- ***Deteriorating neurologic status:*** Repeat lumbar puncture as a matter of urgency, as these symptoms are often a result of increased intracranial pressures. If new focal neurologic signs, including seizures, develop consider referral for CT scan. Also rule out the possibility of other opportunistic infections such as TB meningitis.
- ***Relapse after completion of any portion of therapy:*** Defined as recurrence of symptoms and positive culture. Potential causes:
  - Non-adherence to consolidation or maintenance therapy.
  - India ink and cryptococcal antigen may remain positive if dead organisms are still present in CSF.
  - May be due to lack of resolution of infection or paradoxical IRIS if relapse occurs after ART initiation.
  - Resistance to azoles has been described, but this is often difficult to evaluate.

In cases of Cryptococcal Immune Reconstitution Inflammatory Syndrome (IRIS)

- Begin steroids and discuss with a HIV Specialist.

In cases of non-adherence or defaulting: Reinitiate therapy as a primary infection

11.2 HIV/AIDS-Related Neurological Disease (HAND)

11.2.1 Peripheral Neuropathy:

Peripheral neuropathy can result from either drug toxicity (INH, d4T, ddI, AZT) or HIV itself. Although HIV associated neuropathy will often improve with ART, many cases of peripheral neuropathy remain refractory to treatment.

- When available, gabapentin can be especially effective. Obtain HIV Specialist special order approval when necessary.
- AVOID Carbamazepine due to drug-drug interactions (especially with EFV use).
- To prevent INH drug-induced peripheral neuropathy prescribe pyridoxine 25 mg OD. Patients with suspected INH-induced peripheral neuropathy may require higher doses of pyridoxine, often up to 100 mg OD.

11.2.2 AIDS Dementia Complex/HIV Encephalopathy:.

Symptoms and signs of AIDS Dementia Complex are characterized by progressive impairment in cognitive function that is often accompanied by behavioral changes and motor abnormalities. Symptoms including history given by close relatives or companions include:

- ***Cognition:*** Forgetfulness, difficulties in concentrating, mental slowing in comprehension or processing
- ***Behavioral:*** Loss of drive and initiative, withdrawal from social activities, failure to manage the financial and administrative areas of one's life, depressive mood, emotional blunting
- ***Motor:*** Slowing and impairment of fine movements (e.g. typing, buttoning up), gait disturbances
- ***Autonomous:*** Impaired micturition (urgency), loss of sexual libido, erectile dysfunction

AIDS dementia is a subcortical dementia that is a diagnosis of exclusion after ruling out other possible causes of CNS pathology. Impairment of alertness, neck stiffness, and focal or lateralizing neurological signs (e.g. hemiparesis) are not typical for HIV encephalopathy.

Diagnosis of AIDS Dementia Complex:

Symptoms of AIDS dementia complex can be unmasked or exacerbated by other encephalopathies due to intercurrent infections (e.g., meningitis, severe pneumonia), metabolic disorders (e.g., electrolyte and mineral imbalance, hypoxemia due to pneumonia, sepsis) and sedative drugs (e.g., anti-anxiety, narcotic analgesic, and sleeping medications).

- In children, HIV encephalopathy may initially present as failure to achieve age-appropriate developmental milestones. Always consider HIV encephalopathy in all children with loss of developmental milestones.

MRI brain:

- Patchy, diffuse, T2 hyper-intense and relatively symmetrical lesions in the white matter
- Atrophy with enlargement of the ventricles

Other investigations (e.g., CSF studies) may be needed to rule out other possible causes of CNS pathology.

Treatment of AIDS Dementia Complex:

- ART with complete viral load suppression
- Supportive care

11.3 Spinal Cord Disease (Myelopathy):

Always rule out cord compression in cases presenting as spinal cord dysfunction. Acute compressive myelopathy requires urgent surgical/radio-oncology consult for urgent decompression.

Clinical Diagnosis:

- Spastic para/quadriparesis or plegia (If flaccid with clear sensory level, it is a myelopathy.)
- Sphincteric dysfunction (urinary retention and constipation at onset)
- Loss of sensation presenting as sensory level.

Differential Diagnosis:

- Tuberculosis of the spine (i.e., Pott's disease of the spine).
- Subacute combined degeneration of the spinal cord
- Compressive myelopathy (spinal cord compression) by tumors (primary or secondary)

If CD4 is < 200 cells/µL:

- HIV vacuolar myelopathy (spastic paresis/plegia, sphincteric dysfunction; NO sensory level)
- Opportunistic cytomegalovirus (CMV), varicella zoster virus (VZV) and herpes simplex virus (HSV) myelitis

If CD4 is > 200 cells/µL:

- Idiopathic transverse myelitis
- Vasculitic lesions from connective tissue disorders.
- Cervical spondylotic myelopathy.

Investigations:

MRI of the spine is the gold standard for defining the exact spinal lesion. Tailor additional investigations based upon the other possible etiological factors as enumerated above.

Treatment:

- ART with complete viral load suppression
- Treat other etiologies as appropriate.
- Acute spinal cord compression must be promptly ruled out whenever acute transverse myelopathy is diagnosed. If any cord-compressing lesion is found, urgent surgical decompression must be performed. Full evaluation of the cause of myelopathy is indicated in any of the following situations:

  * Acute onset of paraparesis
  * Presence of sensory/motor level
  * Absence of severe immune suppression
  * Lack of symptom response to ART

11.4 Herpes Simplex Virus (HSV):

Symptomatic HSV infection (>30 days duration or in any visceral site) is a WHO stage 4 condition which qualifies patients for ART regardless of the CD4 count. As both symptomatic HSV disease and asymptomatic shedding increases the risk of HIV acquisition and transmission, prompt diagnosis and treatment are essential.

Diagnosis:

Herpes viruses can also cause meningoencephalitis with symptoms of fever, altered mental status and seizures. Classically, patients will present with a CSF that shows lymphocytic pleiocytosis, increased numbers of RBCs, slightly high protein, and normal glucose.

Treatment:

- ***Oral or genital HSV:*** Acyclovir 800 mg PO TDS for 10 days (for children 40-80 mg/kg/day divided into 3-4 doses each day for 14 days) for an initial episode.
- ***Meningoencephalitis:*** Acyclovir intravenously 10mg/kg every 8 hourly for 21 days.

11.5 Varicella-Zoster Virus (VZV):

Recurrent mono-dermatomal VZV, ophthalmic VZV, or multi-dermatomal VZV (one episode) are Botswana-specific "WHO clinical stage 3" conditions that qualify patients for ART regardless of CD4 count.

VZV Treatment:

- ***Multi-dermatomal VZV (if diagnosed within 72hrs of onset):*** Acyclovir 800 mg PO five times per day for 10 days. (For children: 40-80 mg/kg/day divided into 3-4 doses each day for 14 days).
- ***Disseminated VZV:*** IV acyclovir 10 mg/kg every 8 hours for 7-10 days. (For children: under 1 year of age, 10 mg/kg every 8 hours for 7-10 days is also recommended. For children > 1 year of age, 1500 mg/m2 (body surface area) in 3 divided doses for 7-10 days is recommended.) When afebrile and no visceral involvement, switch to oral acyclovir.
- ***Ophthalmic VZV:*** Acyclovir 800 mg PO five times per day for 10 days. (For Children: Acyclovir 40-80 mg/kg/day divided into 3-4 doses each day for 14 days). ***Ophthalmic disease is a medical emergency necessitating urgent ophthalmologic consultation.***
- ***Primary varicella in an adult:*** Acyclovir IV (preferred) 10mg/kg every 8 hours for 10 days. Once patient is improved and stable: Acyclovir 800 mg PO five times a day to complete at least 10 days (or until last lesion has crusted over whichever comes last). Monitor renal function closely. (For children: 40-80 mg/kg/day divided into 3-4 doses each day for 14 days)

11.6 CMV Retinitis:

Diagnosis:

Fundoscopic findings of white retinal patches and retinal hemorrhages, vasculitis, and retinal necrosis or detachment in a patient with CD4 cell count < 100 cells/µL, with or without visual symptoms.

Treatment:

CMV retinitis is a medical emergency, which requires urgent ophthalmologic evaluation and prompt treatment with intra-ocular and oral ganciclovir.

- Treatment may only marginally improve vision already compromised or lost, but will preserve remaining vision.

- Patients with very low CD4 cell counts should be counseled to return immediately if any visual symptoms develop.

11.7 Pneumonia

HIV-infected individuals have a 100-fold increased risk for pneumococcal disease. A recent retrospective chart review of admissions to Princess Marina Hospital found that up to 70% of all patients presenting with pneumonia are known to be HIV positive. Regional data suggest that Mycobacterium tuberculosis may account for nearly half of adults presenting with pneumonia from the community. Other common causes: S. pneumoniae, H. influenzae, Mycoplasma, S. aureus , and Pneumocystis jiroveci (PCP) should be considered in individuals with CD4 counts < 200 cells/µL.

11.7.1 Diagnostic Evaluation for Pneumonia

- Symptoms suggestive of pneumonia include fever, cough, dyspnea, and pleuritic chest pain. No single or combination of symptoms can confirm the diagnosis of pneumonia.
- Complete chest X-ray to evaluate radiographic findings consistent with pneumonia.
- Send sputum for MCS and AFB smear on all HIV-infected individuals.

11.7.2 Pneumocystis Jiroveci Pneumonia (PCP)

Symptoms of PCP should be suspected in individuals with CD4 count < 200 cells/µL who are not taking cotrimoxazole preventative therapy; or patients with WHO stage III/IV disease who present with cough with either a normal chest radiograph or evidence of diffuse interstitial or alveolar infiltrates and one of the following:

- Dyspnea, particularly exertional dyspnea for at least 2 weeks or unknown duration.
- Fever, non-productive cough, chest discomfort
- Ambulatory or resting hypoxia
- If patients are unable to ambulate secondary to dyspnea and oxygen saturation measurement is not available, a respiratory rate of >30 in adults is a reasonable surrogate.

11.7.2a Treatment for PCP:

- Cotrimoxazole IV 5 mg/kg every 8 hours. Add Prednisolone 40 mg orally (or intravenous equivalent dose) twice daily for patients with hypoxia, defined as an oxygen saturation of less than 92% on room air.
- For children:
  - ***Cotrim 90-120 mg/kg/day divided q 6 hrs IV/po x 14-21 days (TMP 15-20 mg/kg/day + SMX 75-100 mg/kg/day)***
  - ***IV hydrocortisone 2.5 mg/kg QID OR***
  - ***PO Prednisone 2 mg/kg/day***
- If cotrimoxazole is not available or the patient is allergic to cotrimoxazole, consult a HIV specialist for therapy recommendations.
- Change to oral therapy in 72 hours if hypoxia and or dyspnea has resolved.

- Continue therapy for a total of 21 days.
- In all patients with non-TB pneumonia, who are ART-eligible, initiate ART after the patient's clinical condition is stabilized and within 2-3 weeks of presentation.
- Taper steroids as follows:

Table 11.3: Prednisolone/Hydrocortisone Tapering Instructions

Prednisolone dose (mg)	Hydrocortisone dose (mg)	# of Days of therapy
40 twice daily	160mg twice daily (can be given as 320mg divided as 80mg every 6 hours)	5
40 once daily	160mg once daily (can be given as 160mg divided as 80mg every 12 hours)	5
20 once daily	80mg once daily	10

Lack of improvement within 48 hours or clinical deterioration at any time:

- Review current anti-microbial regimen to evaluate for under-dosing; assess if patient has missed doses
- Repeat chest radiography, white blood cell count, renal function tests and liver function tests. Blood cultures should be obtained in all patients with a T>38.0°C or ≤35.6°C.
- Consider performing an ECG in patients with chest discomfort, dyspnea or a history of previous cardiac disease.
- If the patient exhibits a change in mental status, perform a lumbar puncture

Strongly consider the diagnosis of smear negative pulmonary TB and initiation of ATT, especially in individuals with CD4 counts ≤100 cells/μL or in individuals newly diagnosed with HIV and an unknown CD4 count.

(Refer to the 2011 National Tuberculosis Guidelines for recommendations regarding initiation of ATT in suspected smear negative pulmonary TB patients.)

11.8 Mucocutaneous Candidiasis/Oral Candidiasis:

Persistent oral candidiasis is a WHO stage 3 condition (after age 6 weeks in infants). The following types of oral candidiasis are common in patients with HIV infection:

- ***Pseudomembranous candidiasis:*** white removable plaques located on the palate and other oropharyngeal surfaces

- ***Erythematous candidiasis:*** Smooth red areas located on the hard palate or dorsal tongue.
- ***Angular cheilitis:*** fissures located at the corners of the mouth.

If candida is limited to the oropharyngeal cavity and is asymptomatic, only topical antifungals are required: miconazole gel, clotrimazole troches, and/or nystatin swish/swallow.

- Most cases of "thrush" usually resolve promptly with ART.

For all cases of oral candidiasis, esophageal involvement must be ruled out by inquiring about the presence of dysphagia and/or painful swallowing. If esophageal symptoms are present, empiric therapy with systemic antifungal therapy should be initiated as follows:

- Fluconazole 200 mg OD for 10-14 days, adults
- For children, give fluconazole 6 mg/kg one time, followed by 3 mg/kg OD for 14 days.

Esophagitis can also be caused by CMV, HSV, and HIV itself. If odynophagia persists despite a 2 week course of fluconazole, start empiric acyclovir for HSV. If there is no improvement, discuss with a HIV or Pediatric HIV Specialist.

11.9 Lymphoid Interstitial Pneumonitis (LIP):

LIP is a common pediatric lymphoproliferative pulmonary disorder in HIV-infection, with a spectrum of disorders involving lymphocytic infiltration of the lungs and hyperplasia of bronchus-associated lymphoid tissue. LIP is often mistaken for infectious lung diseases such as TB and PCP. Symptomatic LIP is a WHO Stage 3 disorder, and is an indication for ART regardless of CD4 count or percentage.

Diagnosis:

- Fine, bilateral reticulonodular or alveolar infiltrates are often seen on chest X-ray.
- Examination may be normal, or may include wheezing, tachypnea, oxygen desaturation, digital clubbing, and peripheral lymphoid hyperplasia.
- Make the diagnosis of LIP based upon the clinical history, physical examination, and chest X-ray, with exclusion of other treatable lung diseases.

Treatment:

- ART, antibiotics.
- For children with significant pulmonary compromise, inhaled beta-agonists and steroids may be helpful.

11.10 Chronic Diarrhea / Wasting:

Defined as "chronic unexplained diarrhea" for > 30 days in adults and "unexplained persistent diarrhea" for >14 days in pediatric patients, chronic diarrhea is a WHO stage 3 condition that makes patients ART-eligible regardless of CD4 count.

- ***Diagnosis:*** stool for culture, ova and parasites. (Repeat studies are often necessary to make the diagnosis).

- ***Common causes in immunocompromised patients:*** Cryptosporidium parvum, cyclospora cayetanensis, Isospora, Microsporidia, (E. bieneusi, E intestinalis), Giardia lamblia, mycobacteria, e.g., TB. Also, consider antibiotic-associated diarrhea, e.g., C. difficile.
- ***Treatment:*** Vigorous replacement of fluids and electrolytes, especially potassium. Except in cases of hypovolemic shock, oral rehydration is the preferred route, especially in malnourished patients.
- Treat with both CTX and metronidazole (400 mg TDS for 10 days) simultaneously.
- ***Administer CTX:*** 1 DS tablet QID for 10 days, followed by BD dosing for 21 days. For children, 5 mg/kg TMP BD 21 days.

- ***For cases refractory to CTX and metrondizole treat empirically with albendazole:*** 400 mg PO BD x 21 days in adults.

Avoid use of loperamide and calcium carbonate in adults. Because of serious adverse events, loperamide must not be used for children

Adjustments to diet are particularly important and therefore always discuss the importance of proper nutrition and improvement of diet. Advise patients to:

- Avoid milk and milk products (although yogurt can be recommended in those patients who are not lactose intolerant).
- Avoid carbonated soft drinks.
- Avoid excess intake of sugar and sweets.
- Eat small healthy meals throughout the day, preferably stews and soups to aid digestion.
- Drink adequate amounts of replacement liquids throughout the day.

11.11 Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is a potential complication that can occur following the initiation of ART, when improvement in immune function is accompanied by the worsening of a current opportunistic infection or the unmasking of a latent or recent one. IRIS presents as a paradoxical worsening of clinical status despite "favourable" CD4 and viral load responses. Baseline CD4 counts < 50 cells/µL, rapid viral load decline, and robust immune reconstitution with ART are associated with IRIS. The interval between initiation of ART and onset of IRIS is variable, ranging from < 1 week to many months, but it usually occurs in the first 3-6 months of therapy.

- IRIS most commonly occurs in the setting of underlying mycobacterial infections (e.g., TB, MAC), cryptococcal infection, and herpes virus infections(HSV, VZV, CMV, KS). Almost all other OIs have also been associated with IRIS.
- Usually occurring in the first 2 weeks of ART initiation, TB IRIS is an especially common complication of ART initiation (see Chapter 6. Section 6)
- Systemic steroids are often given when inflammatory damage at the site of involvement severely impairs organ function and becomes life-threatening, e.g., upper respiratory obstruction from lymphadenopathy due to TB or KS.

11.12 Toxoplasmosis

In Botswana, the seroprevalence of toxoplasmosis is approximately 6.5% among HIV patients. Absence of seropositivity makes the diagnosis unlikely, as does use of cotrimoxazole prophylaxis.

Diagnosis:

- ***Symptoms:*** Headaches, confusion, lethargy, fever and weight loss over several weeks. Focal neurologic signs eventually develop depending on the location of the lesion with ataxia, hemiparesis, visual field loss, seizures, or cranial nerve abnormalities.

- ***CT scan findings:*** Hypodense lesions (70-80% of cases with multiple lesions); ring enhancement is seen with contrasted studies; however no enhancement may be seen. Lesions can be anywhere but are classically localized to the corticomedullary junction or basal ganglia. May also display marked edema and mass effect.
- ***Toxoplasmosis serum IgG:*** positive (>1:8 in >97% of HIV/AIDS patients with toxoplamosis).

Treatment:

First line:

- Pyrimethamine 200 mg once daily then 75mg orally every 24h + sulfadiazine 1.5 grams orally every 6 hours + folinic acid 20 mg three times weekly for 6 weeks

Second line:

- Cotrimoxazole 15 mg/kg divided every 8 hours for 6 weeks

Third Line:

- Pyrimethamine 200 mg once daily then 75 mg orally every 24 hours + clindamycin 600 mg rally or IV every 6 hours + folinic acid 20 mg three times weekly for 6 weeks.
- Adjunctive corticosteroids are not recommended for CNS toxoplasmosis
- Whenever possible, after 1 month of treatment, send patients for CT scan of the head to assure that lesions are decreasing in size.

For Children:

- Pyrimethamine: 2 mg/kg OD x 3 days (loading dose; max 50mg/day) then 1 mg/kg OD (max 25mg/day) x 6 weeks PLUS
- Sulfadiazine: 25-50 mg/kg/dose given QID (maximum: 1-1.5 g/dose) x 6 weeks PLUS
- Folinic acid: 10-25 mg OD x 6 weeks

CHAPTER 12: OTHER HIV PRIMARY HEALTH CARE TOPICS

12.1 Post-Exposure Prophylaxis (PEP) for Occupational Exposure to HIV

Ideally, PEP should be initiated within 1-4 hours of the incident, and at least within 72 hours of the exposure event. PEP initiation should be based on a step-by-step protocol:

1) Determination of the HIV infectiousness of the body fluid to which the HCW was exposed.
2) Type and extent of exposure
3) Immediate exposure management
4) Estimation of the HIV risk of the specific exposure
5) HCW counselling and determination of the HCW's HIV status
6) Determination of the HIV status of the source patient
7) Decision whether or not to initiate PEP
8) Initiation of PEP and monitoring of the HCW on PEP
9) Repeat HIV testing of the exposed HCW after completion of PEP
10) Thorough documentation of the above steps

1) <u>Body Fluids and their HIV Infectiousness:</u>

- Body fluids which are infectious for HIV are generally those which are contained within enclosed, usually sterile body compartments, such as joints, the central nervous system, or the pleural space ***(e.g., blood, genital secretions, pericardial fluid, pleural fluid, synovial fluid, amniotic fluid, cerebral spinal fluid, ascitic fluid, breast milk, and any normally non-infectious fluid which is visibly contaminated with blood (or, in unusual cases, contaminated with any other infectious fluid))***.
- Fluids not infectious for HIV include: urine, feces, tears, saliva, perspiration, sputum, pus from abscesses, and nasal secretions, unless visibly contaminated with blood.

2) <u>Type and Extent of Exposure:</u>

- ***Percutaneous:*** injury causing break in skin and exposure to body fluid, usually via needle or scalpel injury
- ***Mucosal:*** conjunctival and oral mucous membrane exposure to body fluid
- Cutaneous: contact of HIV-infected material with skin of the HCW

3) <u>Exposure management:</u>

- Wash exposed wounds and skin sites with soap and water.
- Flush mucous membranes with water.
- ***Avoid use of antiseptics, bleach, or other caustic agents,*** including injection of the exposed site with these agents.

4) **Estimation of the HIV Risk of the Specific Exposure:**

- Needle stick injury - average, aggregated transmission risk of 0.3% (i.e., 3 transmissions per 1000 events)
- Transmission rate is greater than above if there was a hollow-bore needle, the needle was in the source patient's artery or vein, there was visible source patient blood or other infectious fluid on the needle, the injury was deep, and the source patient's viral load was high.
- Mucous membrane exposure - estimated 0.09% risk of HIV transmission.
- Factors that may affect this risk are the volume of HIV-infected fluid, the length of exposure, any exposure management undertaken (e.g., eye washing), and the underlying integrity of the conjunctival or oral mucous membranes (e.g., conjunctivitis, oral ulcers, and obvious breaks in the oral mucosa).
- The transmission risk from exposure of HIV-infected fluid to intact skin is believed to be negligible, unless there is underlying dermatitis or significant skin breakage.

5) **HCW Counseling and Determination of HCW HIV Status:**

- If the HCW is already known to already be HIV-infected, PEP is not indicated; however, consider inoculation with HBV immune globulin (if available; the HCW has not been vaccinated against hepatitis).
- To facilitate necessary evaluation and intervention, use double rapid tests.
- If the HCW refuses HIV testing, PEP should not be given.
- If the HCW tests HIV-positive, PEP is not indicated or necessary and reassurance and emotional support must be provided with referral for CD4 and clinical screening.

6) **Determination of the HIV Status of the Source Patient:**

- If the HCW is found to be HIV-negative, then the HIV status of the source patient must be determined, unless the source patient is already known to be HIV-infected.
- ***If the source patient's HIV status is unknown, and if h/she refuses HIV testing, then an HIV (rapid) test should be obtained; however, the results should not be shared with the source patient. If the source patient physically hinders or obstructs performance of rapid testing, then it is necessary to initiate PEP for the HCW.***

7) **Decision Whether or not to Initiate PEP:**

- Decisions regarding initiation of PEP must be based upon clinical evaluation of each exposure event, including the type of exposure, the amount of potentially infectious fluid to which the HCW was exposed, the potential infectiousness of the fluid, and the HIV status of the source patient. Exposures to fluids not normally infectious for HIV, as listed above, do not merit PEP, even if the source patient is HIV-infected. Remember, exposure to potentially HIV-infected fluids may or may not merit PEP.
- PEP is recommended for needle stick injuries when the body fluid is potentially infectious for HIV and the source patient is know to be HIV-infected.
- For a needle stick injury in which the body fluid is potentially infectious for HIV, and in which the source patient tests HIV negative, the decision to initiate PEP must take into account the possibility that the source patient might be recently HIV-infected and is in the "window period" of infection. Whenever the practitioner believes there is a reasonable chance that the source patient who tests HIV negative may be in the "window period," PEP should be given to the exposed HCW. Err on the side of caution.

- For mucosal exposure, the amount of infectious fluid, the length of time of exposure, the condition/integrity of the exposed mucous membrane, whether or not there were any cleansing interventions, and the HIV status of the source patient should be taken into consideration. Many mucosal exposures do not merit PEP, especially when the exposure was minimal, there was no prior inflammation of the mucous membrane, and the source patient tests HIV-negative. An HIV Specialist should be consulted in difficult cases.
- Exposure of intact skin to HIV-infected fluid does not merit PEP.
- Human bites are not infectious for HIV, and do not merit PEP, unless visible blood from the biter was present in the biter's mouth prior to the bite.
- The length of time HIV can survive outside the body is unknown. Nonetheless, needle stick injuries from devices left in the trash or elsewhere merit PEP.
- It is imperative that the medical practitioner be able to make decisions concerning PEP initiation without pressure from the exposed HCW.

12.1.1 ART Regimens for PEP

8) Initiation of PEP and monitoring of the HCW on PEP:

Once the decision to initiate PEP has been made, it should be started as soon as possible, ideally within 1-4 hours after exposure, but no later than 72 hours.

- For adolescents and adults:
  - ***Atripla*** (TDF/FTC/EFV)
  - Children starting PEP require ***CBV/NVP or CBV/EFV***
  - In some cases, baseline and follow-up laboratory testing is not necessary. However, ***obtaining any baseline laboratory tests, if clinically indicated, must not delay initiation of PEP beyond 4 hours after the incident.***

- Assure that the HCW understands the importance of completing the entire 1 month regimen.
- Schedule clinical follow-up 2 weeks after PEP initiation both to evaluate for side effects and to provide adherence counseling and emotional support.
- Monitor laboratory results of HCWs on PEP based on the HCW's medical history.
- Pregnancy is not a contraindication to PEP. Discuss PEP treatment options with HIV Specialist if an exposed female HCWs is <14 weeks pregnant.
- Counsel HCW to practice safe sex during the period of PEP and until repeat HIV testing has been completed.
- Women who are breastfeeding must be counseled regarding the risks of breastfeeding following an HIV exposure and should be advised to abstain from breastfeeding until HIV status is fully known.
- Educate HCW about the signs and symptoms of EFV side effects (e.g., CNS disturbance, dizziness, depression, insomnia) as well as the acute retroviral syndrome. Advise them to return immediately if those symptoms appear.

9) Repeat HIV testing of HCW after PEP:

- The HCW should return for repeat HIV testing at 6 weeks, 3 months, and 6 months after the initial exposure.
- For women who ceased breastfeeding while on PEP, confirm the negative 6 week HIV test with a priority viral load to allow resumption of breastfeeding.

10) Thorough documentation of the above steps:

- All of the above steps must be carefully documented in the HCW's medical record, relevant hospital records, and the standardized Needle Stick Incident Form and PEP Form in the hospital staff clinic.

12.1.2 PEP and Other Indicated Care for Victims of Sexual Violence

Victims of rape, sodomy, and defilement—including infants and children--who present for care within 72 hours of the incident should be offered PEP.

Even if the rapist tests HIV-negative, the result must be interpreted with caution, as it is possible that the rapist is in the "window period."

- Follow the PEP protocol for such victims, including infants and children, exactly as that for HCWs above; this includes the need for baseline HIV testing.
- ***It is essential that police understand that PEP must be started immediately for victims of sexual violence; therefore, victims of sexual violence must first be brought to the hospital or clinic for PEP evaluation before a detailed police interrogation is initiated.***
- ***The practitioner must not wait for a police report before initiating PEP, and is not bound by any police report in determining the need for PEP.***
- A patient history of violent penetrative sex is sufficient for initiating PEP, per the above protocol. Although not a requirement for initiation of PEP, the victim should be encouraged to report the rape to the police once PEP has been initiated.
- Victims of sexual violence, especially children, require special medical and psychosocial care. Although appropriate referrals for this care may be necessary, the treating clinician must also provide such care, and not merely delegate it. Moreover, this care should be given regardless of whether or not the victim receives PEP, as follows:
  - Screening for other STIs which may have been transmitted during the rape should be done by obtaining cultures for chlamydia and gonorrhea, if available, as well as baseline and follow-up RPR.
  - ***After obtaining a screening pregnancy test, patients should also be offered emergency contraception in the forms of "morning after pill" to prevent pregnancy.***
  - The patient/caregiver should receive education about signs and symptoms of STIs, including the importance of ongoing safe sex.
  - If genital/rectal trauma has occurred, promptly refer the patient for appropriate surgical, urological, or gynecological care, as indicated.
  - Obtain baseline, 6 weeks, 3 months, and 6 months HIV rapid tests, and if positive, initiate appropriate support and referrals.
- Depression, shame, guilt, and suicide have followed rape, and ongoing psychosocial interventions and counseling are required, including social worker referral for psychiatric evaluation. ***Since the psychological trauma of rape may not be evident at the initial visit, such interventions must be ongoing at follow-up visits, and should always be conducted within a safe, supportive, and confidential environment.***

12.2 Post-Sexual Prophylaxis

Post-sexual exposure prophylaxis, which often presents as "the-condom-broke" scenario, is often administered on an unstructured ad hoc basis, with subsequent risks of poor patient motivation, PEP side effects, nonadherence, and abandonment of safe sex practices. Accordingly, ***post-sexual prophylaxis should not be administered***.

12.3 The Role of CHBC in the Provision of ART:

The CHBC programme exists to provide care and support to patients suffering from chronic and terminal illnesses. This is done through a continuum of care model. This model ensures that the patient receives integrated comprehensive care throughout every aspect of care and treatment. In addition, the programme has a two way referral system whereby patients are referred for higher institutional health care services through the Botswana primary health care structures and also back to home and community settings upon their discharge using a CHBC discharge referral form *(See Annex 22: CHBC Referral Form : MH 2071, page No. 195).* This process ensures that patients are not lost to follow up and can be easily contacted by community health care providers. The CHBC health care providers include the district CHBC coordinator, focal persons in health facilities and volunteers at community level.

The Role of the CHBC:

- Work closely with the ART site providers and IDCC
- Help identify eligible clients from the community and refer them into HIV care
- Advocate for nutritional and psychosocial support services
- Link clients with relevant support systems such as Social Welfare services
- Conduct regular home visits and follow up of patients
- Promote adherence and provide basic health education on the importance of adhering to ART and positive living.

Referral procedure

- All eligible clients who need constant follow up and support need to be registered with the CHBC programme.
- Immediately after the patient has been enrolled on ART, the doctor or the initiating officer will fill in the CHBC referral form ***MH 2071***.
- This form will notify the CHBC coordinator in the district about the client and the type of support the client need.
- The CHBC will then make arrangements for the client to be assisted

12. 4 HIV and Occupational Health and Workplace Wellness

In addition to PEP, other health interventions that reduce the frequency of workplace injury, illness, and burnout include:

- Completing vaccination series for Hepatitis B, which is made available free to HCWs by the government and is safe and effective. Encourage co-workers to do the same.
- Using appropriate respiratory precautions (N95 masks, etc.) when caring for patients with active TB. This is especially important for HCWs who are HIV-infected. Requesting work transfers to less risky healthcare locations can be made on a case-by-case basis to health facility authorities for consideration.
- Testing and screening for HIV annually.
- Seeking counseling services when your working situation causes you to feel depressed or suffer decreased productivity.

12.4.1 HIV and TB Prevention in Health and Congregate Settings

Health care workers and workers in congregate settings, especially those who are HIV-infected are at higher risk of TB infection than the general population. All HCW and workers in congregate settings must:

- Receive TB infection control training and be offered HIV testing and counseling
- Be referred for ARV care and services, including regular TB screening, if found to be living with HIV.
- Be educated about the signs and symptoms of TB disease and encouraged to seek immediate medical evaluation if symptoms occur.

12.5 Surgery and Medically Invasive Procedures on HIV-Infected Patients:

As ART extends patient life-expectancy to that of non-infected persons, the need for surgical or invasive medical procedures on HIV-infected patients has increased. Delay or postponement of surgery or other invasive medical procedures cannot be justified by asserting that the HIV-infected patient has a "terminal illness". Emergency surgery in an HIV-infected patient must not be delayed simply because of HIV status, low CD4 cell count, or a high viral load. Specifically,

- There has been no consistent evidence of "poor wound healing" in HIV-infected patients after surgery. Thus, lacking any definitive data to the contrary, ***surgery for HIV-infected patients must not be delayed or ruled out simply on the basis of HIV infection alone***. Rather, evaluation for surgery, as well as for other invasive medical procedures, must take into account the overall clinical condition of the patient, including cardiopulmonary status, coagulation profile, baseline level of physical activity, and other non-HIV-related parameters routinely used to judge surgical fitness for patients not infected with HIV.
- ***Evaluation of emergency surgical risk for HIV-infected patients must be impartial, and must follow the same criteria for evaluating non-HIV infected patients.***

Nonetheless, HIV infection can cause a variety of acute and chronic conditions which may make surgery or other invasive medical procedures contraindicated. As a rule:

- Unless the surgery/medical procedure is an emergency, any acute, current WHO clinical stage 3 or 4 condition is a medically valid reason to delay the intervention until the condition has first been rectified, ideally with ART and other condition-specific therapy.
- Remote or resolved stage 3 or 4 conditions are not contra-indications to surgery or medically invasive procedures. For example, malignancies, which are in remission or are resolving (e.g., KS responding to therapy), are not contraindications to surgery, unless there is demonstrable compromise of cardiopulmonary function.
- Once the new HIV-related conditions and/or symptoms have been treated, then the patient's surgical/medical risk should be determined by the same anesthetic and surgical criteria used to evaluate HIV-uninfected patients.

Referrals of HIV-infected patients to private facilities for urgent surgery or other medical interventions not available in Botswana must first ensure that;

1) The patient has no active WHO clinical stage 3 or 4 condition(s);
2) The prognosis of the patient's HIV disease is good;
3) The patient's over-all operative/medical risk for the proposed surgery or Intervention is considered good.

If the above conditions are met, then eligibility for medical/surgical referral to private facilities should follow the same guidelines and standards as those applied to uninfected patients in the same general medical condition.

- ***Pre-operative HIV testing as a precondition for surgery should be discouraged***, unless there is a clearly compelling clinical indication. Strict adherence to universal precautions and sterile technique must prevail, regardless of the patient's HIV status.
- When a patient is otherwise deemed to be an acceptable surgical candidate, advance knowledge of his HIV status provides no clinically useful information with regards to the patient's overall surgical risk.

This policy, however, does not apply to routine opt-out HIV testing of hospitalized patients of unknown HIV serostatus, who should always be encouraged to test for HIV.

12.6 Protocol for ART Nurse Initiation:

The following section has been written specifically for ART nurses who have successfully completed the ARV Nurse Training for Prescribing and Dispensing Antiretroviral Medicines.

Adult ART Eligibility Criteria for ART Nurse Initiation:

General:

- CD4 count: >150 cells/µL and ≤ 350 cells/µL
- Appears well and is ambulatory
- Reports no significant medical issues
- Reports no WHO stage 2, 3, or 4 conditions
- Reports no previous history of receiving sdNVP during labour

Clinical Criteria:
There should be NONE of the following conditions:

- rash involving mucous membranes
- shortness of breath or tachycardia
- unintentional weight loss > 10% baseline weight
- cough, fever or night sweats
- significant cervical lymphadenopathy
- pregnancy
- previous history of seizures, altered mental status
- neurological deficits
- nausea, vomiting or diarrhea
- dehydration
- jaundice or enlarged liver
- headaches, blurred vision
- abnormal Pap smear
- abdominal pain with tenderness, rebound or guarding on examination
- severe depression or suicidal ideation

Laboratory Criteria:

- Hemoglobin > 7 g/dL
- Platelets >150 x 109/L
- Total WBC > 1000/µL
- ALT/AST: Within Normal Limits
- Glucose < 7 mmol/L
- Creatinine < 120 umol/L
- Creatinine Clearance > 60 cc/min

Anyone who does not meet the general, clinical and laboratory criteria for ARV Nurse Initiation MUST ONLY BE INITIATED BY A DOCTOR.

2012 Standard Adult 1st Line Regimen

Men	**Atripla**	1 tab PO Q nocte x (time until next refill)
Non-pregnant Women	**Atripla**	1 tab PO nocte x (time until next refill)

2008 Standard Adult 1st Line Regimen

(Stable follow-up. Note: Both men and women may be taking either CBV or EFV, there is no dosage change based on gender)

Men	**CBV, EFV**	CBV 1 tab PO BD x (time until next refill) EFV 600 mg PO Q nocte x (time until next refill)
Non-pregnant Women	**CBV/NVP**	CBV 1 tab PO BD x (time until next refill) NVP 200 mg PO BD x (time until next refill)

Refer all women desiring pregnancy to a doctor for ART initiation

Adult Cotrimoxazole Prophylaxis

For women and men with CD4 counts < 200 cells/μL:

Cotimoxazole 2 tabs PO OD until CD4 > 200 cells/μL for three months

(2 tabs of 480mg single strength = 960mg OD)

For cotrimoxazole allergy or intolerance:

Dapsone 100 mg PO OD until CD4 > 200 cells/μL for three months

Avoid:

- TDF use in cases of renal insufficiency
- AZT use in cases of anemia
- EFV use in cases of psychiatric history

Table 12.1: Adult Laboratory Monitoring Schedule for Standard 1st Line Regimens containing: TDF/FTC/EFV, TDF/FTC/NVP, CBV/EFV, CBV/NVP, ABC/EFV, ABC/NVP

	Baseline	2 wks	1 month	3 months	6 months	12 months	Thereafter
CD4 Count	✓			✓	✓	✓	q6 months
Viral Load	None			✓	✓	✓	q6 months
FBC	✓		✓ CBV or AZT only	✓ CBV or AZT only		✓	q12 months
Chemistry	✓						As indicated
AST/ALT	✓	NVP only	NVP/EFV only	NVP/EFV only			As indicated
Creatinine & Cr Cl	**TDF**			**TDF**	**TDF**	**TDF**	q6 months
RPR	✓						As indicated

Screen all patients for TB by asking the following questions:
Do you have a recent history of cough, fever, night sweats, or weight loss (for children include decreased playfulness, failure to gain weight or recent TB contact)?

If patients report any of the above symptoms for any duration, they must be immediately screened for TB with AFB sputums and chest x-ray; and be referred to a doctor immediately.

Refer all women for baseline Pap smear
The recommendation for cervical cancer screening is under revision. Currently, any woman with abnormal findings on Pap smear must be immediately referred for doctor follow up (They must also be referred to a doctor for ART). Those women with normal baseline Pap smears should complete a follow up Pap smear within 3-5 years.

Discuss Sexual Reproductive Health with all patients:

- Inquire about the HIV status of their partner(s) and children: TEST or refer for testing
- Inquire about current contraceptive method: prescribe or refer for prescription
- Inquire about date of last menstrual period. If pregnancy is suspected send for pregnancy test; if positive refer to MD for ART initiation.
- Inquire about history or current STIs, refer for treatment if necessary

Complete a full physical exam for ALL patients, as follows:

General Appearance/condition: age, cognition, breathing, ambulatory status
Nutritional status, pallor, sweating, dehydration, fever
Vital Signs: weight, temperature, pulse, BP, respiratory rate
Skin: jaundice, rashes, eruptions, ulcerations
CNS: confusion, speech, balance
Head: deformities, masses, evidence of trauma
Ears: hearing, external canals, discharge, cerumen, tympanic membrane

Eyes: sclera, visual acuity, corneal reflex, extraocular movements
Nose & Paranasal sinuses: rhinorrhea, tenderness in frontal, mastoid, or maxillary areas
Mouth: thrush, dentition, condition of gums, lip fissures
Neck: rigidity, thyroid, cervical lymph nodes
Axilla: lymph nodes, ulcerations
Chest: cough, SOB, wheezes, rhonchi, rales, consolidation
Heart: heart rate, rhythm, murmurs
Abdomen: tenderness, guarding, masses, bowel sounds
Genitals: lymph nodes, ulcerations, penile or vaginal discharge
Extremities: peripheral neuropathy, edema, lesions

All patients found to have significant physical findings must be initiated by a doctor.

Managing Adverse Side Effects to ART:

If a patient returns to the clinic within 6 months of ART initiation with significant complaints related to ART, complete all baseline laboratory investigations, including VL and CD4, and refer immediately for doctor follow-up.

Side Effects Attributable to ART:
CNS effects (insomnia, nightmares, dizziness, headache): EFV
Rash (mild to severe): NVP
Anemia, neutropenia, weakness, fatigue: CBV (AZT)
Renal insufficiency, headache, nausea, vomiting: TDF
GI intolerance, nausea, vomiting, diarrhea: LPV/r

Follow Up Appointments
Year One:
Baseline Visit
Initiation Visit (usually scheduled 2 wks after baseline visit)
2 week visit (only if initiated on NVP)
1 month (from initiation date)
3 months (from initiation date)
6 months (from initiation date)
12 months (from initiation date)

Year Two:
Clinical follow up visit every 3 months
If clinically stable after two years with VL suppression and CD4 >200 cells/µL,
visits may be scheduled every 6 months

Annexes

REFERRAL CARD

SAFE MALE CIRCUMCISION

Client Name: _____

Cell/Tel: _____

Age: _____

_____

Referred to _____

Referred by _____

Date Issued: _____

HIV Test: (YES/NO):

Client Name: _____

Age: _____

_____

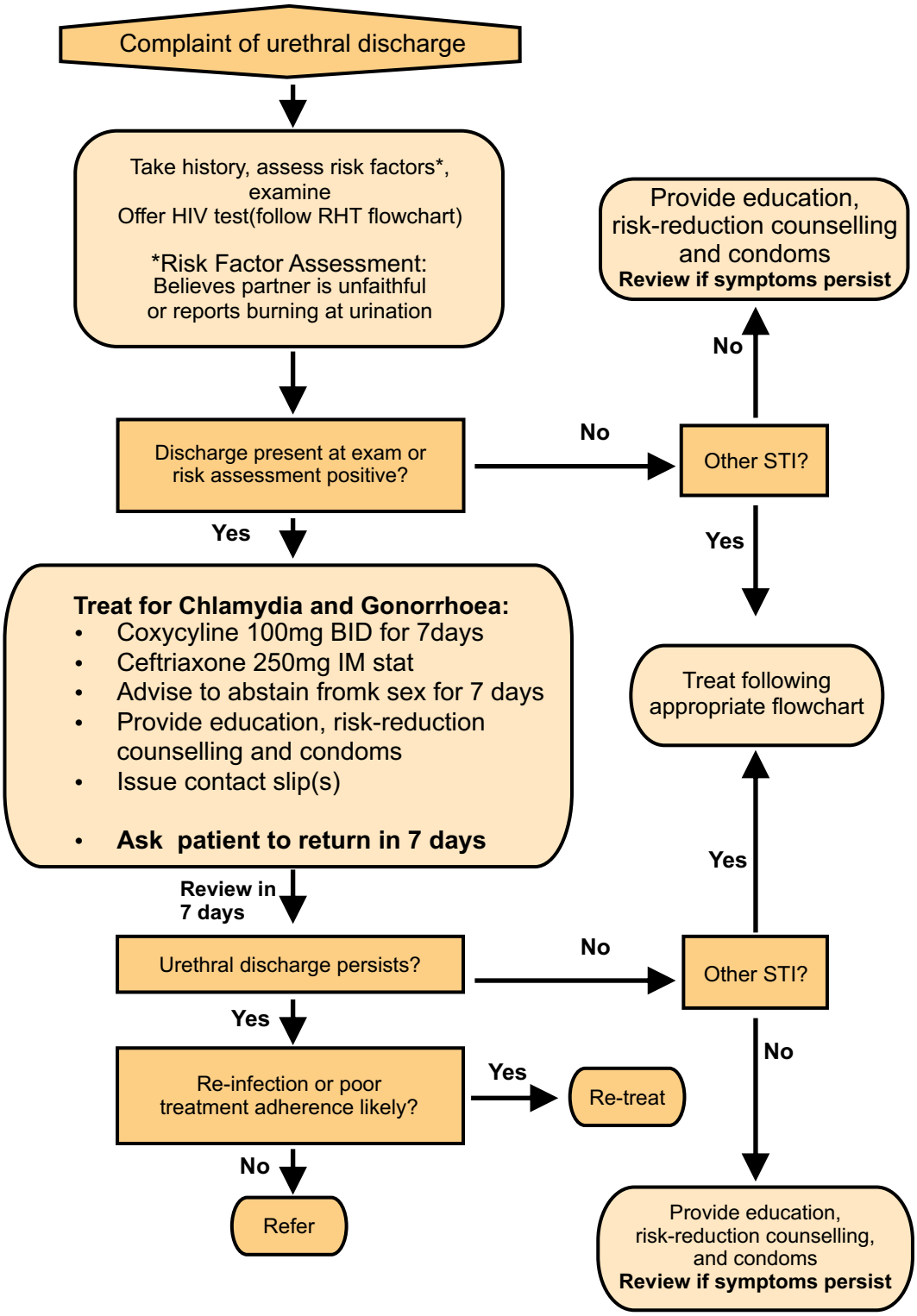
Facility Name _____

Facility Contact Number _____

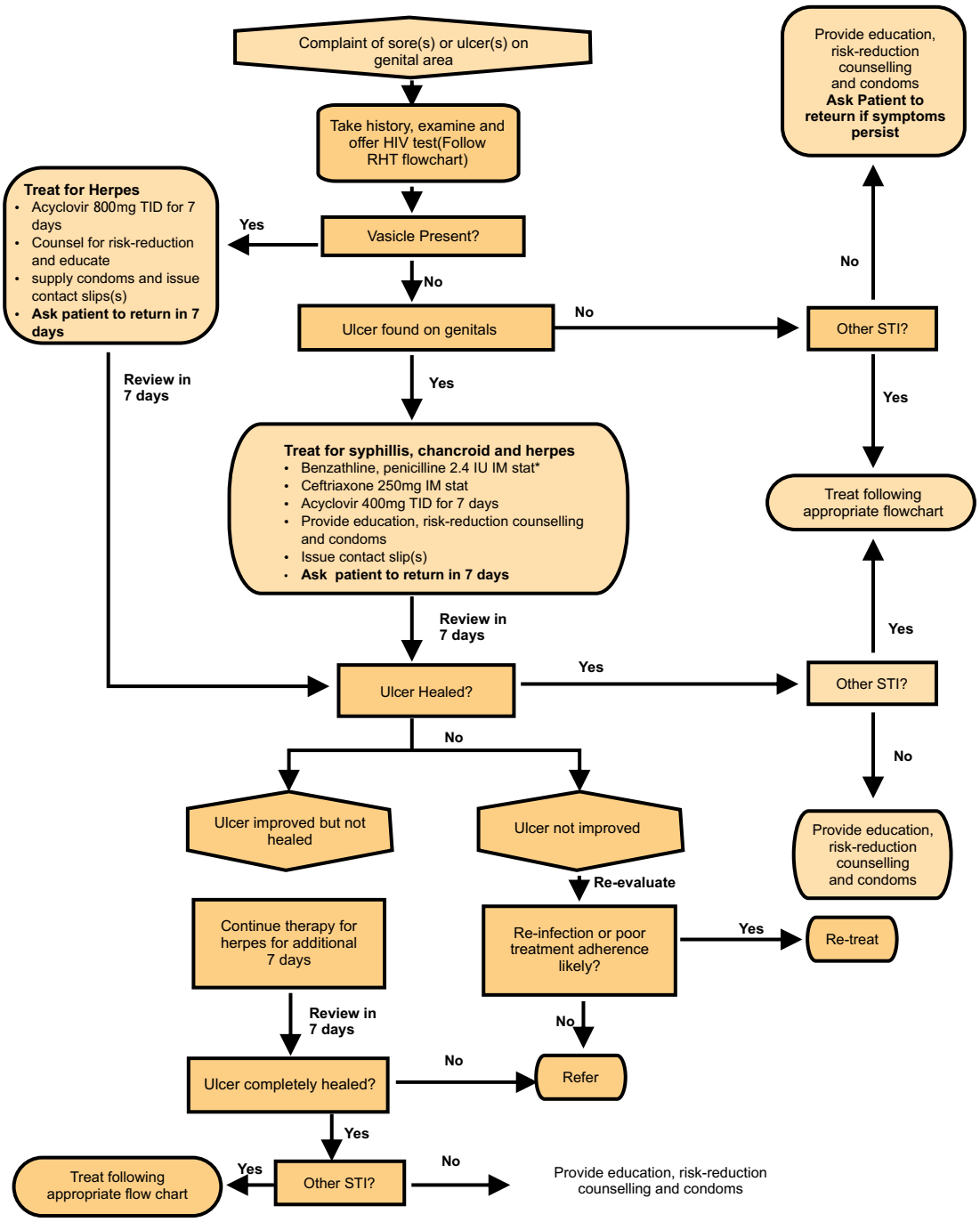
Referred by _____

Date Issued: _____

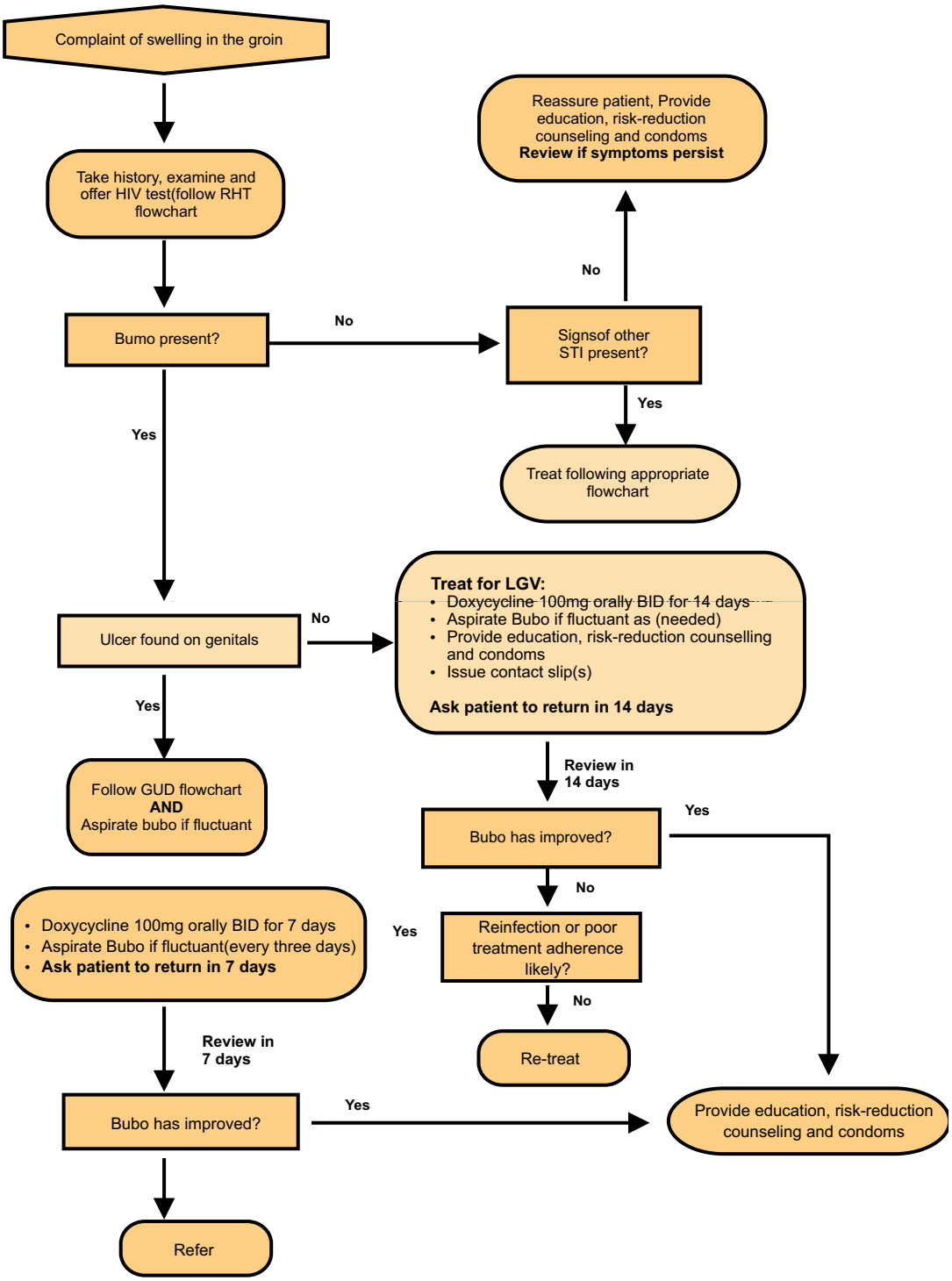
STI Treatment Algorithms: Urethral discharge Flowchart



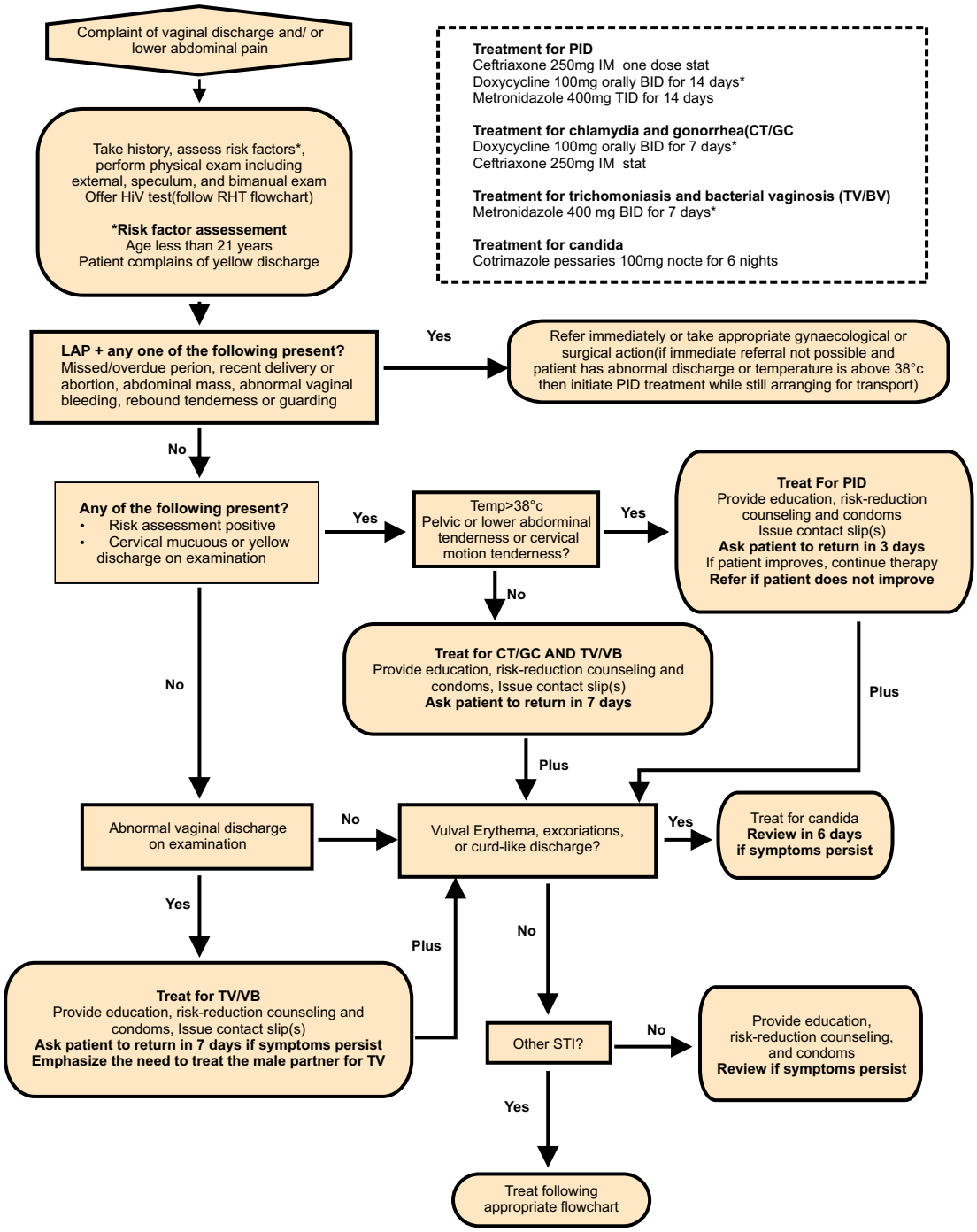
STI Treatment Algorithms: Genital Ulcer Disease Flowchart



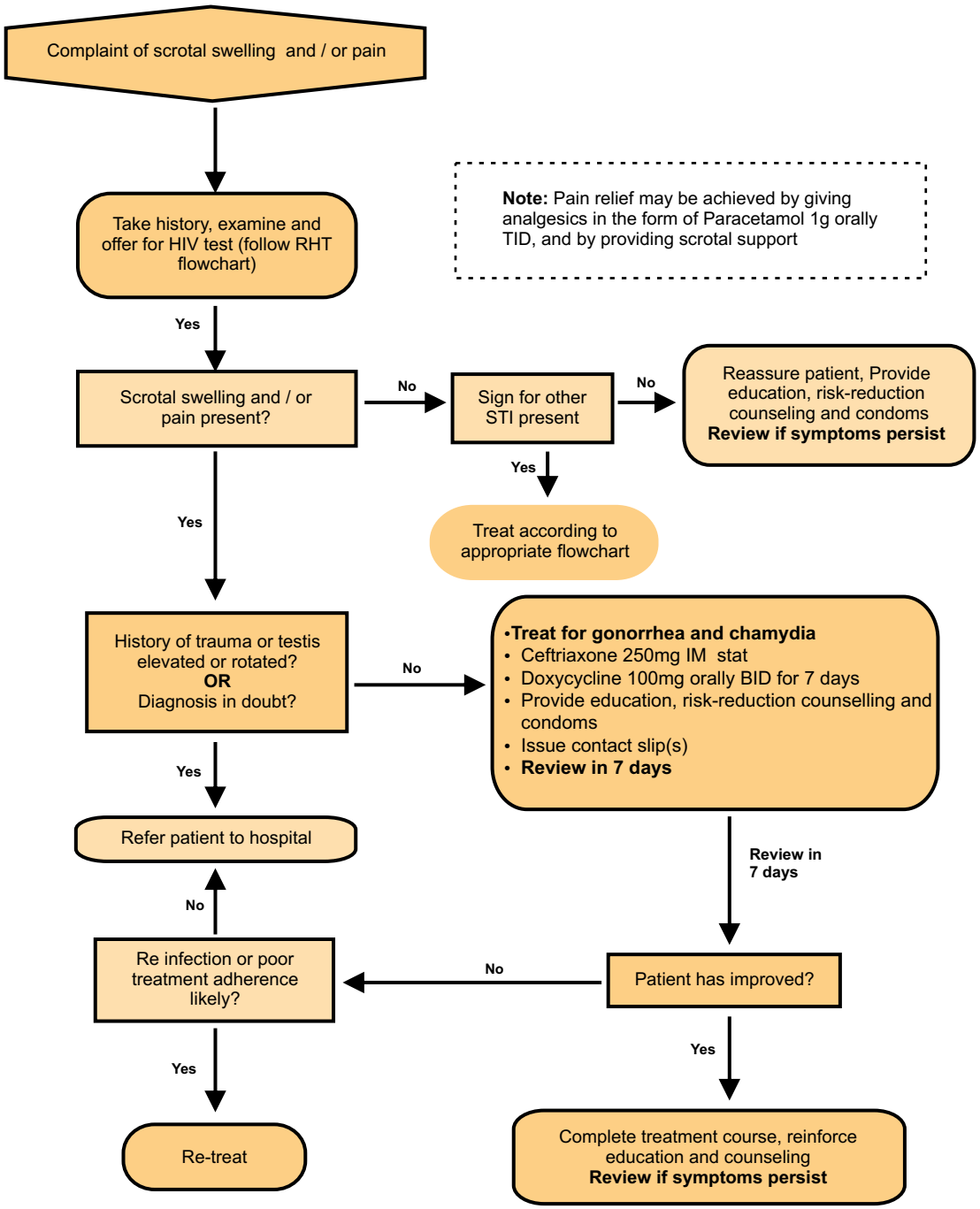
STI Treatment Algorithms: Inguinal Bumo Flowchart



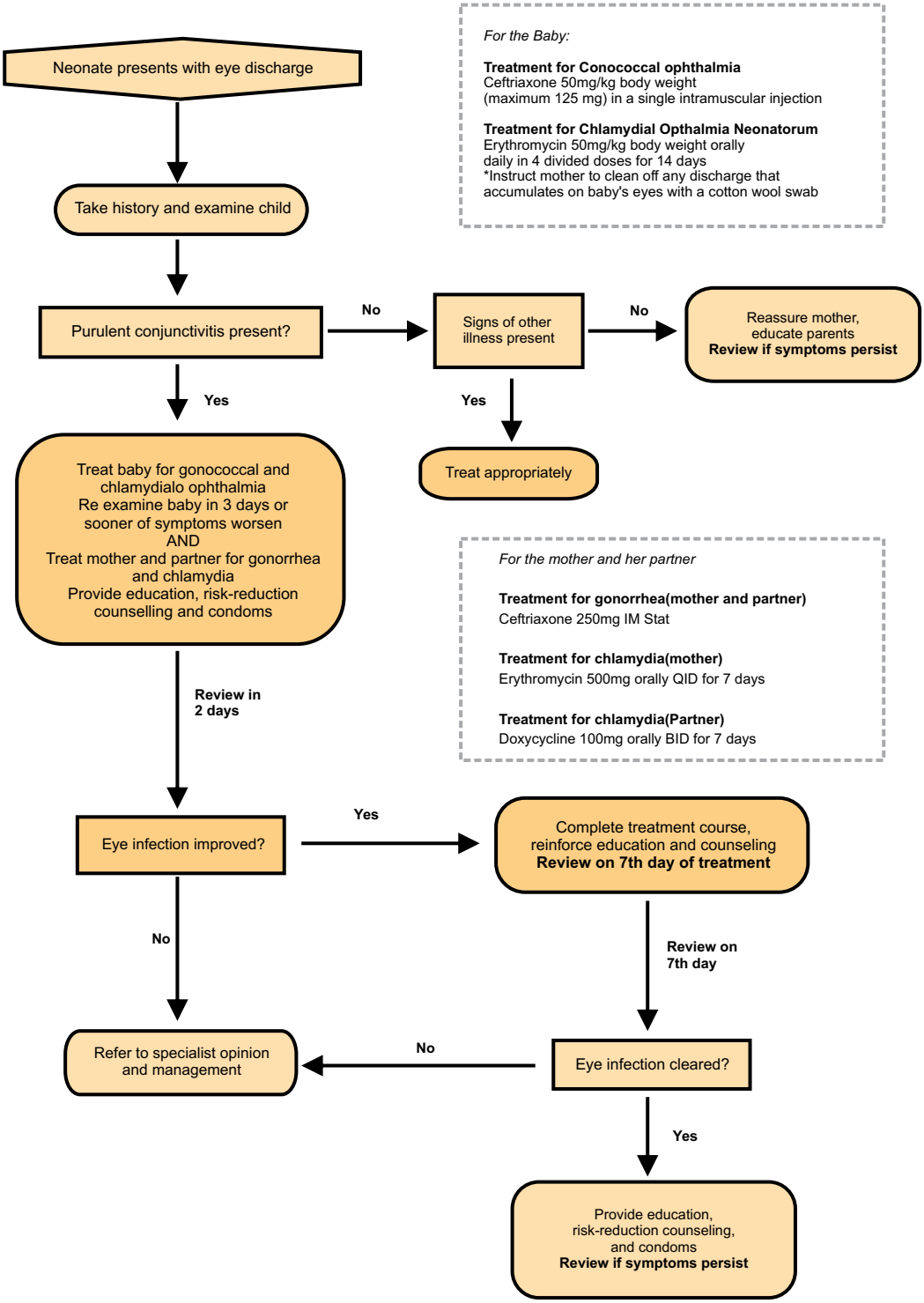
Vaginal Discharge & Abnominal Pain-Cervical or Vaginal Infection



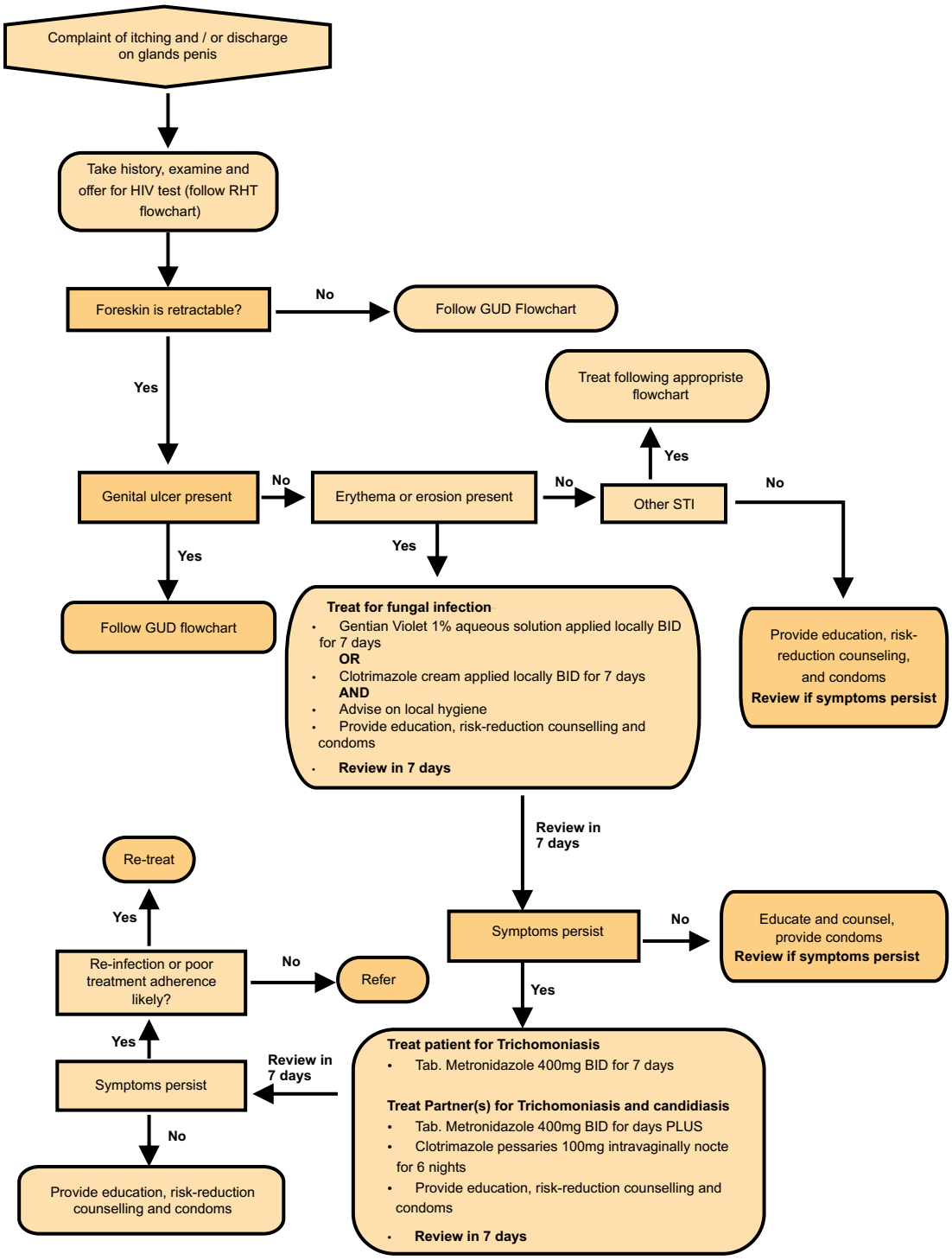
STI Treatment Algorithms: Acute Scotal Swelling Flowchart



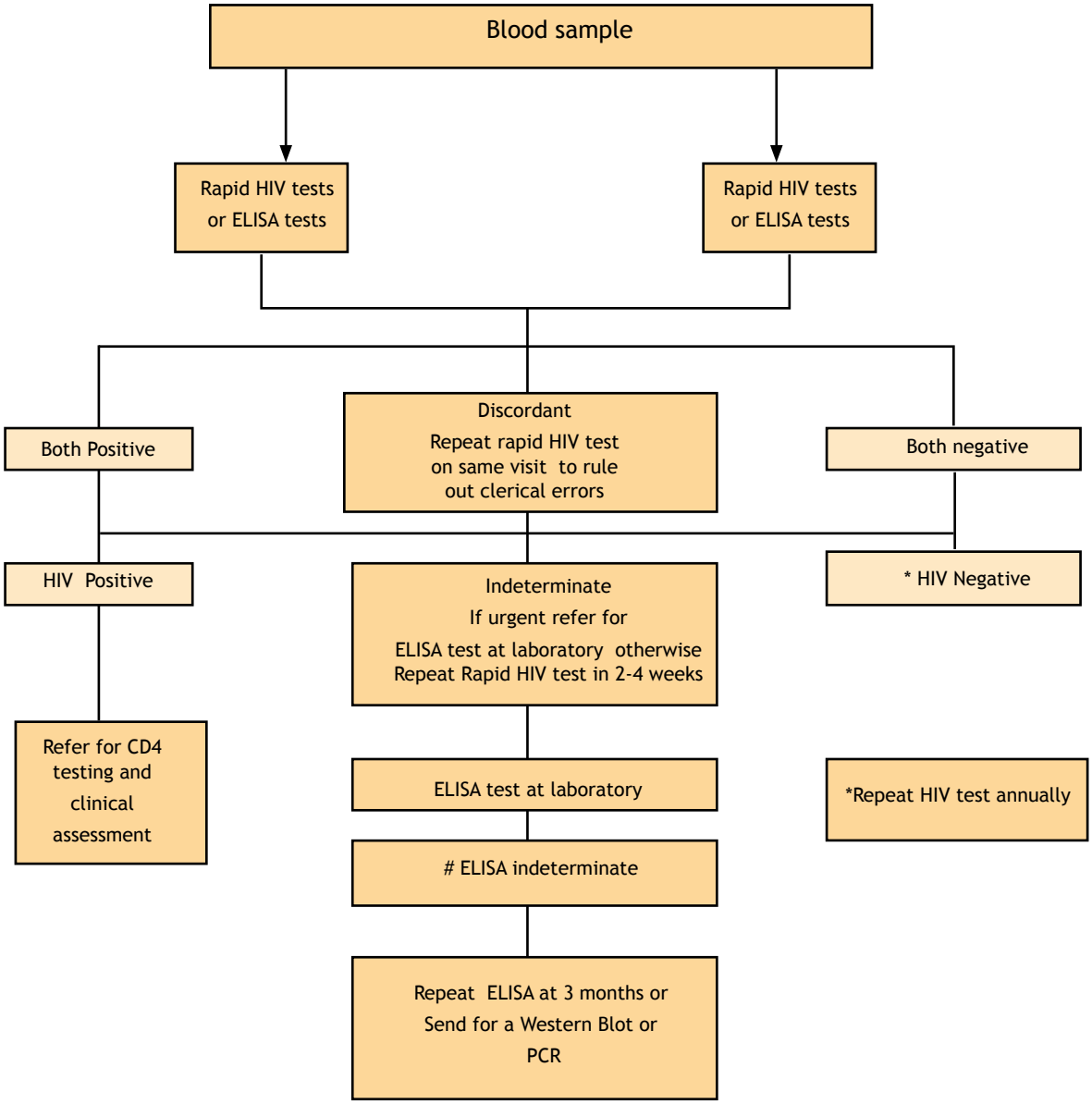
STI Treatment Algorithms: Ophthalmia Neonatorum Flowchart



STI Treatment Algorithms: Balantis Flowchart



Diagnosis of HIV Infection in Patients 18 Months of Age & Older



* Patient is either uninfected or in the "window period" of infection. Counsel on abstinence or safe sex
* Alert laboratory personnel to follow the specimen and results.

NATIONAL PHARMACOVIGILANCE CENTRE, BOTSWANA

ADVERSE REACTIONS REPORTING FORM

I . PATIENT INFORMATION

Patient identity/Omang number: Age(yrs): Sex(M/F): Weight(kgs) Ethnicity:

II. SUSPECT MEDICATIO0N(S)/ VACCINE/HERBAL

List of drugs being used by the patient (please tick the suspect drug)	Route	Daily Dose	Manufacturer	Date Drug Started	Date Drug Stopped	Reasons for use

III. ADVERSE REACTION EXPERIENCED/OBSERVED:

Date of onset of reaction:	Reaction subsided after suspect drug discontinuation:	Rechallanged?

Description of adverse event
(including laboritory test results)

Outcome	Recovered	Hospitalised	Disability	Death(D/M/Y)	Unknown
Treatment for reation:					
Results					

Other Pre-existing medical conditions: (e.g. Allergies, Pregnancy, Smoking, Alcohol, Hepatic/Renal Dysfunction, others)

Additional Information: (if any)

IV. REPORTER:

Name and professional address:

Telephone No. Occupation & Speciality: Health Professional: Yes No

Signature: Date:

For office use only

Received on: Registration No. Received by:

Annex 5

ART Dosages & Formulations (taken from the United States DHHS March 27, 2012 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations	Food Effect	Oral Bioavailability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Tenofovir Disoproxil Fumarate (TDF) VIREAD Also Available as : **ATRIPLA** - w/ EFV + FTC **TRUVADA** - w/ FTC	Viread® 300 mg tablet Atripla™ - EFV 600 mg + FTC 200 mg + TDF 300 mg Truvada® TDF 300 mg + FTC 200 mg	Viread® 1 tablet once daily Atripla™ 1 tablet once daily Truvada® 1 tablet once daily	Take without regard to meals	25% in fasting state; 39% with high-fat meal	17 hours	>60 hours	Renal excretion Dosage adjustment in renal insufficiency ATRIPLA- not for patients with CrCl <50 mL/min TRUVADA - not for patients with CrCl < 30 mL/min	• Asthenia, headache, diarrhea, nausea, vomiting, and flatulence; renal insufficiency; • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)
Zidovudine (AZT, ZDV) RETROVIR COMBIVIR - w/ 3TC TRIZIVIR- w/ 3TC + ABC	**RETROVIR** 100mg capsules, 300mg tablets, 10mg/mL intravenous solution, 10mg/mL oral solution **COMBIVIR** 3TC 150mg + ZDV 300mg **TRIZIVIR** - 3TC 150mg + ZDV 300mg + ABC 300mg	**RETROVIR** 300mg two times/ day or 200mg three times/ day **COMBIVIR or TRIZIVIR** 1 tablet two times/day	Take without regard to meals	60%	1.1 hours	7 hours	Metabolized to AZT glucuronide (GAZT). Renal excretion of GAZT Dosage adjustment in renal insufficiency COMBIVIR & TRIZIVIR - not for patients with CrCl < 50 mL/min	• Bone marrow suppression: macrocytic anemia or neutropenia; • Gastrointestinal intolerance, headache, insomnia, asthenia; • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity associated with use of NRTIs.

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations	Food Effect	Oral Bioavailability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Abacavir (ABC) ZIAGEN TRIZIVIR – w/ ZDV + 3TC EPZICOM – w/ 3TC	ZIAGEN 300mg tablets or 20mg/mL oral solution TRIZIVIR-ABC 300mg + ZDV 300mg + 3TC 150mg EPZICOM-ABC 600mg + 3TC 300mg	300mg two times/ day; or 600mg once daily; or as TRIZIVIR- 1 tablet two times/day EPZICOM-1 tablet once daily	Take without regard to meals; Alcohol increases abacavir levels 41%; abacavir has no effect on alcohol	83%	1.5 hours	12–26 hours	Metabolized by alcohol dehydrogenase and glucuronyl transferase. Renal excretion of metabolites 82% TRIZIVIR & EPZICOM not for patients with CrCl < 50 mL/min	Hypersensitivity reaction that can be fatal, symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath
Didanosine (ddI) VIDEX EC, Generic didanosine enteric coated (dose same as VIDEX EC)	VIDEX EC 125, 200, 250, or 400mg Buffered tablets (non-EC) are no longer available	Body weight ▫ 60kg: 400mg once daily EC capsule with TDF: 250mg/ day < 60 kg: 250mg daily EC capsule with TDF: 200mg/ day	Levels decrease 55%; Take 1/2 hour before or 2 hours after meal	30–40%	1.5 hours	>20 hours	Renal excretion 50% Dosage adjustment in renal insufficiency	Pancreatitis; peripheral neuropathy; nausea Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs.

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations	Food Effect	Oral Bioavailability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Emtricitabine (FTC) EMTRIVA Also available as : ATRIPLA -w/ EFV & TDF TRUVADA - w/ TDF	EMTRIVA200mg hard gelatin capsule and 10mg/mL oral solution ATRIPLA - EFV 600mg + FTC 200mg + TDF 300mg TRUVADA FTC 200mg + TDF 300mg	EMTRIVA 200mg capsule once daily or 240mg (24 mL) oral solution once daily ATRIPLA - One tablet once daily TRUVADA One tablet once daily	Take without regard to meals	93%	10 hours	>20 hours	Renal excretion Dosage adjustment in renal insufficiency ATRIPLA - not for patients with CrCl <50 mL/min TRUVADA - not for patients with CrCl < 30 mL/min	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs.) Hyper-pigmentation/ skin discoloration
Lamivudine (3TC) EPIVIR COMBIVIR- w/ ZDV EPZICOM - w/ ABC TRIZIVIRw/ ZDV+ABC	EPIVIR 150mg and 300mg tablets or 10mg/mL oral solution COMBIVIR- 3TC 150mg + ZDV 300mg EPZICOM - 3TC 300mg + ABC 600mg TRIZIVIR – 3TC 150mg + ZDV 300mg + ABC 300mg	EPIVIR 150mg two times/day; or 300mg daily COMBIVIR - 1 tablet two times/day EPZICOM -1 tablet once daily TRIZIVIR - 1 tablet two times/day	Take without regard to meals	86%	5-7 hours	18-22 hours	Renal excretion Dosage adjustment in renal insufficiency COMBIVIR, TRIZIVIR & EPZICOM not for patients with CrCl < 50 mL/min	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations	Food Effect	Oral Bioavailability	Serum half-life	Elimination	Adverse Events
Efavirenz (EFV)/ SUSTIVA Also Available as **ATRIPLA** – with FTC + TDF	50, 100, 200mg capsules or 600mg tablets ATRIPLA - EFV 600mg + FTC 200mg + TDF 300mg	600mg daily on an empty stomach, at or before bedtime	High-fat/ highcaloric meals increase peak plasma concentrations of capsules by 39% and tablets by 79%; take on an empty stomach	Data not available	40–55 hours	Metabolized by cytochrome P450 (3A mixed inducer/ inhibitor); No dosage adjustment in renal insufficiency if EFV is used alone; ATRIPLA - not for patients with CrCl <50 mL/min	• Rash*; • Central nervous system symptoms;† • Increased transaminase levels; • False-positive cannabinoid test; • Teratogenic in monkeys ‡
Nevirapine (NVP)/ VIRAMUNE	200mg tablets or 50mg/5 mL oral suspension	200mg daily for 14 days; thereafter, 200mg by mouth two times/day	Take without regard to meals	> 90%	25–30 hours	Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites; <5% unchanged); 10% in feces	• Rash including Stevens-Johnson syndrome* • Symptomatic hepatitis, including fatal hepatic necrosis, have been reported

* During clinical trials, NNRTI was discontinued because of rash among 7% of patients taking nevirapine, 4.3% of patients taking delavirdine, 1.7% of patients taking efavirenz. Rare cases of Stevens-Johnson syndrome have been reported with the use of all NNRTIs, the highest incidence seen with nevirapine use.
† Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Overall frequency of any of these symptoms associated with use of efavirenz was 52%, as compared with 26% among controls subjects; 2.6% of those persons on efavirenz discontinued the drug because of these symptoms; symptoms usually subside spontaneously after 2–4 weeks.
‡ Symptomatic, sometimes serious, and even fatal hepatic events (accompanied by rash in approximately 50% of cases) occur with significantly higher frequency in treatment-naive female patients
with pre-nevirapine CD4 counts >250 cells/mm^3 or in treatment-naive male patients with pre-nevirapine CD4 counts >400 cells/mm . Nevirapine should not be initiated in these patients unless the benefit clearly outweighs the risk. This toxicity has not been observed when nevirapine is given as single doses to mothers or infants for prevention of mother-to-child HIV transmission.

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations	Food Effect	Oral Bioavailability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Lopinavir + Ritonavir (LPV/r)/ **KALETRA**	Each tablet contains LPV 200mg + RTV 50mg Oral solution: Each 5 mL contains LPV 400mg + RTV 100mg Note: Oral solution contains 42% alcohol	LPV 400mg + RTV 100mg (2 tablets or 5 mL) twice daily or LPV 800mg + RTV 200mg (4 tablets or 10mL) once daily (Note: once-daily dosing only recommended for treatment-naïve pts; not for patients receiving EFV, NVP, FPV, or NFV) With EFV or NVP: For treatment-experienced pts: LPV 600mg + RTV 150mg (3 oral tablets) twice daily or LPV 533 mg + RTV 133 mg (6.7 mL oral solution) twice daily with food	Oral tablet -No food effect; take with or without food Oral solution -Moderately fatty meal Ĺ LPV AUC & Cmin by 80% & 54%, respectively; take with food	Not determined in humans	5-6 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Oral tablet is stable at room temperature Oral solution is stable at 2°- 8°C until date on label; is stable when stored at room temperature (up to 25ºC or 77ºF) for 2 months	• GI intolerance, nausea, vomiting, diarrhea (higher incidence with once-daily than twice-daily dosing) • Asthenia • Hyperlipidemia (esp. hypertriglyceridemia) • Elevated serum transaminases • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Characteristics of Integrase Inhibitor

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations	Serum/Half-Life	Route of Metabolism	Adverse Events
Raltegravir (RAL)/ Isentress	* 400mg Tablet * 25-100mg Chewable Tab-lets	400mg BID With Rifampin : 800mg BID Take without regard to meals	~9 hours	UGT1A1 - Mediated glucuronidation	* Rash, Including Stevens-Johnson syndrome, HSR, and toxic epidermal necrolysis * Nausea * Headache * Diarrhea * Pyrexia * CPK elevation, muscle weakness and rhabdomyolysis

Key : BID = twice daily; CPK = creatine phosphokinase; HSR = hypersensitivity reaction; RAL = raltegravir; UGT = uridine diphosphate

Annex 6

Clinical Presentation, Investigations and differential diagnosis of the most common forms of EPTB in Botswana

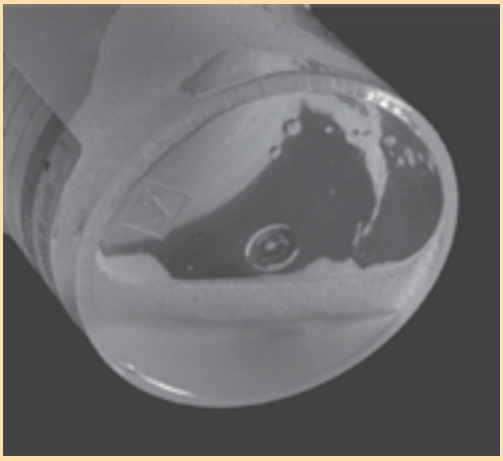
Type of EPTB	Symptoms*	Investigations**	Differential Diagnosis
Meningitis	Chronic headache, altered mental status, focal neurological deficits.	Lumbar Puncture: AFB smear and culture, cytology, protein, glucose, India ink. High suspicion for TB • Cerebrospinal fluid India ink negative • Evidence of TB elsewhere, especially PTB • No response to broad-spectrum antibiotics	• Cryptococcal meningitis • Bacterial meningitis • Viral meningitis • Syphilis
Lymphadenitis	Firm, asymmetrical lymph nodes > 2 cm May be fluctuant or develop a fistula Cervical nodes most common	Fine Needle Aspiration (FNA) with microscopy and cytology (Annex 4) Lymph node biopsy with histology	• HIV lymphadenopathy • Malignancy • Bacterial infection
Pericarditis	Chest pain, dyspnoea, hypotension, tachycardia, elevated jugular venous pressure, ascites	CXR: enlarged heart Echo: pericardial effusion and thickening If tamponade, perform urgent pericardial fluid aspiration	• Heart failure: valvular disease, hypertension • Bacterial pericarditis • Viral pericarditis
Pleural	Chest pain, cough, dyspnoea	CXR: pleural effusion Pleural fluid aspiration: AFB smear and culture, cytology and protein Pleural biopsy for histology High suspicion for TB: Unilateral effusion Chronic symptoms	• Kaposi's Sarcoma (KS) • Bacterial empyema • Heart failure
Disseminated	General symptoms: fever, weight loss, night sweats, enlarged liver and spleen	Bacterial blood cultures TB blood culture (obtain bottles from NHL) CXR: miliary pattern Malaria blood film, serum cryptococcal antigen	• Sepsis: Pneumococcus, Salmonella, Cryptococcus • HIV wasting syndrome • Malaria
Peritonitis	Chronic abdominal pain, ascites	Ultrasound: ascites, enlarged abdominal lymph nodes, hepatomegaly, splenomegaly Peritoneal fluid aspiration: AFB smear and culture, cytology and protein	• Liver failure: cirrhosis, drug toxicity, alcohol • Heart failure
Renal	Chronic urinary tract infection, haematuria, renal failure	Early morning urine sample for AFB smear and culture	• Renal abscess • Renal cell carcinoma
Spinal (Pott's Disease)	Chronic back pain, gibbous deformity, lower extremity neurological deficits, may have abscess or fistula formation	Spinal x-ray	• Malignancy • Osteoarthritis • HIV-related neuropathy • Bacterial infection

* Symptoms are related to the site of infection. General symptoms are common to all patients with EPTB: fever, malaise, night sweats, weight loss
**HIV testing is an essential investigation for all patients who are being evaluated for TB. Sputum specimens should be obtained on all EPTB patients with a cough.

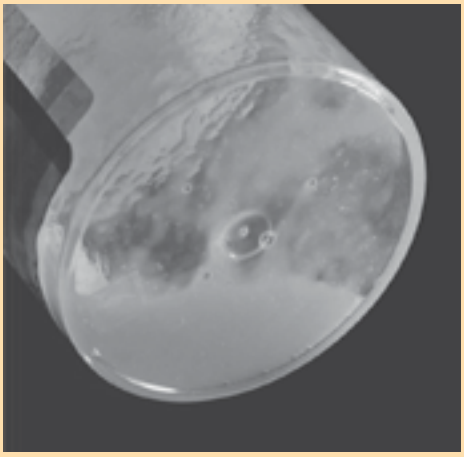
Sputum Collection

Sputum collection:

- Use sterile plastic containers with screw caps
- Sputum collection must be done in an isolated area with open air
- Clearly explain the procedure and the importance of sputum collection to the patient
- Supervise the procedure and do not stand in front of the patient
- Sputum (2 – 5 ml) and not saliva must be accepted as a good specimen. *Induced sputum may resemble saliva and is an acceptable specimen.*



Bad sputum (saliva)



Good sputum

Sputum collection technique:

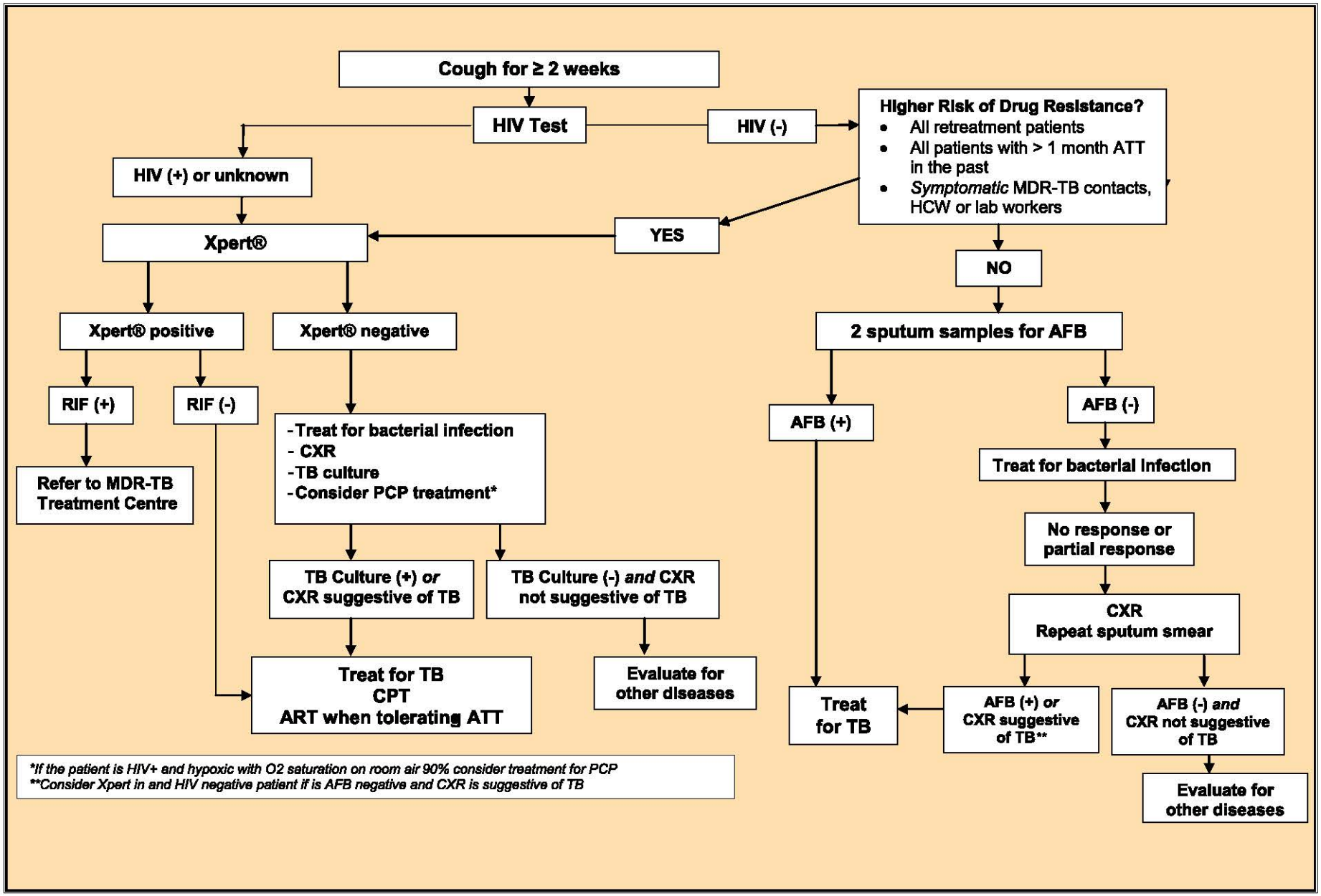
- Rinse mouth and throat before producing the specimen
- Open the container and keep it near the mouth
- *Lean forward and take two deep breaths, holding the breath for a few seconds after each inhalation and then exhale slowly*
- Breathe in a third time and forcefully blow the air out
- Breathe in again and then cough, producing sputum into the container
- Close the lid securely
  Wash hands

Transportation of sputum specimen:

- Label the container on the side (NOT the lid) with date, patient's name and clinic
- Enter the specimen data into the SD Register before dispatch
- Each specimen must be accompanied by a completely filled Mycobacteriology Request and Report Form (MH 2011)
- Place the specimen into a leak proof rigid container such as a cooler box
- Wash your hands after handling specimens
- Send the specimens to the laboratory as soon as possible
- Transport in a cooler box and use ice packs if travelling long distance
- If transport is delayed, store the specimens in a fridge but do not freeze. *All specimens sent for culture must be refrigerated.*
- Do not leave specimens directly exposed to the sun at any time

Annex 8

Algorithm for the diagnosis of PTB using Xpert



The Tuberculin Skin Test (TST)

TST has been used since the 1930s to detect infection with TB. In Botswana, TST is primarily used to identify children < 5 years with TB infection. TST is not routinely used in adults because a high proportion may be latently infected with TB, but will never develop TB disease. Like young children, adults living with HIV are more likely to develop TB disease after infection. In the future TST may be used in Botswana to identify HIV-infected individuals who are most likely to benefit from IPT.

The Mantoux method is the standard method of TST. It is the intradermal injection of mycobacterial antigens which elicit an immune response (delayed-type hypersensitivity), represented by induration, which can be measured in millimetres. Reliable administration and interpretation of TST requires a standard procedure, training and practice.

Administration:

1. Locate and clean injection site 2 finger widths below the elbow joint on the inner surface of the forearm
   - Place forearm palm-side up on a firm, well-lit surface
   - Select an area free of barriers (e.g. scars, sores)
   - Clean the area with alcohol and dry with a sterile swab

2. Prepare syringe
   - Check expiration date on the vial and ensure it contains tuberculin PPD-S (5 TU per 0.1 ml). Once the vial has been opened it is good for one month from the date of opening.
   - Fit a single-dose tuberculin syringe with a short (5mm to 10mm) 27-gauge needle with a short bevel. The needle must fit very tightly on the syringe.
   - Fill the syringe with 0.1 ml tuberculin

3. Inject tuberculin
   - Insert the needle slowly, bevel up, at an angle of 5-15° lengthwise of the arm, while lightly stretching the skin in the direction of the needle
   - The needle bevel should be visible just below skin surface
   - Hold the syringe by the barrel only and do not touch the plunger until the needlepoint has been satisfactorily inserted
   - Slowly inject the 0.1 ml tuberculin
   - Remove the finger from the end of the plunger before withdrawing the needle

4. Check injection site
   - The injection should produce a pale elevation of the skin, 6-10 mm in diameter (see Figure A6.1)
   - If not, the injection was too deep. Repeat the injection at a site at least 5 cm away from the original site.
   - The wheal should disappear within 10-30 minutes
   - The injection is only slightly painful and gives a sensation comparable to that of an insect bite, which lasts for one or two minutes

5. Record information
   - Record the date of test administration, injection site location, lot number of tuberculin and name of the person giving the injection in the patient record.

Reading:

Read the test between 48 and 72 hours afteradministration. A patient who does not return within 72 hours should be rescheduled for another TST. Measure the reaction with a small transparent ruler calibrated in millimetres.

1. Inspect site
   - Visually inspect the injection site under goodlight, and measure induration (thickening of the skin), not erythema (reddening of the skin).
   - Sometimes a small red spot the size of a pinpoint remains at the site of the entry of the needle. When the reaction is negative, it is sometimes very difficult to determine where the injection was made. *This may be avoided by drawing a circle on the skin at the time of inoculation.*

2. Palpate induration
   - Carefully palpate the test site with fingertips to find the margins of induration
   - The induration may vary from a firm, well-circumscribed density in the skin to a soft, ill-defined swelling. The latter type may easily escape notice unless the test site is palpated with a light touch.
   - The reaction may be intense with a large papule 10-20 mm in diameter, surrounded by a pink circle, which may be several centimetres wide. In these cases, the reaction is often accompanied by itching. In a few cases, the centre of the papule may look like a blister.

3. Mark induration
   - Use fingertips as a guide for marking the widest edges of induration across the forearm (transverse to the arm)
   - If the reaction is positive, the zone around the injection site will be red, indurated and elevated. Erythema alone is not a positive reaction. *The essential factor is induration,* which is always easy to feel.

4. Measure diameter of induration using a clearflexible ruler or callipers (see Figure A6.2).
   - Place "0"of ruler line on the inside-left edge of the induration
   - Read ruler line on the inside-right edge ofthe induration (use lower measurement if between two gradations on mm scale).

5. Record diameter of induration
   - Do not record as "positive" or "negative", *only record measurement in millimetres*
   - If no induration, record as 0 mm

Interpretation:

The TST should be regarded as positive if:
- ≥ 5 mm diameter of induration in high-risk individuals (HIV infection or other immune suppression, severe malnutrition)
- ≥ 10 mm diameter of induration in all others(whether they have received BCG vaccine or not)

ATT Fixed Dose Combinations and Single Dose Formulations

Table A7.1: Treatment for New Cases in Adults and Children > 30 kg: 2(HRZE)/4(HRE)

Weight (kg)	Intensive Phase for 2 months	Continuation Phase for 4 months
	$R_{150}H_{75}Z_{400}E_{275}$ [1]	$R_{150}H_{75}E_{275}$ [2]
30 - 39	2 tabs	2 tabs
40 - 54	3 tabs	3 tabs
55 - 70	4 tabs	4 tabs
>70	5 tabs	5 tabs

[1] *$R_{150}H_{75}Z_{400}E_{275}$ = Adult fixed-dose combination of Rifampicin 150mg, Isoniazid 75mg, Pyrazinamide 400mg and Ethambutol 275mg*

[2] *$R_{150}H_{75}E_{275}$ = Adult fixed-dose combination of Rifampicin 150mg, Isoniazid 75mg and Ethambutol 275mg*

Table A7.2: Treatment for New Cases in Children ≤ 30 kg: 2(HRZE)/4(HRE)**

Weight (kg)	Intensive Phase for 2 months		Continuation Phase for 4 months	
	R60H30Z150[1]	Ethambutol (400mg tab)	R60H30[2]	Ethambutol (400mg tab)
2-2.9	½ tab	----	½ tab	----
3-5.9	1 tab	do not use if <4kg ¼ tab if wt 4-7.5kg ½ tab if wt 7.5-11.9 kg	1 tab	do not use if <4kg ¼ tab if wt 4-7.5kg ½ tab if wt 7.5-11.9 kg
6-8.9	1 ½ tab		1 ½ tab	
9.0-11.9	2 ½ tab		2 ½ tab	
12-14.9	3 tab	¾ tab	3 tab	¾ tab
15-19.9	4 tab	1 tab	4 tab	1 tab
20-24.9	5 tab	1 tab	5 tab	1 tab
25-29.9	6 tab	1 ½ tab	6 tab	1 ½ tab

***For children with TBM, severe TB or TB/HIV co-infection, consider adding additional INH to optimize the INH dose to 10-15mg/kg daily.*
[1] *$R_{60}H_{30}Z_{150}$ = Paediatric fixed-dose combination of Rifampicin 60mg, Isoniazid 30mg and Pyrazinamide 150mg*
[2] *$R_{60}H_{30}$ = Paediatric fixed-dose combination of Rifampicin 60mg and Isoniazid 30mg*

Table A7.3: Treatment for Retreatment Cases in Adults and Children > 30 kg: 2S(HRZE)/1(HRZE)/5(HRE)

Weight (kg)	Intensive Phase for 2 months		Intensive Phase for 1 month	Continuation Phase for 5 months
	Streptomycin (mg)	$R_{150}H_{75}Z_{400}E_{275}$ [1]	$R_{150}H_{75}Z_{400}E_{275}$ [1]	$R_{150}H_{75}E_{275}$ [2]
30 - 39	500	2 tabs	2 tabs	2 tabs
40 - 54	750	3 tabs	3 tabs	3 tabs
55 - 70	1000	4 tabs	4 tabs	4 tabs
>70	1000	5 tabs	5 tabs	5 tabs

[1] *$R_{150}H_{75}Z_{400}E_{275}$ = Adult fixed-dose combination of Rifampicin 150mg, Isoniazid 75mg, Pyrazinamide 400mg and Ethambutol 275mg*
[2] *$R_{150}H_{75}E_{275}$ = Adult fixed-dose combination of Rifampicin 150mg, Isoniazid 75mg and Ethambutol 275mg*

Table A7.4: Treatment for Retreatment Cases in Children ≤ 30 kg: 2S(HRZE)/1(HRZE)/5(HRE)**

Weight (kg)	Intensive Phase for 2 months			Intensive Phase for 1 month		Continuation Phase for 5 months	
	SM (mg)	$R_{60}H_{30}Z_{150}$	Ethambutol 400mg tab	$R_{60}H_{30}Z_{150}$	Ethambutol 400mg tab	$R_{60}H_{30}$	Ethambutol 400mg tab
2-2.9	40	½ tab	----	½ tab	---	½ tab	---
3-5.9	75	1 tab	do not use if <4kg	1 tab	do not use if <4kg	1 tab	do not use if <4kg
6-8.9	125	1 ½ tab	¼ tab if 4-7.5kg	1 ½ tab	¼ tab if 4-7.5kg	1 ½ tab	¼ tab if 4-7.5kg
9-11.9	150	2 ½ tab	½ tab if 7.5-11.9kg	2 ½ tab	½ tab if 7.5-11.9kg	2 ½ tab	½ tab if 7.5-11.9kg
12-14.9	200	3 tab	¾ tab	3 tab	¾ tab	3 tab	¾ tab
15-19.9	250	4 tab	1 tab	4 tab	1 tab	4 tab	1 tab
20-24.9	350	5 tab	1 tab	5 tab	1 tab	5 tab	1 tab
25-29.9	450	6 tab	1 ½ tab	6 tab	1 ½ tab	6 tab	1 ½ tab

***For children with TBM, severe TB or TB/HIV co-infection, consider adding additional INH to optimize the INH dose to 10-15mg/kg daily.*
$R_{60}H_{30}Z_{150}$ = Paediatric fixed-dose combination of Rifampicin 60mg, Isoniazid 30mg and Pyrazinamide 150mg
$R_{60}H_{30}$ = Paediatric fixed-dose combination of Rifampicin 60mg and Isoniazid 30mg

Table A7.5: Single Dose Formulations for Adults and Children*

Drug	Adult Dose mg/kg (range)	Paediatric Dose mg/kg (range)
Isoniazid (H)	5 mg/kg (4-6) Maximum 300mg daily	10 mg/kg (10-15) Maximum 300mg daily
Rifampicin (R)	10 mg/kg (8-12) Maximum 600mg daily	15 mg/kg (10-20) Maximum 600mg daily
Pyrazinamide (Z)	25 mg/kg (20-30)	35 mg/kg (30-40) Maximum 2.0g daily
Ethambutol (E)	15 mg/kg (15-20)	20 mg/kg (15-25) Maximum 1.2g daily
Streptomycin (S)	15 mg/kg (12-18) Maximum dose 1.0g daily	15 mg/kg (15-20) Maximum dose 1.0g daily

**Use single dose formulations when FDCs are not available.*

Overlapping and additive toxicities of ART and ATT

Toxicity	ARV	TB Drugs	Comments
Peripheral neuropathy	d4T	Isoniazid Cycloserine Ethionamide Linezolid	In Botswana, d4T is used only as a second-line ARV drug in children. The risk of peripheral neuropathy is less in children than in adults.
Neuropsychiatric problems[1]	EFV	Cycloserine Isoniazid Ethionamide Levofloxacin	EFV may be used with Cycloserine with close monitoring.
Headache	AZT, EFV, ABC	Isoniazid Cycloserine	Consider other possible opportunistic infections
Nausea and vomiting	RTV > LPV/r, d4T, AZT, ABC	Ethionamide PAS Pyrazinamide	Common side effects, usually manageable. All patients with persistent vomiting should be evaluated for hepatitis. Patients on d4T or AZT must be evaluated for pancreatitis and lactic acidosis.
Pancreatitis	d4T > 3TC	Linezolid	Pancreatitis due to 3TC is more common in children.
Diarrhoea	LPV/r, RTV d4T, TDF	Ethionamide PAS Pyrazinamide	Consider other possible opportunistic infections
Hepatitis	NVP > EFV, LPV/r, RTV	Isoniazid Pyrazinamide Rifampicin Ethionamide PAS	For patients on ART and ATT monitor ALT at baseline and monthly for the first 3 months of ATT. Severe exacerbation of Hepatitis B may follow discontinuation of 3TC, FTC and TDF. Do not re-introduce NVP in patients after hepatitis from this drug.
Rash	NVP > EFV, ABC	All	*Do not re-introduce NVP or ABC in patients after rash from these drugs.*
Lactic Acidosis	d4T, AZT, 3TC	Linezolid	
Renal failure	TDF (rare)	Streptomycin Amikacin Capreomycin	TDF may be used with the aminoglycosides with close monitoring. Monitor creatinine and electrolytes monthly and refer to a TB/HIV Specialist if renal failure occurs.
Anaemia Neutropenia	AZT	Linezolid Rifampicin Isoniazid	Macrocytosis is expected in patients taking AZT Stop AZT in all patients with Hgb < 7 or a decrease more than 25% from baseline.
Arthralgias/ Myalgias	AZT, ABC	Pyranzinamide	Patients on AZT with severe myalgias must be evaluated for lactic acidosis. Patients on ABC with severe myalgias/arthralgias must be evaluated for hypersensitivity reaction.

Management of common side effects to ATT

Side Effect	Drug(s) likely to cause	Management
Minor 1. Rule out other possible causes of presenting symptom 2. Symptomatic treatment 3. Continue ATT		
Nausea Vomiting Abdominal pain	Pyrazinamide Rifampicin Ethionamide PAS	*Check LFTs to rule out hepatitis* Take drugs with non-fatty foods Metochlopramide 10mg or promethazine 25-50mg 30 minutes before anti-TB drugs
Skin rash or itching *No blisters or mucous membrane involvement*	All	Chlorpheniramine 4 mg TDS or Promethazine 25-50 mg TDS.
Numbness, tingling or burning sensation in hands and/or feet (Peripheral neuropathy)	Isoniazid Ethionamide Cycloserine Linezolid	Pyridoxine 25 mg OD for prevention. Pyridoxine 50 - 150 mg OD for treatment. Amitriptyline 25-150 mg before bed.
Joint pain	Pyrazinamide	Paracetamol 1000 mg TDS. Buprofen 500 mg TDS.
Major 1. Rule out other possible causes of presenting symptom 2. Patient may need admission 3. ATT (and other drugs) should be stopped		
Skin rash with blisters or mucous membrane involvement	All	Stop all drugs. Admit to hospital
Jaundice	Isoniazid Rifampicin Pyrazinamide PAS Ethionamide	Stop all drugs. Check LFTS. Admit to hospital
Confusion Seizures Depression/psychosis	Isoniazid Cycloserine Ethionamide	Stop anti-TB drugs. Admit to hospital.
Visual impairment	Ethambutol Ethionamide Cycloserine Linezolid	Stop Ethambutol. If on MDR-TB treatment, refer to MDR-TB treatment centre.
Thrombocytopenia Anaemia	Rifampicin Linezolid	Stop Rifampicin or Linezolid. If on MDR-TB treatment, refer to MDR-TB treatment centre.
Tinnitus Hearing loss Acute Renal Failure	Streptomycin Amikacin Capreomycin	Stop Streptomycin Admit to hospital if renal failure If on MDR-TB treatment, refer to MDR-TB treatment centre.

OD is once a day, TDS is three times a day.

MYCOBACTERIOLOGY REQUEST AND REPORT FORM (MH 2011)

District□Facility Number: .....
OMANG/Passport (*required*): .....
MEDITE□□ number: .....
LIS Number: .....

A Specimen collected: Date____/_____/_____ Time ___/___
B Specimen collected: Date____/_____/_____ Time ___/___
C Specimen collected: Date____/_____/_____Time ___/___

SURNAME .....**FORENAME** ..... SE□ **M F AGE** .....
PATIENT□S P□□SI□AL ADDRESS .....
PATIENTS□S P□ONE NUMBER (□) .....(W)..... MOBILE NUMBER.....
CLINIC/HOSPITAL ..... **PHONE(s)** ..... **FAX** .....
DOCTOR/NURSE .....**PHONE(s)** .....**E-MAIL:** .....SIGNATURE .....

PATIENT CATEGORY **Contact**
Category I All new adult cases of TB regardless of site, bacteriology or severity of disease; and Severe TB in children.
Category II Previously treated cases of TB. Re-treatment after: **Relapse** **Default** **Treatment failure**
Category III Less severe cases of TB in children
Category IV MDR-TB cases or still sputum positive after adequately supervised retreatment regimen
HIV RESULT Positive Negative Unknown
TYPE OF SPECIMEN sputum induced sputum other (please specify) .....
TEST REQUIRED: AFB microscopy **C** ulture Drug susceptibility testing (**First line drugs** **Second line drugs**)
SPECIMEN COLLECTION PERIOD (months): 0 (diagnosis) 2 3 6 8 other (__months)

District Laboratory AFB Microscopy Result (*for specimens submitted for microscopy* ONLY): Tested by: _____

Specimen:	Lab Number	Received (Date/Time)	Appearance	Volume (ml)	Result(s)				
A	_____	D_____T_____	MP S	_____	No AFB seen	Scanty(__AFB)	1+	2+	3+
B	_____	D_____T_____	MP S	_____	No AFB seen	Scanty(__AFB)	1+	2+	3+
C	_____	D_____T_____	MP S	_____	No AFB seen	Scanty(__AFB)	1+	2+	3+

NTRL AFB Microscopy Result (*for specimens submitted for culture* ONLY):

Specimen:	Lab Number	Received (Date/Time)	Appearance	Volume (ml)	Result(s)				
A	_____	D_____T_____	MP S	_____	No AFB seen	Scanty(__AFB)	1+	2+	3+
B	_____	D_____T_____	MP S	_____	No AFB seen	Scanty(__AFB)	1+	2+	3+
C	_____	D_____T_____	MP S	_____	No AFB seen	Scanty(__AFB)	1+	2+	3+

Mycobacterial Culture (*IF RESULT "CONTAMINATED" PLEASE SUBMITANOTHER SPECIMEN*):

Method: LJ media MGIT Other _____

NTRL No:	Date Inoculated	Result(s)						Date	Read by (name):
_____	_____	Negative	Positive (	__Col	1+	2+	3+)	Contaminated	_____ _____
_____	_____	Negative	Positive (	__Col	1+	2+	3+)	Contaminated	_____ _____
_____	_____	Negative	Positive (	__Col	1+	2+	3+)	Contaminated	_____ _____

Identification Test Method: _____ **Date:** _____ **Tested by (Name):** _____
Result: ***Mycobacterium Tuberculosis*** **MOTT** _____ **Mixed Culture**
Drug Susceptibility Testing: (R – resistant, S – susceptible)

Method			First Line Drugs			
LJ	MGIT	Other _____	INH	S	RL	R□
LJ	MGIT	Other _____	STR	S	R	
LJ	MGIT	Other _____	RIF	S	R	
LJ	MGIT	Other _____	EMB	S	R	

Reported (name) _____Date_____Time _____
Signature _____

Method		Second Line Drugs				
MGIT	Other _____	PZA S R	Other _____	S	R
MGIT	Other _____	ETH S R	Other _____	S	R
MGIT	Other _____	OFL S R	Other _____	S	R
MGIT	Other _____	KAN S R	Other _____	S	R

Reported (name) _____Date_____Time _____
Signature _____

Preliminary
Final

REPORTED by (for AFB microscopy): Name _____ Date _____ Time _____ Signature _____

AUTHORISED by: Name _____ Date _____ Time _____ Signature_____

RETURN TO CLINIC/HOSPITAL

Annex 14

PMTCT PROPHYLAXIS / TREATMENT ALGORITHM

HIV-INFECTED PREGNANT WOMAN

- Seen <14 weeks of gestation → Priority CD4, WHO clinical staging and baseline tests → CD4 >350 or WHO clinical stage 1 or 2 → At 14 weeks gestation, initiate Triple ARV Prophylaxis → TDF+FTC+EFV If poor renal function AZT+3TC+LPV/r → At Labour: Supplemental AZT 300mg 3hourly, not exceeding 1500mg
- Seen ≥14 weeks but <28 weeks of gestation → Priority CD4, WHO clinical staging and baseline tests → CD4 ≤350 or WHO clinical stage 3 or 4 → Initiate ART → TDF+FTC+EFV If poor renal function and CD4>250 AZT+3TC+LPV/r → At Labour: Supplemental AZT 300mg 3hourly, not exceeding 1500mg
- Seen ≥28 weeks gestation : Initiate AZT → CD4 >350 or WHO clinical stage 1 or 2 → Switch to Triple ARV Prophylaxis → TDF+FTC+EFV If poor renal function and Cd4≤250 AZT+3TC+NVP → At Labour: Supplemental AZT 300mg 3hourly, not exceeding 1500mg
- Seen at onset of or in labour → Give sd-NVP+AZT 300mg 3 hourly, not exceeding 1500mg → At Labour: Supplemental AZT 300mg 3hourly, not exceeding 1500mg

Immediate Postpartum:

- CD4 and WHO Clinical Staging
- Refer to IDCC for clinical management

Postpartum:
Continue with ART for own health & care at IDCC. Switch to current first line ART

Postpartum:

1. If formula feeding discontinue triple ARV prophylaxis @ next physicians appointment. 6 weeks postpartum
2. If breastfeeding and not eligible for ART continue triple ARV prophylaxis for up to 6 months and encourage early weaning.
3. All breast feeding mothers wishing to discontinue and exclusively formula feed, should be encouraged and supported.
4. Clinical and laboratory monitoring according to the National 2012 ART Guidelines.

HIV EXPOSED BABY

- Seen within 72 hours after delivery → AZT 4mg/kg q12 hours for 4 weeks, sd-NVP syrup 6mg
- Seen after 72 hours after delivery → Refer baby to the HIV specialist/doctor

- Infant feeding according to AFASS criteria
- Introduce complementary food at 6 months of age
- At 6 weeks: Start Cotrimaxazole, test baby

ALL NEWBORNS REGARDLESS OF MATERNAL PMTCT INTERVENTION

1. SD-NVP syrup 6mg as soon as possible after delivery, no later than 72 hrs.

   * If <35 weeks gestation or low birth weight (<2.5kg): 2mg/kg sd-NVP

2. AZT 4mg /kg q 12 hrs for 4 weeks

   * if <35 weeks gestation or weight <2.5kg: AZT 2mg /kg q12 hrs for 2 weeks, then increase to 2mg/kg q 8hrs (TDS) for the final 2 weeks

For more information contact :
PMTCT Program
Department of HIV & AIDS Prevention and Care
Ministry of Health

P/Bag 00451, Gaborone, Botswana
Tel : 363 2051; 363 2312; 363 2318; 363 2316
email : kokeapoletswe@gov.bw; cpetlo@gov.bw; kmolefi@gov.bw; jtlale@gov.bw
www.hiv.gov.bw

How to Stop Breastfeeding Early

All HIV infected breastfeeding mothers should be reassessed at or just before the baby is six months of age to find out if formula feeding may have become AFASS for the mother and her infant. Formula feeding is considered AFASS only if the mother meets all five of the AFASS criteria. HIV infected mothers for whom formula feeding has become AFASS may consider stopping breastfeeding when baby is about six months of age and transitioning to formula.

Reasons for breastfeeding cessation at six months include the following:

Early cessation of breastfeeding:
Responsibility of healthcare workers

Healthcare workers that encourage women to wean their infants before they are six months of age are potentially putting the life of the infant at risk.

No women with a six month old infant should be encouraged to stop breastfeeding unless the healthcare worker is convinced that she meets all five of the AFASS criteria. Even then, that mother will need support to stop breastfeeding early.

- The mother may need to return to work
- The mother may wish to discontinue her baby's risk of MTCT

Gven the advantages of breastfeeding and the risks associated with formula feeding; only women for whom formula feeding is AFASS should be encouraged to stop breastfeeding from 6 months of baby's age. There are no advantages to early cessation before six months of baby's age and mothers of infants known to be HIV infected should breastfeed for two years and beyond.

Early cessation is not advisable, even after 6 months, if formula feeding is not AFASS. Risks of transitioning before the mother or infant are ready include malnutrition, illness (diarrhoea) and even early death. Healthcare workers are responsible for ensuring that their AFASS assessment is undertaken in a manner that solicits honest and accurate responses for clients and providing mothers with information that supports breastfeeding if their situation is not yet AFASS.

Early cessation of breastfeeding is not recommended for infants who are already infected with HIV. If the infant is diagnosed with HIV infection based on a presumptive diagnosis or through HIV testing, the mother should be encouraged to continue exclusive breastfeeding until 6 months and then continue breastfeeding for two years and beyond with the introduction of safe, nutritious complementary foods.

How to stop breastfeeding early

Rapid transition from breastfeeding to formula feeding is NOT recommended. Rapidly stopping breastfeeding can be traumatic for the woman and can cause problems for the infant, such as dehydration (not having enough liquid), refusal to eat, the loss of sucking comfort, weight loss and malnutrition, and these can increase the risk of HIV transmission. Common problems for the woman

include breast engorgement, mastitis, depression, increased risk of pregnancy, increased risk of HIV transmission during the transition and stigmatisation. Support from the woman's family members may make the transition easier.

The transition from breast milk to infant formula should be gradual and take place over a period of one month. Before starting the process of early cessation, mothers who are infected with HIV should receive psychosocial support, infant nutrition information and support and guidance to maintain breast health. She will require support to avoid mixed feeding. Suggestions for easing the transition appear below.

Making the transition from exclusive breastfeeding to replacement feeding

1. Accustom the infant to cup feeding with expressed breast milk. This milk may be heat-treated to destroy the HIV.

- Have the mother feed expressed breast milk to the infant by cup between breastfeeds.
- If the infant refuses the expressed breast milk in a cup, have another caregiver try.
- If the infant still refuses the expressed breast milk, wait until the infant is very hungry and try again.
- Repeat these steps until the infant readily takes breast milk from a cup.
- Once the infant readily takes breast milk from the cup, eliminate one breastfeeding, feeding the infant instead with a cup of expressed milk.

2. Replace breastfeeding with cup feeding. From this point on, it is best to heat-treat the breast milk.

- First, replace a single breastfeed with heat-treated expressed breast milk.
- Once the infant accepts milk from the cup, eventually replace two or three breastfeeds with heat-treated expressed breast milk or a breast-milk substitute.
- Breastfeed for the last time when ready to replace all feeds with heat-treated expressed breast milk or a breast-milk substitute.
- Finally, once the infant adjusts to the breast-milk substitute, stop expressing breast milk and feed the infant only the breast-milk substitute.
- Do not replace milk feedings with family foods until the transition away from breastfeeding has been completed and the infant is six months of age and growing well.

3. Monitor the infant's urine output to ensure that the infant is taking in enough milk during transition and after starting replacement feeding. Infants less than 6 months should be urinating at least 6 times every 24 hours.

4. Find alternative means to comfort the infant during day and night.

- Help the baby to sleep through the night to avoid night time food preparation and feeding. Feed your baby late in the evening as part of a late evening ritual of bathing, cuddling and feeding.
- As feedings are reduced, find alternative ways to meet the infant's suckling needs, such as sucking on the mother's or infant's finger or forearm or sucking a special toy or cloth that is always kept clean.
- Comfort the infant when he or she wakens by rocking, singing, carrying or massaging him/her. If comforting alone is insufficient to soothe the infant, have the mother or other caregiver feed the infant with expressed milk in a cup during the night.

5. Provide the mother adequate support and care to avoid complications of early, rapid breastfeeding cessation.

- Prevent and treat breast engorgement.
- Provide supportive counselling and education on how to feed and care for non-breastfed infants.
- Instruct the mother to not begin breastfeeding again once she has stopped. If she breastfeeds after introducing formula feeding, the risk of HIV transmission is greater than if she were still exclusively breastfeeding.
- If she has not already done so, encourage the mother to begin using a family planning method as soon as the breastfeeds are reduced.

When the mother comes back for a follow-up visit, discuss the following:

- What has she been feeding her baby instead of breast milk, and how has she been pre paring it?
- What has she been doing to help her baby sleep?
- How has she been comforting her baby when he or she cries?
- How has she dealt with depression?
- How has she coped or how is she coping with any breast problems (engorgement, mastitis)?

Adapted from:

- WHO, UNICEF and USAID. 2005. *HIV and Infant feeding Counselling Tools: Reference Guide. Available at: http://whqlibdoc.who.int/publications/2005/9241593016.pdf*
- USAID. 2001. *Issues, Risks and Challenges of Early Breastfeeding Cessation to Reduce Postnatal Transmission of HIV in Africa. Available at: http://www.aed.org/ghpnpubs/publications/4-issuesriskschallengesbreastfeedingcessation.pdf*

Pediatric Fixed Dose Combination Formulations

FORMULATION	3-3.9KG	4-5.9KG	6-9.9KG	10-13.9KG	14-19.9KG	20-24.9KG	25-39.9KG	≥40 KG
AZT/3TC/NVP (60/30/50) Triple paed FDC	1 BD	1 BD	1½ BD	2 BD	2½ BD	3 BD	Adult FDC 1 BD	Adult FDC 1 BD
AZT/3TC (60/30) Dual paed FDC	1 BD	1 BD	1½ BD	2 BD	2½ BD	3 BD	Adult dual 1 BD	Adult dual 1 BD
EFV (>3yrs)	Not recommended			200 mg PM	300 mg PM	300 mg PM	400 mg PM	600 mg PM
ABC/3TC (60/30)	1 BD	1 BD	1½ BD	2 BD	2½ BD	3 BD	Adult dual 1 BD	Adult dual 1 BD

Sexual Maturity Rating - Tanner Staging

Stage	Age Range (Yrs)	Breast Growth	Pubic Hair Growth	Other Changes	Age Range (Yrs)	Testes Growth	Penis Growth	Pubic Hair Growth	Other Changes
I	0 - 15	Pre-adolescent	None	Preadolescent	0 - 15	Pre-adolescent testes (¤2.5 cm)	Preadolescent	None	Pre-adolescent
II	8 - 15	Breast budding (thelarche); areolar hyperplasia with small amount of breast tissue	Long downy pubic hair near the labia, often appearing with breast budding or several weeks or months later	Peak growth velocity often occurs soon after Stage II	10 - 15	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long, downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable
III	10 - 15	Further enlargement of breast tissue & areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls in late stage III	10.5 - 16.5	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	Not applicable
IV	10 - 17	Separation of contours; areola & nipple form secondary mound above breast tissue	Adult in type, but not in distribution	Menarche occurs in most girls in Stage IV, 1 - 3 years after thelarche	Variable: 12 - 17	Further enlargement	Further enlargement, especially in diameter	Adult in type, but not in distribution	Development of axillary hair and some facial hair
V	12.5 -18	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in Stage V	13 - 18	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs, linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period

Pediatric Antiretroviral Dosing in Resource - Limited Settings

BIPAI: Adapted from: Baylor International Pediatric AIDS Initiative

Weight range (kg)	Abacavir (Ziagen®, ABC)		Didanosine (Videx®, DDI)			Lamivudine (Epivir®, 3TC)		Stavudine (Zerit®, d4T)		Zidovudine (Retrovir®, ZDV, AZT)		
	8 mg/kg/dose TWICE daily		90-120 mg/ m^2/dose TWICE daily	120 mg/ m^2/dose TWICE daily	180-240 mg/ m^2/dose ONCE daily	4 mg/kg/dose TWICE daily		1 mg/kg/dose TWICE daily		180-240 mg/m^2/dose TWICE daily		
	20 mg/ml solution	300 mg tablets	10 mg/ml suspension	25, 50, 100 mg chewable tablets	125, 200, 250, 400 mg EC capsules	10 mg/ml solution	150 mg tablets	1 mg/ml solution	15, 20, 30 mg capsules	10 mg/ml syrup	100 mg capsules	300 mg tablets
5 - 5.9	2 ml		4 ml	25 mg + 25 mg tabs		3 ml		6 ml		6 ml		
6 - 6.9	3 ml		5 ml	25 mg + 25 mg tabs		3 ml		7 ml	10 mg (as 0.5 x 20 mg)	7 ml		
7 - 7.9	4 ml		6 ml	25 mg + 25 mg tabs		4 ml		8 ml	10 mg (as 0.5 x 20 mg)	8 ml		
8 - 8.9	4 ml		6 ml	25 mg + 25 mg tabs		4 ml		9 ml	10 mg (as 0.5 x 20 mg)	9 ml	1 cap	
9 - 9.9	4 ml		6 ml	25 mg + 25 mg tabs		4 ml		10 ml	10 mg (as 0.5 x 20 mg)	10 ml	1 cap	
10 - 10.9	5 ml		6 ml	50 mg + 25 mg tabs in am 25 mg +25 mg tabs in pm	125 mg EC cap	5 ml			15 mg cap	10 ml	1 cap	
11 - 11.9	5 ml	0.5 tab	7 ml	50 mg + 25 mg tabs	125 mg EC cap	5 ml			15 mg cap	10 ml	1 cap	
12 - 13.9	6 ml	0.5 tab	7 ml	50 mg + 25 mg tabs	125 mg EC cap	6 ml	0.5 tab		15 mg cap	11 ml	1 cap	
14 - 16.9		0.5 tab	8 ml	50 mg + 50 mg tabs in am 50 mg + 25 mg tabs in pm	200 mg EC cap		0.5 tab		20 mg cap		2 caps in am 1 cap in pm	0.5 tab
17 - 19.9		0.5 tab	9 ml	50 mg + 50 mg tabs	200 mg EC cap		0.5 tab		20 mg cap		2 caps in am 1 cap in pm	0.5 tab
20 - 24.9		1 tab in am 0.5 tab in pm		100 mg + 25 mg tabs	250 mg EC cap		1 tab in am 0.5 tab in pm		20 mg cap		2 caps	0.5 tab
25 - 29.9		1 tab		100 mg + 25 mg tabs	250 mg EC cap		1 tab		30 mg cap		2 caps	1 tab in am 0.5 tab in pm
30 - 34.9		1 tab		100 mg + 25 mg tabs	250 mg EC cap		1 tab		30 mg cap		3 caps	1 tab
35- 39.9		1 tab		100 mg + 25 mg tabs	250 mg EC cap		1 tab		30 mg cap		3 caps	1 tab

Weight range (kg)	Efavirenz (Stocrin®, Sustiva®, EFV)	Nevirapine (Viramune®, NVP)				Lopinavir/ritonavir (Kaletra®, LPV/r)			Ritonavir (Norvir®, RTV)	
	Dose as shown ONCE daily for children 3 YEARS AND OLDER	INDUCTION DOSE: 160-200 mg/m^2/dose ONCE daily		MAINTENANCE DOSE: 160-200 mg/m^2/dose TWICE daily		10-16 mg/kg/dose TWICE daily			STARTING DOSE: 250 mg/m^2/dose TWICE daily	MAINTENANCE DOSE: 400 mg/m^2/dose TWICE daily
	50, 100, 200 mg capsules, 600 mg tablets	10 mg/ml suspension	200 mg tablets	10 mg/ml suspension	200 mg tablets	80 mg lopinavir/ 20 mg ritonavir per ml solution	133 mg lopinavir/ 33 mg ritonavir capsules	200 mg lopinavir/ 50 mg ritonavir tablets	80 mg/ml solution	80 mg/ml solution
5 - 5.9		6 ml		6 ml		1 ml			1 ml	1.5 ml
6 - 6.9		7 ml		7 ml		1.5 ml			1 ml	2 ml
7 - 7.9		8 ml		8 ml		1.5 ml	1 cap		1 ml	2 ml
8 - 8.9		9 ml		9 ml		2 ml	1 cap		1.5 ml	2 ml
9 - 9.9		9 ml	0.5 tab	9 ml	0.5 tab	2 ml	1 cap		1.5 ml	2.5 ml
10 - 10.9	200 mg cap	10 ml	0.5 tab	10 ml	0.5 tab	2 ml	1 cap		1.5 ml	2.5 ml
11 - 11.9	200 mg cap	10 ml	0.5 tab	10 ml	0.5 tab	2 ml	1 cap		1.5 ml	2.5 ml
12 - 13.9	200 mg cap	11 ml	0.5 tab	11 ml	0.5 tab	2 ml	2 caps in am 1 cap in pm	1 tab	1.5 ml	3 ml
14 - 16.9	200 mg + 50 mg caps		0.5 tab		1 tab in am 0.5 tab in pm	2 ml	2 caps in am 1 cap in pm	1 tab	2 ml	3 ml
17 - 19.9	200 mg + 50 mg caps		1 tab		1 tab in am 0.5 tab in pm	2.5 ml	2 caps in am 1 cap in pm	1 tab		
20 - 24.9	200 mg + 100 mg caps		1 tab		1 tab in am 0.5 tab in pm	3 ml	2 caps	1 tab		
25 - 29.9	200 mg + 100 mg + 50 mg caps		1 tab		1 tab	3.5 ml	2 caps	2 tabs in am 1 tab in pm		
30 - 34.9	200 mg cap (x2)		1 tab		1 tab	4 ml	3 caps	2 tabs		
35- 39.9	200 mg cap (x2)		1 tab		1 tab	5 ml	3 caps	2 tabs		

This dosing card contains information on pediatric ARV drugs commonly used in resource-limited settings for which there are pediatric formulations or sufficient information and evidence to provide guidance on prescribing and dosing. The weight based tables were compiled by estimation of the body surface area, and decisions about dosing are based on the manufacturer's information, ARV drug formulation, data from clinical trials and expert pediatric pharmacology consultation. Optimal dosing is given for single ARV drugs and where possible combination solid fixed dose combinations.

ABACAVIR (Ziagen®, ABC)

Formulations

Oral solution: 20 mg/ml; Tablet: 300 mg

Dosing

Target dose: <16 years or <37.5 kg: 8 mg/kg/dose twice daily
Maximum dose: >16 years or ≥37.5 kg: 300 mg/dose twice daily
Note: Once-daily dosing is not yet approved for children.

General comments

Parents must be warned about potential hypersensitivity reaction. ABC should be stopped permanently if hypersensitivity reaction occurs. No food restrictions.
Tablets: Can be crushed and contents mixed with small amount water or food and immediately ingested. Store at room temperature of 20°C to 25°C.
Oral solution: Store at room temperature of 20°C to 25°C; may be refrigerated.

DIDANOSINE (Videx®, DDI)

Formulations

Pediatric powder for oral solution: 10 mg/ml when reconstituted with water (in many countries must be made up with additional antacid)
Chewable tablets: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg
Enteric-coated beadlets in capsules (EC): 125 mg, 200 mg, 250 mg, 400 mg (designed for once-daily dosing)

Dosing

Target dose: <3 months: 50 mg/m^2/dose twice daily
Target dose: ≥ 3 months <13 years: 90 - 120 mg/m^2/dose twice daily
Maximum dose: ≥13 years or >60 kg: 200 mg/dose twice daily or 400 mg once daily.
Once-daily dosing for chewable tablets is authorized in United Kingdom for children >6 years.

General comments

DDI is degraded rapidly unless given as an enteric formulation or combined with buffering agents or antacids. It is recommended to administer ddl 30 minutes before or two hours after meals.
Oral suspension: Difficult to use and should be avoided. Must be kept refrigerated; stable for 30 days; must be well shaken.
Tablets: At least two tablets of appropriate strength must be used at any one time for adequate buffering (e.g. if the child's dose is 50 mg, administer two 25 mg tablets instead of one 50-mg tablet). Tablets should be chewed, crushed or dispersed in water before they are taken; should not be swallowed whole.
Enteric-coated beadlets in capsules: Can be opened and sprinkled on a small amount of food.

LAMIVUDINE (Epivir®, 3TC)

Formulations

Oral solution: 10 mg/ml; Tablet: 150 mg

Dosing

Target dose: 4 mg/kg/dose twice daily to a maximum of 150 mg/dose twice daily
Dose at <30 days: 2 mg/kg/dose twice daily
Dose at ≥30 days: 4 mg/kg/dose twice daily
Dose at >50 kg: 150 mg/dose twice daily
Once-daily dosing is not yet approved for children.

General comments

Well tolerated, no food restrictions. Also active against hepatitis B.
Oral solution: Store solution at room temperature (i.e. 25 °C). Use within one month of opening.
Tablets: Store at 25 °C (permitted range: 15 °C to 30 °C). Can be crushed and contents mixed with a small amount of water or food and immediately taken.

STAVUDINE (Zerit®, d4T)

Formulations

Oral solution: 1 mg/ml; Capsules: 15 mg, 20 mg, 30 mg, 40 mg

Dosing

Target dose: 1 mg/kg
Dose at <30 kg: 1 mg/kg/dose twice daily
Dose at 30 to 60 kg: 30 mg/dose twice daily
Maximum dose at >60 kg: 40 mg/dose twice daily

General comments

Well tolerated. Do not use d4T with ZDV due to antagonistic effect.
Oral solution: Palatable and well tolerated but requires refrigeration after reconstitution. Powder for oral solution should be protected from excessive moisture and stored in tightly closed containers at 25°C (permitted range: 15°C to 30°C). After constitution, needs refrigeration and storage in original container; discard any unused portion after 30 days. Must be well shaken before use.
Capsules: Can be opened and mixed with small amount of food or water (stable in solution for 24 hours if kept refrigerated).

ZIDOVUDINE (Retrovir®, ZDV, AZT)

Formulations

Syrup: 10 mg/ml; Capsules: 100 mg and 250 mg sizes; Tablet: 300 mg

Dosing

Target dose for infants >6 weeks old: 180-240 mg/m^2 per dose given twice daily (total daily dose of 360-480 mg/m^2)
Maximum dose: 300 mg/dose twice daily

General comments

For children with suspected nervous system involvement, a dose of 240mg/m^2 per dose given twice daily may be beneficial. Do not use d4T with ZDV due to antagonistic effect. No food restrictions. Use with caution in children with anaemia due to potential for bone marrow suppression.
Syrup: Stable at room temperature but light-sensitive; store in glass jar.
Capsules: May be opened and dispersed in water or on to a small amount of food and immediately ingested. Store at 15°C to 25°C.
Tablets: 300mg tablets are often not scored; may be cut in half with a tablet splitter in a pharmacy. Tablets may be crushed and combined with a small amount of food or water and immediately ingested. Store at 15°C to 25°C.

EFAVIRENZ (Stocrin®, Sustiva®, EFV)

Formulations

Syrup: 30 mg/ml. Note: syrup has lower bioavailability and ratio of 1.3 syrup to solid formulation is suggested to achieve an equivalent dose.
Capsules: 50 mg, 100 mg, 200 mg; Tablets: 600 mg

Dosing

Target dose for children >3years: 19.5 mg/kg/day (syrup) or 15 mg/kg/day (capsule/tablet)
Weight >40 kg: 600 mg once daily

General comments

EFV is not approved for children <3 years. Store at 25°C (permitted range: 15°C to 30°C). EFV can be given with food but if taken with food, especially high-fat meals, absorption is increased by an average of 50%. Best given at bedtime to reduce CNS side-effects, especially during first two weeks.
Capsules: May be opened and added to small amount of food or liquid; they have a very peppery taste but can be mixed with sweet foods to disguise taste.

NEVIRAPINE (Viramune®, NVP)

Formulations

Oral suspension: 10 mg/ml; Tablet: 200 mg

Dosing

Target dosing for maintenance: 160-200 mg/m^2/dose to a maximum dose of 200 mg taken twice daily
Special considerations on dosing:
a) Induction dose: once daily for first 14 days; it is generally half the daily maintenance dose given once daily except where the maintenance dose is divided unequally between a.m. and p.m.
b) Maintenance dose: 160 - 200 mg/m^2 given twice daily adjusted for more aggressive dosing in younger ages.
c) For children 14-24.9 kg: the suggested dose is 1 tablet a.m. and 0.5 tablet p.m.

If a mild rash occurs during the first 14 days of induction dosing, continue once daily dosing and only escalate dose once the rash has subsided and the dose is well tolerated. If a severe rash occurs (especially if accompanied by fever, blistering or mucosal ulcerations), discontinue drug.

General comments

Parents must be warned about a potential severe, life-threatening rash during the 14-day lead-in period. The once-daily induction dose is used to reduce the frequency of rash. NVP should be permanently discontinued and not restarted in children who develop severe rash. Drug interactions: avoid nevirapine if rifampicin is coadministered. Can be given without regard to food. Store at 25°C (permitted range 15°C to 30°C).

Oral suspension: Must be well shaken.

Tablets: Are scored and can be divided into two equal parts to give a 100 mg dose; can be crushed and combined with a small amount of water or food and immediately administered.

LOPINAVIR/RITONAVIR (Kaletra®, LPV/r)

Formulations

Oral solution: 80 mg/ml lopinavir plus 20 mg/ml ritonavir
Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir
Tablets: 200 mg lopinavir plus 50 mg ritonavir

Dosing

Lopinavir target doses:
5-7.9 kg: 16 mg/kg/dose twice daily; 8-9.9 kg: 14 mg/kg/dose twice daily
10-13.9 kg: 12 mg/kg/dose twice daily; 14-39.9 kg: 10 mg/kg/dose twice daily
Ritonavir target doses:
7-15 kg: 3 mg/kg/dose twice daily; 15-40 kg: 2.5 mg/kg/dose twice daily
Maximum dose: 400 mg lopinavir plus 100 mg ritonavir twice daily

General comments

Should be taken with food. Oral solution and capsules should be refrigerated; however, can be stored at room temperature up to 25°C for two months; at >25°C drug degrades more rapidly. There are many drug-to-drug interactions because RTV inhibits cytochrome P450.

Oral solutions: Low volume but bitter taste.

Capsules: Large. Should not be crushed or opened; must be swallowed whole.

Tablets: No food restrictions although bioavailability is increased when administered with food. Cannot be split.

RITONAVIR (Norvir®, RTV)

Formulations

Oral solution: 80 mg/ml; Capsule: 100 mg

Dosing (from Norvir® package insert)

Rarely used as sole PI except for TB co-treatment in children < 3 years.
Target Dose: > 1 month: 350-400 mg/m^2 /dose twice daily. Maximum dose 600 mg twice daily (when used as single PI therapy).
Special considerations on dosing: Initiate therapy at 250 mg/m^2/dose twice daily and increase as tolerated to full dose over 5 days. Usually used at lower doses as a pharmacokinetic enhancer with other PIs.

General comments

Should be taken with food. Techniques to increase tolerance in children; mix oral solution with milk, dull taste buds with ice chips, coat mouth with peanut butter, follow dose with strong-tasting food such as cheese or gum. There are many drug-drug interactions because it is a potent inhibitor of cytochrome P450.

Oral solution: Low volume but bitter taste. Do not refrigerate, store at room temperature (20°-25°C) in original container, limited shelf life of 6 months.

Capsule: Should be refrigerated, can store at room temperature 25°C if used within 30 days.

STAVUDINE (d4T) + LAMIVUDINE (3TC)

Formulations

Oral solution: stavudine 10 mg plus lamivudine 40 mg/5ml
Tablets: d4T (40 mg) plus 3TC (150 mg) or d4T (30 mg) plus 3TC (150 mg)

Dosing

Target dose: stavudine: 1 mg/kg/dose twice daily; lamivudine: 4 mg/kg/dose twice daily
Maximum dose: One 40 mg d4T-based tablet twice daily

General comments

See comments under individual drug components.

Tablets: Preferably, should not be split unless scored.

STAVUDINE (d4T) + LAMIVUDINE (3TC) + NEVIRAPINE (NVP)

Formulations

Tablet: d4T (40 mg) plus 3TC (150 mg) plus NVP (200 mg) or
d4T (30 mg) plus 3TC (150 mg) plus NVP (200 mg)
As of June 2006 not yet WHO prequalified:
Tablet: 6 mg stavudine / 30 mg lamivudine / 50 mg nevirapine (baby)
Tablet: 12 mg stavudine / 60 mg lamivudine / 100 mg nevirapine (junior)
Suspension: stavudine 10 mg/5 ml plus lamivudine 40 mg plus neviraprine 70 mg

Dosing

Target dose: stavudine: 1 mg/kg/dose twice daily; lamivudine: 4 mg/kg/dose twice daily; nevirapine: 160-200 mg/m^2/dose twice daily
Maximum dose: One 40 mg d4T-based tablet twice daily

General comments

Contains a fixed dose of NVP, therefore cannot be used for nevirapine induction as nevirapine dose escalation required (see NVP dosing recommendations). See comments under individual drug components.

Tablets: Preferably, should not be split unless scored.

ZIDOVUDINE (ZDV) + LAMIVUDINE (3TC) (Combivir®)

Formulation

Tablet: ZDV (300 mg) plus 3TC (150 mg)

Dosing

Target dose:
Zidovudine: 180 - 240 mg/m^2/dose twice daily
Lamivudine: 4 mg/kg/dose twice daily
Maximum dose: 1 tablet/dose twice daily

General comments

See comments under individual drug components.

Tablets: No food restrictions. Can be crushed and contents mixed with a small amount of water or food and immediately taken. Store between 2°C and 30°C.

ZIDOVUDINE (ZDV) + LAMIVUDINE (3TC) + ABACAVIR (ABC) (Trizivir®)

Formulation

Tablet: ZDV (300 mg) plus 3TC (150 mg) plus ABC (300 mg)

Dosing

Target dose:
Zidovudine: 180-240 mg/m^2/dose twice daily;
Lamivudine: 4 mg/kg/dose twice daily; Abacavir: 8 mg/kg/dose twice daily
Maximum dose: 1 tablet/dose twice daily

General comments

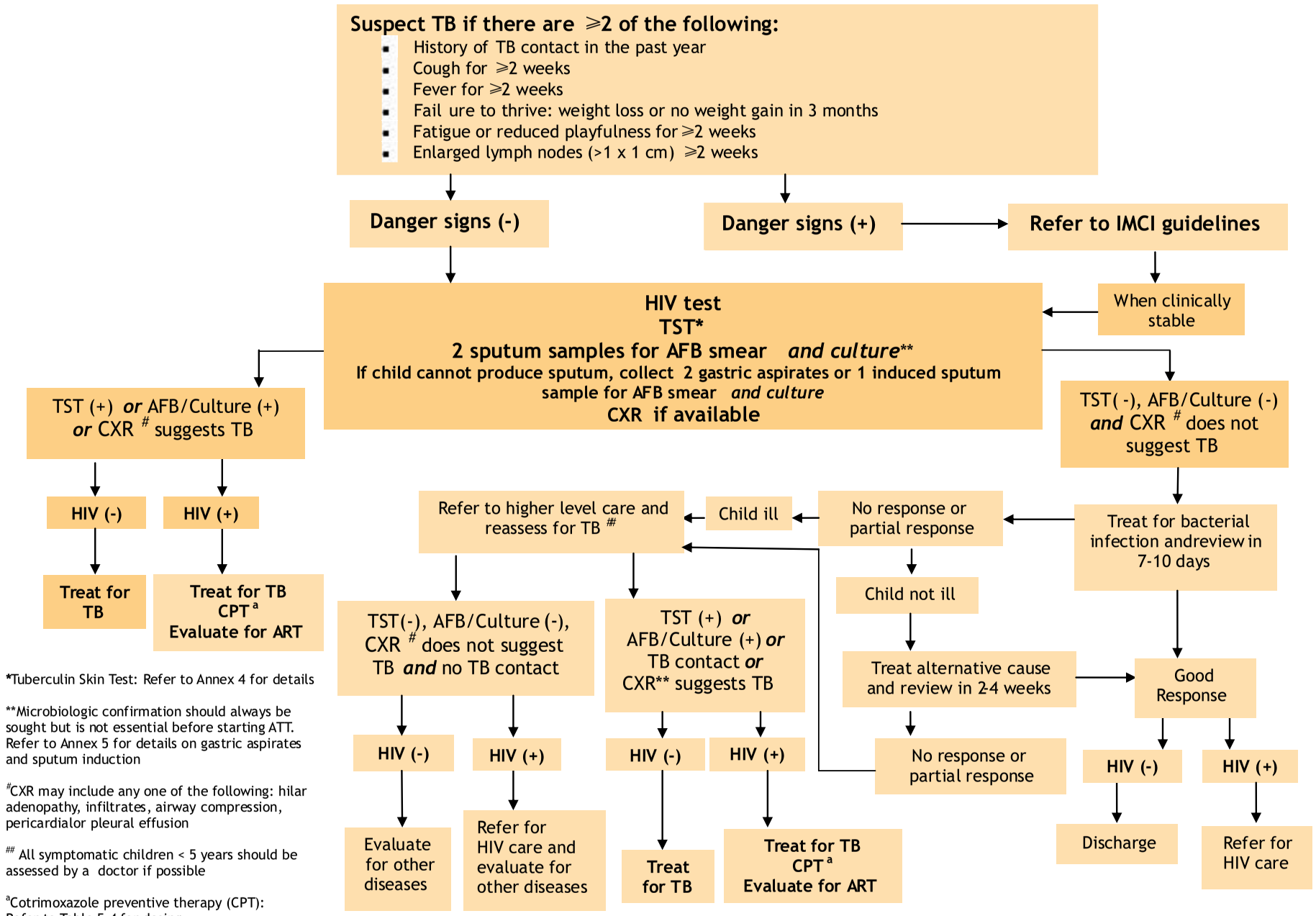
See comments under individual drug components. Parents must be warned about potential hypersensitivity reaction. ABC should be stopped permanently if hypersensitivity reaction occurs.

Tablets: Should not be split.

TRIMETHOPRIM/SULFAMETHOXAZOLE (Cotrimoxazole, Septrim®, Bactrim®, TMP/SMZ)

Annex 19

Diagnostic Algorithm for Pulmonary TB in Children under 12 years



*Tuberculin Skin Test: Refer to Annex 4 for details

**Microbiologic confirmation should always be sought but is not essential before starting ATT. Refer to Annex 5 for details on gastric aspirates and sputum induction

#CXR may include any one of the following: hilar adenopathy, infiltrates, airway compression, pericardialor pleural effusion

All symptomatic children < 5 years should be assessed by a doctor if possible

aCotrimoxazole preventive therapy (CPT): Refer to Table 5.4 for dosing

Princess Marina Hospital, Gaborone, Botswana.
TEL: +267 390 2671 FAX: +267 390 1284

GENOTYPIC RESISTANCE TESTING REQUEST

SITE NAME: **SITE CODE:**

INSTRUCTIONS: Please print in block letters.

PATIENT DETAILS

OMANG / Birth Certificate Number:
- - -
CM/MASA File Number:

DATE of BIRTH:
– –
d d - m m - y y y y

GENDER
M or F
M F

PATIENT SURNAME:

PATIENT FIRST NAME/S:

CLINICIAN REQUESTING TEST

INITIALS

SURNAME:

SIGNATURE:

SPECIMEN DETAILS

Tube Type
R **PURPLE**

DATE DRAWN
/ / 2 0
d d / m m / y y y y

PHLEBOTOMIST.
SURNAME_____

LABORATORY.
DATE RECEIVED
/ / 2 0
d d / m m / y y y y

DATE TESTED
/ / 2 0
d d / m m / y y y y

VIRAL LOAD: _____**RNA copies/ml**

DATE: _____

Continued to Genotyping: Y/N

LABORATORY SCIENTIST/TECHNOLOGIST:

SURNAME:_____

INITIALS: _____ **SIGNATURE:** _____

PLEASE TURN TO NEXT PAGE FOR PATIENT HISTORY

Virological Failure Clinical History Sheet: Completed by (circle): DOCTOR/NURSE

Clinic/ART Site: _____ Clinic file # _____

PT NAME: _____ OMANG # _ _ _ _ _ _ _ _ _ MALE/FEMALE

Date of Birth: Pediatrics: Height at last visit: _____ cm

D D M M Y Y Weight at last visit: _____ kg

History of sdNVP: (circle) Yes/No Date: _____

1) Most Recent Viral load and CD4 Result s (if possible attach computer printout):

Dates	4 Count	Viral Load result	Weight (KG)	History of Previous Resistance Testing	
				te:	viewed by:
				te:	

2) History of Antiretroviral Therapy: (Continue on the next page if necessary)

Dates	Regimen/Drugs	Reasons for Treatment Switch/Toxicities
FROM: M M Y Y TO: M M Y Y	i. AZT ☐ v. TDF ☐ ix. NVP ☐ ii. 3TC ☐ vi. ABC ☐ x. EFV ☐ iii. D4T ☐ vii RAL ☐ xi. LPV/r ☐ iv. DDI ☐ viii DAR ☐ xii. SQR ☐ xiii RIT ☐	Poor Adherence ☐ Defaulting ☐ Drug toxicity ☐ Drug: _____ Reaction: _____ GI issues: vomiting/ diarrhea/wasting/ malabsorption ☐ Single Dose NVP ☐ Drug/Drug Interactions ☐ Psycho-Social issues ☐ Non-Disclosure/stigma ☐ Other:
FROM: M M Y Y TO: M M Y Y	i. AZT ☐ v. TDF ☐ ix. NVP ☐ ii. 3TC ☐ vi. ABC ☐ x. EFV ☐ iii. D4T ☐ vii RAL ☐ xi. LPV/r ☐ iv. DDI ☐ viii DAR ☐ xii. SQR ☐ xiii RIT ☐	Poor Adherence ☐ Defaulting ☐ Drug toxicity ☐ Drug: _____ Reaction: _____ GI issues: vomiting/ diarrhea/wasting/ malabsorption ☐ Single Dose NVP ☐ Drug/Drug Interactions ☐ Psycho-Social issues ☐ Non-Disclosure/stigma ☐ Other:
FROM: M M Y Y TO: M M Y Y	i. AZT ☐ v. TDF ☐ ix. NVP ☐ ii. 3TC ☐ vi. ABC ☐ x. EFV ☐ iii. D4T ☐ vii RAL ☐ xi. LPV/r ☐ iv. DDI ☐ viii DAR ☐ xii. SQR ☐ xiii RIT ☐	Poor Adherence ☐ Defaulting ☐ Drug toxicity ☐ Drug: _____ Reaction: _____ GI issues: vomiting/ diarrhea/wasting/ malabsorption ☐ Single Dose NVP ☐ Drug/Drug Interactions ☐ Psycho-Social issues ☐ Non-Disclosure/stigma ☐ Other:

3) Other current medications: (Anti-epileptics, Steroids, Warfarin, Statins particularly important)

1.	2.	3.

4 History of TB therapy:

Start Date				Regimen/Drugs
M	M	Y	Y	i. 1 st Line ☐ ii. Retreat ☐ iii. MDR ☐
Completion Date				Notes:

5 Most Recent Blood Results:

Dates		Calculated Creatinine Clearance	HB	ALT/AST
M	Y			
M	Y	Other significant Labs:		

6. Adherence Review:

- Has the patient experiences any side-effects to ART? **YES/NO**
- Do they have an adherence partner/mompati? **YES/NO**
- Have they completed adherence counseling? **YES/NO**
- Do they use traditional remedies/ immune boosters? **YES/NO**
- Hepatitis B Status: POS/NEG/NOT TESTED
- Alcohol consumption: NONE/AVERAGE/HEAVY (>3 drinks most days of the week)
- Currently Pregnant? **YES/NO**
- Has there been any exposure to Single Dose NVP at delivery? **YES/NO**

  If YES; Year(s) :___ _____

- Patient estimate of adherence in last 3 months:

  GOOD (>90% doses taken) **LESS GOOD** (<90%) **POOR** (<50%)

Other Co-morbidities:_____

Summary:

_____
_____
_____
_____
_____
_____
_____
_____

Annex 21

Interactions between antineoplastic therapy (chemotherapy and radiation) and antiretroviral therapy.

Understanding of possible interactions between chemotherapy and antiretroviral agents remains limited and is a priority for future research. Possible interactions described in this table are drawn from several sources including package inserts, Micromedex, published reports, and expert opinion. Interested readers are directed to two useful review articles: Rudek MA et al. Lancet Oncology 2011, 12:905-12 and Antoniou T and Tseng AL. Clinical Pharmatockinetics 2005, 44:111-145.

	Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)						Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		Protease Inhibitors (PIs)		Others	
	TDF	FTC/3TC	ABC	D4T	DDI	ZDV	EFV	NVP	LPV/r	DRV/r	RAL	TMP/SMX
Doxorubicin (DOXO, adriamycin, hydroxydaunorubicin) Frequently used for treatment of lymphoma, KS, and breast cancer.	**Caution** Potential interaction	**Caution** Potential interaction	No interaction	**Caution** Possible reduction in D4T activity	No interaction	**AVOID** Possible antagonism exacerbate cytopenias	No interaction	No interaction	No interaction	No interaction	No interaction	**Caution** May slow recovery of cytopenias
Bleomycin (BLEO) Frequently used for KS, Hodgkin's lymphoma and head & neck cancers	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction
Carboplatin (CARB) Frequently used for lung cancer, head & neck, colon, anus/ penis cancers.	**Caution** Exacerbate nephrotoxicity	No interaction	No interaction	**Caution** Exacerbate neuropathy	**Caution** Exacerbate neuropathy	**AVOID** Exacerbate cytopenias	No interaction	No interaction	No interaction	No interaction	No interaction	**Caution** May slow recovery of cytopenias
Cisplatin (CIS) Frequently used for lung cancer, head & neck, colon, anus/ penis cancers.	**AVOID** Exacerbate nephrotoxicity	No interaction	No interaction	**AVOID** Exacerbate neuropathy	**AVOID** Exacerbate neuropathy	**AVOID** Exacerbate cytopenias	No interaction	No interaction	No interaction	No interaction	No interaction	**Caution** May slow recovery of cytopenias
Cyclophosphomide (CTX, cytoxan) Frequently used for lymphoma and breast cancer.	No interaction	No interaction	No interaction	No interaction	No interaction	**AVOID** Exacerbate cytopenias	**Caution** Levels of CTX may be decreased	**Caution** Levels of CTX may be decreased	**Caution** possible interaction	**Caution** possible interaction	No interaction	**Caution** May slow recovery of cytopenias
Cytrarabine (Ara-C) Frequently used for leukemia and aggressive lymphomas.	No interaction	No interaction	No interaction	No interaction	No interaction	**AVOID** Exacerbate cytopenias	No interaction	No interaction	No interaction	No interaction	No interaction	**Caution** May slow recovery of cytopenias
Dexamethasone, prednisone, and other systemic steroids Frequently used in lymphomas and for palliation of symptoms	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	**Caution** Levels of steroid will be increased	**Caution** Levels of steroid will be increased	No interaction	No interaction

Docetaxel (Taxotere) Frequently used for breast, prostate, and lung cancers.	No interaction	No interaction	No interaction	**Caution** Exacerbate neuropathy	**Caution** Exacerbate neuropathy	**AVOID** Exacerbate cytopenias	**Caution** Levels of docetaxel are reduced	**Caution** Levels of docetaxel are reduced	**AVOID** Levels of docetaxel and toxicity increased	**AVOID** Levels of docetaxel and toxicity increased	No interaction	**Caution** May slow recovery of cytopenias
Etoposide (VP-16) Frequently used for lung cancer, Castleman's, and lymphomas.	No interaction	No interaction	No interaction	No interaction	No interaction	**AVOID** Exacerbate cytopenias	**Caution** May decrease etoposide levels	**Caution** May decrease etoposide levels	**Caution** May increase etoposide levels	**Caution** May increase etoposide levels	No interaction	**Caution** May slow recovery of cytopenias
5-Fluorouracil (5-FU) Frequently used for breast, head & neck, colon, anus/penis cancers.	No interaction	No interaction	No interaction	No interaction	No interaction	**AVOID** Exacerbate cytopenias	**Caution** possible interaction	**Caution** possible interaction	**Caution** possible interaction	**Caution** possible interaction	No interaction	**Caution** May slow recovery of cytopenias
Leucovorin Used to reduce toxicity of 5-fllourouricil	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	**AVOID** Cotrimoxazole less effective
Methotrexate (MTX) Frequently used for breast cancer and leukemia.	No interaction	No interaction	No interaction	No interaction	No interaction	**AVOID** Exacerbate cytopenias	No interaction	No interaction	No interaction	No interaction	No interaction	**Avoid** Increased toxicity of MTX
Paclitaxel (Taxol) Frequently used for breast, prostate, and lung cancers, KS.	No interaction	No interaction	No interaction	**Caution** Exacerbate neuropathy	**Caution** Exacerbate neuropathy	**AVOID** Exacerbate cytopenias	No interaction	No interaction	**Caution** Levels of paclitaxel may be increased	**Caution** Levels of paclitaxel may be increased	No interaction	**Caution** May slow recovery of cytopenias
Radiation (XRT) Frequently used for breast, cervical, and many advanced cancers.	No interaction	No interaction	No interaction	No interaction	No interaction	**Caution** Exacerbate cytopenias	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction
Rituximab (Rituxan) Frequently used for lymphomas.	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction
Tamoxifen Frequently used for breast cancer.	No interaction	No interaction	No interaction	No interaction	No interaction	No interaction	**Caution** Levels of NVP may be reduced	**Caution** Levels of EFV may be reduced	**Caution** Levels of LPV/r may be reduced	**Caution** Levels of DRV/r may be reduced	No interaction	No interaction
Vincristine (VINC, VNC, oncovin) Frequently used for KS and lymphoma.	**Caution** possible interaction	**Caution** possible interaction	No interaction	**AVOID** Exacerbate neuropathy	**AVOID** Exacerbate neuropathy	**AVOID** exacerbate cytopenias	**Caution** May decrease vincristine levels	**Caution** May decrease vincristine levels	**Caution** Increased vincristine may increase neuropathy	**Caution** Increased vincristine may increase neuropathy	No interaction	**Caution** May slow recovery of cytopenias
Vinblastine Frequently used for KS, breast cancer, and lymphoma.	**Caution** possible interaction	**Caution** possible interaction	No interaction	**AVOID** Exacerbate neuropathy	**AVOID** Exacerbate neuropathy	**AVOID** exacerbate cytopenias	**Caution** May decrease vincristine levels	**Caution** May decrease vincristine levels	**Caution** Increased vincristine may increase neuropathy	**Caution** Increased vincristine may increase neuropathy	No interaction	**Caution** May slow recovery of cytopenias

MH 2071

HOME BASED CARE PROGRAMME REFERRAL FORM

(To be filled in triplicate, Copy: 1. Health facility through patient, 2. D.M.O. 3. Patient's file)

REFERRING FACILITY _____

1. SOCIAL HISTORY

Name of client: _____ Sex: F/M Age: _____

Occupation: _____ Educational Level: _____

Marital Status: _____ Religion: _____

Ward: _____ Name of Headman: _____

Present Address: _____ Tel: _____

Home Address: _____ Tel: _____

Name of Carer: _____ Tel: _____

Physical Address: _____

2. MEDICAL HISTORY:

DOA: _____ DOD: _____ Diagnosis: _____

Treatment: _____

3. SOCIO - ECONOMIC HISTORY _____

_____

_____

_____

4. RECOMMENDED H.B.C. ACTIVITIES AND FOLLOW - UP

Adherence/Management:

TB Drugs: _____

ARVT: _____

_____

Other: _____ Specify: _____

Condition on Discharge: _____

Feeding Method: _____ Dressing: _____ Turning: _____

Bathing: _____ Catheter Care: _____ Help with Toilet: _____ Other: _____

Specify: _____

Discharging Officer: _____ Designation: _____

Signature: _____ Date: _____

Complete the form below, tear off and send to the HBC Coordinator at the DHT where the patient is referred

Name of the facility: _____

Full name of patient: _____

Date patient seen: _____ Condition of patient when seen: _____

Signature of the nurse: _____

Notes