November 1st, 2008 Edition

MINISTRY OF HEALTH

BOTSWANA NATIONAL HIV/AIDS TREATMENT GUIDELINES : 2008 VERSION

DEPARTMENT OF HIV/AIDS PREVENTION AND CARE

Botswana National HIV/AIDS Treatment Guidelines : 2008 Version

November 1, 2008, Edition

These guidelines are also available on the Masa page of the website of the Ministry of Health: www.moh.gov.bw.

Contents

List of Abbreviations and Symbols (Non-ARV):

>, <	greater than, less than
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATT	anti-tuberculosis therapy
ART	antiretroviral therapy
ARV	antiretroviral
BD	twice a day
BMD	bone mineral density
BMI	body mass index
CDC	United States Centers for Disease Control
CMV	cytomegalovirus
CSF	cerebral spinal fluid
CTX	cotrimoxazole
C_{creat}	creatinine clearance
DBS	dried blood spot
DS	"double-strength" CTX (= 2 "single-strength" CTX)
DNA PCR	DNA polymerase chain reaction
E	ethambutol
ELISA	enzyme-linked immunosorbant assay
FBC	full blood count
GFR	glomerular filtration rate
H	isoniazid
HAART	highly active antiretroviral therapy
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCW	healthcare worker
HgB	hemoglobin
HIV	human immunodeficiency virus, type 1 (HIV-1)
hrs	hours
HSV	herpes simplex virus
ICP	intracranial pressure
INH	isoniazid
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
IV	intravenous
kg	kilogram
KS	Kaposi's sarcoma
LIP	lymphoid interstitial pneumonitis
LP	lumbar puncture (spinal tap)
mg	milligram
mL	milliliter
mmol	millimole
mos	months
µL	microliter (cubic millimeter, mm^3)
MDR-TB	multidrug-resistant tuberculosis
MOH	Botswana Ministry of Health
MTCT	mother-to-child transmission (of HIV)

NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OD	once daily
OI	opportunistic infection
PCP	pneumocystis carinii (now *jeroveci*) 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
q	every, e.g., q3hours= every 3 hours
QID	four times a day
R	rifampicin
S	streptomycin
sd-NVP	single-dose nevirapine
SJS	Stevens-Johnson syndrome
STI	sexually transmitted infection
SMX	sulfamethoxazole
SS	single-strength CTX (TMP 80mg/SMX 400mg)
TAM	thymidine analogue mutation
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

ARV Abbreviations:

AZT (zidovudine, ZDV)
3TC (lamivudine)
FTC (emtricitabine)
d4T (stavudine)
ddI (didanosine)
ABC (abacavir)
TDF (tenofovir)
NVP (nevirapine)
EFV (efavirenz)
LPV/r (ritonavir-boosted lopinavir [“Kaletra,” “Aluvia”])
NFV (nelfinavir)
SQV (saquinavir)
RTV (ritonavir)
DRV (darunavir)
RAL (raltegravir)
r (“low dose” ritonavir, usually 100mg dose)

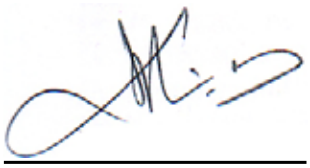
Free-of-Charge On-Line HIV/AIDS Educational Information for Clinicians:

- **www.medscape.com/hiv**
- **www.aidsmap.com**
- **www.haart4africa.com**
- **www.clinicaloptions.com/hiv**
- **www.iasusa.org**
- **www.hopkins-aids.edu**

Forward

Botswana's response to its HIV/AIDS crisis has been one of gradual expansion of comprehensive care for its HIV-infected citizens, such that Botswana is regarded as the beacon of hope for the rest of the continent suffering from HIV/AIDS. With the release of the 2008 National HIV/AIDS Guidelines, the nation is again enacting important, incremental improvements in the scope and depth of its HIV/AIDS programs, while still ensuring that its resources are being put to the best possible use for all of its citizens. Whereas internationally accepted HIV/AIDS standards have been integrated as much as possible into these revised guidelines, there are instances where the guidelines have been modified to reflect Botswana's ongoing experience in HIV/AIDS care, as well as its resources. Moreover, these guidelines are *fully consistent* with current Botswana PMTCT, testing, and TB guidelines.

These guidelines, which are valid for both public and private patients, are not a substitute for clinical judgment. *In consultation with an HIV Specialist*, there will be instances in which, for an individual patient, the practitioner must deviate from them. Nonetheless, it is expected these 2008 revised guidelines represent a major step forward for the Botswana National HIV/AIDS Program, and will further enhance the already comprehensive care the nation provides its people living with HIV/AIDS.



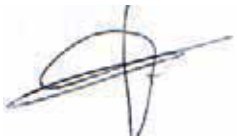
Dr. L. Mazhani,
Deputy Permanent Secretary/Director of Health Services
Ministry of Health
May 1, 2008

Preface

Revision of the 2005 Botswana Guidelines on Antiretroviral Treatment has been a major collaborative endeavor, involving the time, dedication, and expertise of many major stakeholders. The members of the Committee for the Clinical Care of HIV/AIDS in Botswana represent a spectrum of important participants in the country's HIV/AIDS programs, including the Ministry of Health, the private sector, partner institutions, and medical aid schemes.

The Committee has organized Botswana's HIV/AIDS Guidelines into a comprehensive document, integrating into it the principles of ARV therapy, prevention, testing, STI management, PMTCT, failure management, HIV/TB co-infection, and OI treatment. Pediatric and adolescent issues in HIV/AIDS care have been given special emphasis.

The Ministry of Health will work with the committee to disseminate these guidelines, as well to provide practitioner training on the changes therein. In addition, the Ministry of Health looks forward to working with the Committee in monitoring and evaluating clinic and practitioner application of these guidelines.



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May 1, 2008

Acknowledgements

Undertaking a task of this magnitude involves the hard work and tireless dedication of many individuals and organizations, working together in a concerted manner. Masa, the Botswana National ARV Program, Ministry of Health, wishes to be the first to acknowledge the commitment of members of the Committee for the Clinical Care of HIV/AIDS in Botswana for their collective efforts in developing these guidelines:

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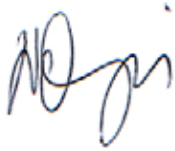

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May 1, 2008

Changes in the 2008 Botswana National HIV/AIDS Treatment Guidelines: November 1, 2008 Edition

The 2008 Botswana National HIV/AIDS Treatment Guidelines, which were introduced on May 1, 2008, have been extremely well received by clinicians across the country, and have already been implemented at all ARV clinics. In monitoring the response to these guidelines, the Committee for the Clinical Management of HIV/AIDS in Botswana has identified important issues of HIV/AIDS care which require further clarification or revision. Accordingly, the Committee has approved the following changes and updates for incorporation into the May 1, 2008, Botswana National HIV/AIDS Treatment Guidelines (2008 Version). These changes are summarized below, under the indicated sections of each chapter.

Free-of-Charge On-Line HIV/AIDS Educational Information for Clinicians:

- www.medscape.com/hiv
- www.aidsmap.com
- www.haart4africa.com
- www.clinicaloptions.com/hiv
- www.iasusa.org
- www.hopkins-aids.edu

2.1 Diagnosis of HIV Infection in Patients 18 Months of Age and Older: Follow-up HIV testing re: the "window period"

A patient with a negative result and with recent high risk exposure (e.g., unsafe sex, STI or STI exposure, pregnancy) should be cautioned about the "window period," and should return for repeat testing in 3 months. Otherwise, the patient should be advised to return for routine testing in 12 months, unless high risk exposure occurs before then. In all instances, safe sex must be reviewed in detail with the patient.

2.3 Acute HIV Infection:

Clinicians must be alert to the signs and symptoms of the acute retroviral syndrome in a patient of unknown HIV status, especially if there has been recent high-risk exposure. Rapid testing should be performed to rule out HIV infection, and, if rapid testing is negative, and there is clinical suspicion of acute HIV infection, repeat rapid testing in 6 weeks should be done. Since up to 50% of new HIV transmissions are estimated to occur when the infected partner is in the acute phase of HIV infection, *safe sex counseling is imperative.* Although acute HIV infection is not, in and of itself, an indication for HAART initiation in Botswana, a patient with severe symptoms of the acute retroviral syndrome should be discussed with an HIV Specialist for possible HAART initiation.

4.2 Indications for HAART Initiation in Adolescents and Adults (pregnant and non-pregnant):

- When beginning HAART in an adult/adolescent without a CD4 count, the possibility that the patient might have a high baseline CD4 count requires initiation with EFV- or LPV/r-based HAART instead of NVP, because of increased risk of NVP-induced hepatotoxicity with high baseline CD4 counts.

5.2 Recommended First and Second Line Regimens in Botswana:

- New ARV formulations:

"Atripla" is co-formulated TDF, FTC, and EFV, and is taken OD. It will be available to the National Program by the end of 2008. "Truvada" is co-formulated TDF and FTC, and is now available to the National Program

- TDF use in adolescents:

In order to reduce the chances of bone demineralization, TDF may be used only in adolescents at Tanner Stage 4 or higher (See Appendix for detailed Tanner staging). Nonetheless, TDF-associated bone demineralization is occasionally seen in children who are at Tanner 4 or higher, but at a lower frequency than is seen in younger children (Tanner 3 and lower). Clinicians should be aware of this possibility, if a child on TDF presents with frequent fractures.

- TDF in pregnancy:

If at all possible, TDF should be avoided in pregnancy, and AZT-based HAART used instead. If AZT cannot be used, e.g., due to anemia, then d4T should be used instead, but after delivery, d4T should be changed to TDF. If the woman has already failed an AZT- or d4T-based regimen, then an HIV Specialist should be consulted.

- NRTI doses in renal insufficiency:

As a rule, all NRTIs, excluding ABC, require dose-reduction with renal insufficiency, but there are sparse data on how best to address this subject for the African setting. At baseline, many African patients with advanced or severe immunodeficiency have mild to moderate renal insufficiency, *which usually improves significantly over time on HAART prescribed at standard ARV dosages*.

- All patients with baseline C_{Creat} < 30 cc/minute, or who are on dialysis, must be discussed with an HIV Specialist before initiating NRTIs, excluding ABC.
- Patients with baseline C_{Creat} between 30 and 90 cc/minute may be initiated on standard doses of NRTIs, but require follow-up C_{Creat} in three months. If the follow-up C_{Creat} has not improved compared to baseline, then an HIV Specialist must be consulted for possible dose reduction of the NRTIs.
    - If any NRTI is prescribed at a lower dose due to renal insufficiency, *it is imperative to monitor C_{Creat} at every three month intervals*, until the clearance has increased to > 50 cc/minute, *at which point the NRTI dose(s) must be increased to standard levels.* Failure to do so risks ARV under-dosing, with subsequent risk of treatment failure.

- TDF, renal insufficiency, and calculation of creatinine clearance:
    - Although some guidelines permit use of reduced TDF doses when baseline C_{Creat} is < 60 cc/minute, this approach is not recommended in Botswana, because of the risk of adherence problems with every 48 or 72 hour TDF dosing schedules for renal insufficiency. TDF should not, as a rule, be initiated when baseline C_{Creat} is < 60 cc/minute.

1) When baseline creatinine clearance is < 60cc/minute:
    - *Recalculate the creatinine clearance 2-3 days later*, repeating the serum creatinine and patient weight, which should be verified with another set of scales. If the repeat clearance is still < 60cc/minute:

        - Initiate HAART with AZT, or, if there is significant baseline anemia, d4T. If already on d4T, continue d4T and do not switch to TDF.
            - Patients initiated on AZT should continue this ARV indefinitely, as long as there are no AZT side effects.
        - For patients initiated on d4T, or who have already been on d4T, monitor the creatinine clearance every 3 months, until it is > 60cc/minute, at which time switch to TDF can be done. Also, monitor the patient at every visit for any adverse effects of d4T.
        - If side effects from either AZT or d4T develop, and creatinine clearance remains < 60cc/minute, then consult an HIV Specialist.

2) <u>When serum creatinine cannot be done:</u>

- Proceed with TDF initiation or switch, *unless* 1) the patient is over 60 years of age, 2) the patient has a history of renal disease (insufficiency, chronic infection, stones), 3) there is greater than trace proteinuria on urinalysis, 4) serum urea is above the upper limit of normal range, <u>or</u> 5) the patient has conditions such as diabetes or uncontrolled hypertension, which might impair renal function. When serum creatinine can eventually be done, monitor creatinine clearance per usual laboratory schedules.
- For patients who fall into one or more of the above five clinical situations, initiate HAART with AZT (or d4T, if there is anemia). If already on d4T, continue d4T and do not switch to TDF.
    - Patients initiated on AZT should continue this ARV indefinitely, as long as there are no AZT side effects.
    - Once serum creatinine can be done, monitor creatinine clearance every 3 months for patients on d4T, until it is > 60cc/minute, at which time switch to TDF can be done. Also, monitor the patient at every visit for any adverse effects of d4T.
    - If side effects from either AZT or d4T develop, then consult an HIV Specialist.
- When it is necessary to use d4T, as above, the adult dose should ideally be 30mg BD, regardless of weight, in order to minimize potential d4T side effects. However, the 40mg BD dose may be used, if the 30mg dose is not available.

<u>5.3 Third Line Regimens in Botswana:</u>

By late 2008, two new, highly potent ARVs will be available for use as "salvage" therapy for patients who have failed multiple ARV regimens, and who have significant resistance mutations. Darunavir (DRV) is a potent protease inhibitor, which is active against HIV with multiple PI resistance mutations. Raltegravir (RAL) is an integrase inhibitor which has shown great efficacy in highly treatment-experienced patients. A successful "salvage" regimen must contain *at least two fully active ARVs*, in order to prevent the eventual emergence of resistance due to *de facto* monotherapy. "Salvage" therapy consisting of both DRV and RAL (plus optimized background therapy) is anticipated to be a highly potent regimen in Botswana, which, if used properly, should result in full virologic suppression in the majority of cases. Access to these two important ARVs will be controlled by the HIV Specialists

comprising the Resistance Technical Working Group (TWG) of the Ministry of Health. A patient who may require such "salvage" HAART should be referred to an HIV Specialist, who will then discuss the case with the TWG. Clinicians should familiarize themselves with details of these two new ARVs, and listed below is a brief summary of essential points about their use:

- DRV dosing (300mg tablets): 600mg BD *with 100mg RTV BD*, taken with food. Major side effects: diarrhea, hepatitis, rash (rare SJS). Metabolized by CYP450 3A4, and drug interactions are anticipated.
- RAL dosing (400mg tablets): 400mg BD. No significant side effects or drug interactions have been reported to date.

5.4 Goals of ARV Therapy:

- Studies have shown an increased risk of virologic failure when NNRT-based HAART is initiated in women who have received sd-NVP in the past, especially within 6 months of taking sd-NVP. Current guidelines permit initiation of NNRTI-based HAART in women who have received sd-NVP more than 6 months in the past, but these patients require close monitoring for virologic failure. *Any such woman whose viral load at 3 months after initiation of NVP or EFV is not < 400 copies/mL must promptly be discussed with an HIV Specialist*.

5.5 Recommended Schedule for Monitoring Patients on HAART:
In the listing of priority viral loads and CD4 counts, all viral loads in patients under 20 years of age require prioritization, but not their CD4 counts.

6.0 HIV/TB Co-infection:

- All MDR-TB patients with CD4 cell counts > 250 cells/μL should be started on HAART at 2 months after ATT initiation, with close monitoring for additive drug toxicities, especially hepatitis.
- All TB patients with CD4 cell counts > 250 cells/μL, and who have another active WHO stage 3 or 4 condition, should be started on HAART at 2 months after ATT initiation. If the WHO stage 3 or 4 condition is life-threatening, HAART should be initiated much sooner after ATT initiation, the exact timing of HAART initiation depending upon the seriousness of the patient's medical condition.
- Ideal dose adjustment of LPV/r in pediatric patients on ATT remains unclear. Recent studies in South Africa showed suboptimal LPV levels in pediatric TB patients when the standard LPV/r dose was doubled, whereas therapeutic levels were documented when extra RTV was given in 1:1 ratio (with standard LPV doses). Although further studies are necessary, it may be advisable to use the latter dosing strategy in such patients.

7.4 Clinical Care of Pregnant HIV-Infected Women and Prevention of Mother-to-Child Transmission: Late-term HIV testing of pregnant women who initially test negative
Pregnant women who initially test HIV negative at ante-natal care registration should be retested either at 36 weeks gestation or at onset of labor, whichever comes first, in order to detect intercurrent HIV infection during pregnancy. If HIV positive, the patient should be managed as indicated by her eligibility for HAART.

8.7 HIV Specialist Panel: The list of HIV Specialists in Section 8.7 has been updated. If necessary, messages for Specialist assistance can be left at the toll-free number 0 800 600 691.

10.1 Cryptococcal Meningitis: Diagnosis

The lumbar puncture is the cornerstone of diagnosis, and, if performed promptly, is also therapeutic and potentially life-saving. LPs are safe, and cause serious complications only very rarely, if at all. Nonetheless, to ensure patient safety, a neurological examination must be performed before performing an LP. Defer an LP until after an urgent non-contrast head CT scan has been done *only* if a patient has focal neurological findings (unequal/irregular pupils, hemiparesis), focal seizures, or clinical signs of impending brainstem herniation (pupil changes, abnormal respiratory pattern). When CT scanning is not immediately available for the above clinical situations, and the suspicion of meningitis is high, *the potential benefits of an LP outweigh any theoretical risks*: proceed with the LP, using a 20-24 gauge needle, if available. An HIV Specialist should be consulted for any difficult cases, but *obtaining a CT scan or consulting an HIV Specialist must not significantly delay the LP and subsequent initiation of treatment*. In all cases, reasons for not doing an LP must be valid and well documented, *and casual, poorly founded reasons for initiating "empiric" treatment without ever performing an LP are not acceptable.*

10.2 Tuberculosis:

- Childhood TB:

Children with severe TB (excluding TB meningitis) should be treated with 2 months of HRZE followed by 4 months of HR *under the supervision of a pediatric specialist.* (Streptomycin should replace ethambutol in the treatment of TB meningitis). "Severe" childhood TB includes meningitis, miliary disease, spinal TB, adenitis with compressive complications, and pericarditis with effusion and tamponade.

- Additional indication for culture and drug susceptibility for TB: TB IRIS, or suspected TB IRIS

10.12 Chronic Diarrhea:

- For *documented* microsporidia infection: albendazole 400mg BD until the CD4 cell count is > 200 cells/μL. Laboratories are strongly encouraged to gain necessary capacity to identify microsporidia infection, but when the laboratory is not able to screen stool specimens for this specific pathogen, empiric albendazole can be used, after several courses of empiric CTX and metronidazole have proven ineffective.

Appendix: Protocol for Special Order ARV Drugs
Authorization to approve such drugs has been extended to include all of the HIV Specialists on the HIV Specialist Panel, as listed in the updated Section 8.7.

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November 1, 2008

Editorial Notes

The major changes and additions to HIV/AIDS care which are contained within these guidelines include the following points:

- WHO staging is now the recommended method for classifying the clinical and immunological status of HIV-infected patients.
- HIV-exposed babies should have DNA PCR testing at 6 weeks of age, preferably by DBS, with immediate follow-up DNA PCR to confirm a positive result. *Infants whose first DNA PCR is positive should immediately be referred for HAART initiation, without waiting for the confirmatory DNA PCR.*
    - When DNA PCR results are not rapidly available, HIV-exposed babies should be clinically evaluated *monthly*, since HIV-infected babies are at high risk for severe illness and death. The clinical evaluation should include WHO clinical staging. An *HIV-exposed baby with WHO clinical stage 2, 3, or 4 condition(s), and whose DNA PCR is not available, must be discussed with a pediatric HIV Specialist for consideration of beginning HAART while a definitive diagnosis of HIV infection is pending*.
    - A rapid HIV test should be performed at 18 months on all HIV-exposed children who initially tested negative by DNA PCR, and who have not been breastfed, to detect undisclosed breastfeeding and rare false-negative PCR results.
    - Breastfed babies with a negative DNA PCR at 6 weeks should have repeat HIV testing 6 weeks after complete cessation of breastfeeding, the type of HIV test performed depending upon the age of the patient.
- For all adolescents and adults (pregnant and non-pregnant), eligibility for HAART is determined by having one of the following two criteria:
    - WHO clinical stage 3 or 4, *or*
    - CD4 cell count ≤ **250** cells/μL (previously < 200 cells/μL)
- For HIV-infected children, eligibility for HAART is determined by having one of the following criteria:
    - Age <1 year, regardless of clinical or immunologic status
    - WHO clinical stage 3 or 4
    - "Advanced" or "Severe" immune suppression, as defined by age-related CD4%/count, according to WHO criteria (refer to Chapters 3 and 4)
- 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*: begin the patient on HAART on the basis of the patient's having a WHO clinical stage 3 or 4 condition and being in poor clinical condition. Likewise, do not delay CTX prophylaxis.
    - When beginning HAART in an adult/adolescent without a CD4 count, the possibility that the patient might have a high baseline CD4 count requires initiation with EFV-based or LPV/r-based HAART instead of NVP, because of increased risk of NVP-induced hepatotoxicity with high baseline CD4 counts.
- First and second line HAART regimens for *new* non-pregnant adult/adolescent patients have been changed:

    - First line: TDF + FTC (or 3TC) + EFV or NVP, according to the woman's reproductive potential
    - Second line: AZT + 3TC + LPV/r
- Patients who are stable on prior first line regimen of AZT + 3TC + EFV or NVP, and who are having no AZT-associated side effects, should continue this regimen.
- Provisions have been made for switching adult/adolescent patients currently on d4T to TDF, and those patients on d4T+ddI to TDF+FTC (or 3TC), to prevent d4T-related side effects and toxicities.
- There are detailed algorithms to guide N[t]RTI choices for renal insufficiency and when serum creatinine cannot be performed.
- By late 2008, darunavir and raltegravir will be available for "salvage" HAART for patients who have failed multiple ARV regimens,
- First line ARV regimen for pediatric patients remains unchanged (AZT + 3TC + NPV or EFV), but the new second line regimen has been changed to ABC + d4T + LPV/r.
    - Pediatric patients on the previous second line regimen of d4T + ddI + LPV/r, and who are having no adherence problems with ddI, can be maintained on this regimen. Patients experiencing adherence problems with ddI should be switched to ABC in place of ddI.
- WHO pediatric dosage charts should be used instead of dosage calculations.
- *All pediatric patients whose viral load is not < 400 copies/mL by 6 months after initiation of ARV therapy must be discussed with a pediatric HIV Specialist.*
- *When initiating HAART in women and infants, it is necessary to determine whether or not they received PMTCT interventions*. Single-dose NVP (maternal and infant) can cause NVP resistance in the recipient, which in turn may adversely affect NNRTI-based HAART started at a later date:
    - All non pregnant women who have received sd-NVP for PMTCT within the prior 6 months must be initiated on TDF + FTC (or 3TC) + LPV/r. Non-pregnant women initiated on HAART more than 6 months after sd-NVP may be initiated on standard first line HAART (TDF + FTC [or 3TC] + NVP or EFV), but must be closely monitored for any evidence of treatment failure.
    - Infants who have received sd-NVP, and who are initiated on HAART within the first 6 months of life, must be discussed with a pediatric HIV Specialist. For such infants starting HAART *after* 6 months of age, LPV/r-based HAART should be used. A history of maternal participation in PMTCT is sufficient to assume that the infant received sd-NVP at birth.
- PMTCT guidelines emphasize the importance of HAART for all pregnant women who require it for their own HIV infection, per adult criteria listed above.
    - There is an expedited algorithm for discordant HIV test results in a pregnant woman, to avoid delay in HIV diagnosis.
    - Pregnant women who initially test HIV negative at ante-natal care registration should be retested either at 36 weeks gestation or at onset of labor, whichever comes first, in order to detect intercurrent HIV infection during pregnancy.

- CD4 count and clinical screening must be prioritized and expedited for all pregnant women not yet on HAART. When the CD4 count does not return within 2 weeks, the head of the relevant laboratory must be contacted.
- In all cases, a pregnant woman who is eligible for HAART for her own HIV infection *must* be started on HAART, *without exception*. If the woman's immune status is poor, HAART must not be deferred until the second trimester.
- During labor, pregnant patients on HAART must still be given high-dose AZT per prior PMTCT protocols, but *should not be given sd-NVP*.
- Women not eligible for HAART should begin short-course AZT 300mg BD beginning at 28 weeks gestation, or *immediately upon any presentation beyond 28 weeks*. Use of sd-NVP at labor depends upon the length of short-course AZT:
  - sd NVP should *not* be given at labor *if the woman has received at least 4 weeks of AZT.*
  - If the woman has received < 4 weeks of AZT prior to labor, then sd-NVP should be given at onset of labor. Do *not* repeat the sd-NVP.
  - If at labor the patient *and* her medical records are uncertain or unclear as to whether or not she has received AZT for at least 4 weeks, *administer sd-NVP*, as well as AZT 300mg po every 3 hours (to a maximum of 1500mg).
- If transfusion cannot resolve AZT-associated anemia in patients on AZT-containing HAART or in patients on short-course AZT prophylaxis, then d4T-containing HAART should be used, including for those women only on short-course AZT prophylaxis. After delivery, women initially not eligible for HAART should be discussed with an HIV Specialist as to whether HAART should be continued or stopped. Women who were initially eligible for HAART should be switched from d4T to TDF after delivery.

- Recommendations for baseline and monitoring laboratory tests for HAART have been changed:
  - *Baseline viral load must no longer be done either in adult or pediatric patients*. *After full virologic suppression has been achieved 6 months post-HAART initiation in adults, viral load should be performed every 6 months*.
  - Pediatric and adolescent patients require indefinite every-3-month viral loads.
  - *After initial 3 and 6 month CD4 count/%, all age groups require only every 6 month measurements of immune status*.
  - Monitoring of FBC and AST/ALT for patients on HAART has been extensively streamlined, and *in most cases must not be done on a routine, q3-month basis*.
- The following viral loads and CD4 counts must be run on a *priority* basis:
  - Viral load on all patients < 20 years of age
  - Confirmation of virologic failure in a patient on HAART

    - Follow-up 6 week VL to confirm continued virologic suppression after switching from suppressive 2nd line adult and pediatric regimens (2005 guidelines) to the new 2nd line regimens under these guidelines
    - Follow-up 6 week VL after restarting/continuing HAART after completed interventions for treatment failure due to non-adherence, drug interactions, inappropriate ARV dose, and gastroenteritis
    - Follow-up 6 week VL after ARV switch for side effects or toxicity, when there had previously been full virologic suppression prior to the switch
    - VL done prior to switching from a prior adult or pediatric regimen containing d4T and/or ddI, when there has been no viral load performed within the previous 6 months
    - *CD4 cell count for any pregnant woman who is not yet on HAART, in order to determine her eligibility for HAART.*
- CTX prophylaxis must be given to all adults and adolescents with advanced or severe immunosuppression, as evidenced by CD4 cell count < 200 cells/μL *or* active, current WHO clinical stage 3 or 4 condition.
- CTX prophylaxis must be given to all HIV-*exposed* babies, starting at 6 weeks of age. Babies *not breastfed* and with a negative DNA PCR at 6 weeks of age may discontinue CTX. HIV-infected babies must continue CTX until at least 12 months of age, regardless of CD4 count/% and clinical condition. *At age 12 months, stopping or continuing CTX must be based on the infant's immunologic and clinical status*:
    - HIV-infected children between ages 1 and 5 years of age with **CD4 % < 25%** should receive CTX prophylaxis. *This threshold for CTX prophylaxis is higher than the previous CD4% threshold of < 15%.*
    - HIV-infected children over 5 years of age with either CD4% < 15% or absolute CD4 cell count < 200 cells/μL require CTX prophylaxis.
    - HIV-infected children with active, current WHO clinical stage 2, 3, or 4 disease should continue (or begin) CTX prophylaxis until the clinical condition has resolved or been stable for at least 6 months.
- Other important clinical situations require CTX prophylaxis for pediatric patients:
    - HIV-*exposed* breastfeeding infants with negative DNA PCR at 6 weeks must continue CTX until HIV-infection is ruled out 6 weeks after complete cessation of breastfeeding.
    - Children of any age who qualify for HAART but are not currently receiving HAART for any reason should be given CTX.
    - HIV-infected children on HAART who develop virologic failure should restart CTX until the viral load has re-suppressed and there are no other indications, as above, for CTX prophylaxis.
- For all ages, CTX prophylaxis should be given OD, not TIW, to ensure protection against diarrheal diseases and respiratory infections other than PCP. Regardless of immune status, CTX should be administered during ATT and, if indicated by the above adult criteria, during pregnancy or breastfeeding.
- If an HIV-infected patient of any age has an active WHO clinical stage 3 or 4 condition (or, for pediatric patients, an active WHO clinical stage 2, 3, or 4 condition), and the CD4 cell count or % is pending, *do not wait for the CD4 count or % to return:* start CTX prophylaxis.

- There is specific discussion of infant feeding practices in light of recent information about the risks and benefits of various feeding options.
- *Clinics which dispense formula must not turn away a mother who requests additional formula for her baby, and must provide additional formula.* However, follow-up home visits should be done to access proper formula use.
- Safe sex prevention messages must be targeted, and must not present all sexual activity as inherently dangerous or unsafe.
- There is increased risk of NVP-associated hepatotoxicity with high *baseline* CD4 cell counts: > 250 cells/μL for women and > 400 cells/μL for men. If possible, NVP should be avoided in such patients, and EFV or LPV/r used instead.
- For adult patients who have remained stable on HAART for at least two years, clinical monitoring visits can be decreased to every six months.
- *All ARV clinics must develop and implement an ongoing, contemporaneous, and sustainable procedure for promptly reviewing returning laboratory tests for abnormal results, including any detectable viral loads.*
- *It is imperative to obtain TB cultures with drug susceptibility testing for any indications listed in section 10.2 (from recently revised national TB guidelines), in order to detect early cases of MDR TB.*
- All MDR-TB patients with CD4 cell counts > 250 cells/μL should be started on HAART at 2 months after ATT initiation, with close monitoring for additive drug toxicities, especially hepatitis.
- With rifampicin, EFV does not require any weight-based dose adjustment.
- Decisions regarding initiation of PEP must take into account the possibility that a source patient whose HIV test result is negative may nonetheless be in the "window period" of HIV infection, and thus highly infectious for HIV.
- Pre-operative evaluation for surgical risk must not regard asymptomatic HIV infection as a reason to delay surgery.
- Pre- and post-exposure sexual prophylaxis is of unproven benefit, and must not be administered, except for cases of rape or defilement.
- *PAP smear screening must be done annually on all HIV-infected women, with prompt referral for any abnormalities.*
- Lumbar puncture is an "opt out" procedure, not requiring family consent.
- There is a protocol for establishing a Failure Management Clinic and Team at every ARV clinic, to coordinate interventions for failure management.
- There is a streamlined procedure for requesting "Special Order" ARVs.
- An HIV Specialist Panel has been formed to provide ongoing and readily available consultative support to all clinicians, and to expedite approval of "Special Order" ARVs.

Because HIV care is a rapidly evolving area of medical science, changes and updates in these guidelines will be posted as needed on the Ministry of Health website at www.moh.gov.bw, on the Masa webpage.

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1.0 HIV Prevention: Sexual and Workplace Transmission

1.1 Prevention of Sexual Transmission:

- Abstinence and life-long *mutual* monogamy between HIV-uninfected partners are 100% effective methods to prevent sexual acquisition of HIV infection.
- Parents and clinicians must initiate frank discussions of sex with adolescents, including nonjudgmental discussion of safe sex methods to satisfy sexual needs.
- Monogamy must be *mutual* and 100% consistent.
- Notifying partners from sexual networks is essential to prevent HIV transmission.
- Consistent and proper condom use for rectal and/or vaginal intercourse is the core of "safe sex" messages, which must always be targeted, with frank review of the risks of various sexual activities. *Any safe sex discussion which presents all sexual activity as dangerous or "risky" is likely to fail*.
    - 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.
    - Sexual kissing is "safe sex."
    - Mutual masturbation is "safe sex," as long as transfer of genital secretions between partners is avoided.
    - The HIV risk of oral-genital sex is not known, but is low.
    - Prompt identification and treatment of STIs is crucial.
    - *The importance of safe sex must be reviewed at every patient visit*.
    - Patients should be counseled that HIV transmission can occur at any viral load, including "undetectable" values.
- *Counseling of couples about safe sex and HIV testing is an important opportunity for discussing family planning issues*.
- 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.
- In 2008, the Ministry of Health began to roll out a male circumcision (MC) initiative, as a new intervention for preventing sexual acquisition of HIV. This intervention may also be considered in the private sector.
    - To prevent enhanced HIV acquisition (and subsequent transmission) via an unhealed surgical scar*, it is imperative that MC patients be counseled not to resume sexual activities until complete healing of the surgical scar has been verified by a clinician experienced in such determination, ideally the practitioner who performed the procedure*.

- MC patients must be rigorously counseled about the importance of continuing safe sex practices, since the documented efficacy of MC in reducing HIV acquisition has been reported to be no more than 50-60%.

1.2 Prevention of Healthcare Workplace Transmission:

"Universal precautions" must be practiced by all healthcare workers when handling *all* body fluids, since HIV, HBV and other serious pathogens are transmissible.

- HIV-infected HCWs, including those who perform invasive procedures on patients, do not pose any risk of HIV transmission to their patients, as long as they adhere to routine infection control policies and universal precautions.
- HIV-infected HCWs must exercise great caution when caring for patients with TB or suspected TB, especially MDR- and XDR-TB. Respiratory isolation precautions must be observed at all times.
- Home and family healthcare workers are not at 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 of non-intact skin to infectious secretions should be stressed.

1.3 Sexually Transmitted Infections and Their Treatment:

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 (HSV) and syphilis have been shown to significantly enhance HIV transmission and acquisition, to elevate viral load, and to lower CD4 cell count. In patients of unknown HIV sero-status, STIs are important markers of concomitant HIV infection, and mandate obligatory HIV testing and safe sex counseling. In Botswana, management of STIs must follow the "syndromic" approach, wherein STI signs/symptoms are matched to a specific STI syndrome. (See Appendix).

KEY POINTS:

- ***Consistent and proper condom use for rectal and/or vaginal intercourse is the core of "safe sex" messages, which must be targeted, with frank review of the risks of various sexual activities. Any safe sex discussion which presents all sexual activity as dangerous or "risky" is likely to fail.***
- ***Counseling of couples about safe sex and HIV testing is an important opportunity for discussing family planning issues.***
- ***All HIV-positive patients are infectious for HIV, regardless of viral load or CD4 cell count.***
- ***HIV-infected HCWs must exercise great caution when caring for patients with TB or suspected TB, especially MDR- and XDR-TB. Respiratory isolation precautions must be observed at all times.***
- ***The syndromic approach to management and treatment of STIs is an important tool for HIV prevention.***
- ***Male circumcision patients must be counseled not to resume sexual activities until complete healing of the surgical scar has been verified by a clinician experienced in such determination.***

2.0 Screening and Testing for HIV Infection:

For *all* age groups, HIV testing should continue to be universal, routine, and on an "opt out" basis, and should be conducted in all clinical and outreach settings throughout the country.

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

The rapid test is now the preferred method of HIV testing in patients 18 months of age and older. The ELISA, which remains "the gold standard" for testing, is best reserved for specimens which arrive in the laboratory, and for mass screening of large numbers of patients. 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

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

- The patient should be advised to return in 2-4 weeks for repeat testing by rapid test, during which time abstinence or safe sex should be practiced.
- If the repeat rapid test 2-4 weeks later is still discordant, ELISA testing is required *at that visit*.
- If the EILSA, as above, remains indeterminate, another ELISA should be drawn after 3 months. If at 3 months the result is still indeterminate, PCR testing or Western Blot is necessary.

Prompt and accurate HIV diagnosis in pregnant women is essential for indicated referral and interventions for PMTCT, as well as for the mother's health. Discordant rapid test results (repeated) in a pregnant woman require *priority ELISA testing at that visit*, with results available within two days of testing. If the ELISA test is discordant, then repeat ELISA with Western Blot and viral load must be done immediately, with results within two days of testing. If these tests are equivocal or discordant, an HIV Specialist must be consulted at once.

- Pregnant women who test HIV-negative must receive ongoing counseling regarding safe sex, in order to avoid undetected HIV infection during pregnancy, which could be transmitted to the baby. Such women should be advised to have repeat HIV testing if they have possible exposure to HIV infection during pregnancy.
- Pregnant women who initially test HIV negative at ante-natal care registration should be retested either at 36 weeks gestation or at onset of labor, whichever comes first, in order to detect intercurrent HIV infection during pregnancy.

Protocol for opt-out HIV testing:

- The provider should tell the patient that an HIV test is going to be done, including the medical reasons for this test and assurance that the results will be confidential.
- If the patient does not voice objections to the HIV test, it should be obtained at that time. The results should be discussed with the patient, as below.
- If the patient refuses the HIV test, then the practitioner should explore with the patient the reason(s) for the refusal, and should address the patient's concerns. If the patient still refuses, then he/she should be referred for full pre-test counseling.
- At no time should the patient be pressured into agreeing to HIV testing.
- Post-test counseling should be performed after the HIV test result has returned, and should be tailored according to the test result:
    - A patient with a negative result and with recent high risk exposure (e.g., unsafe sex, STI or STI exposure, pregnancy) should be cautioned about the "window period," and should return for repeat testing in 3 months. Otherwise, the patient should be advised to return for routine testing in 12 months, unless high risk exposure occurs before then. In all instances, safe sex must be reviewed in detail with the patient.
    - If the patient's result is positive, then post-test counseling must emphasize hope and support for the patient.
        - The patient should be encouraged to disclose his HIV status to a close friend or family member, for social and family support.
        - *Disclosure of positive results to adolescents must be done in a supportive environment* (refer to Chapter 7).
        - Referral procedures for follow-up care must be reviewed with the patient, *including prompt referral for CD4 and clinical screening*.
        - If indicated, the patient should be referred to a social worker and/or other community support services.

2.2 Diagnosis of HIV Infection in Patients less than 18 Months of Age:

It is recommended that HIV-exposed babies in Botswana undergo DNA PCR testing at 6 weeks of age, to determine their HIV status, with immediate follow-up DNA PCR to confirm a positive result. (If an infant presents between 4 and 6 weeks of age, *perform the DNA PCR at that visit,* in order not to miss testing at 6 weeks of age.). DBS is the recommended testing method and should be used whenever available. Infants whose first DNA PCR is positive should immediately be referred for HAART initiation, without waiting for the confirmatory DNA PCR.

Babies 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, do not have to undergo further HIV testing. *However, an ELISA or rapid test should be performed at 18 months of age, to allow for situations in which there has been undisclosed breastfeeding or a rare false negative result*.

Breastfed babies with a negative DNA PCR at 6 weeks should have repeat HIV testing 6 weeks after complete cessation of breastfeeding, the type of HIV test performed depending 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 HAART initiation*.

When DNA PCR results are not readily available, HIV-exposed babies should be clinically evaluated monthly, since HIV-infected babies are at high risk of severe illness and death. The clinical evaluation should include WHO clinical staging. *An HIV-exposed baby with WHO clinical stage 2, 3, or 4 condition(s), and whose DNA PCR is not available, must be discussed with a pediatric HIV Specialist for consideration of beginning HAART, while a definitive diagnosis by PCR is pending*.

2.3 Acute HIV Infection:

Clinicians must be alert to the signs and symptoms of the acute retroviral syndrome in a patient of unknown HIV status, especially if there has been recent high-risk exposure. Rapid testing should be performed to rule out HIV infection, and, if rapid testing is negative, and there is clinical suspicion of acute HIV infection, repeat rapid testing in 6 weeks should be done. Since up to 50% of new HIV transmissions are estimated to occur when the infected partner is in the acute phase of HIV infection, *safe sex counseling is imperative.* Although acute HIV infection is not, in and of itself, an indication for HAART initiation in Botswana, a patient with severe symptoms of the acute retroviral syndrome should be discussed with an HIV Specialist for possible HAART initiation.

KEY POINTS:

- ***The preferred HIV screening test in Botswana is the rapid test. The ELISA test is best reserved for mass screening and for specimens which arrive in the laboratory.***
- ***Use of "opt out" testing does not lessen the importance of post-test counseling, which is an important opportunity to reinforce safe sex messages and, for patients who test positive, to begin important HIV-related education and care, including prompt referral for CD4 and clinical screening.***
- ***It is recommended that HIV-exposed babies have DNA PCR testing at 6 weeks of age, with immediate follow-up DNA PCR to confirm a positive result. (If an infant presents between 4 and 6 weeks of age, perform the DNA PCR at that visit, in order not to miss testing at 6 weeks of age.). DBS is the recommended testing method, and should be used whenever available.***
- ***Infants whose first DNA PCR is positive should immediately be referred for HAART initiation, without waiting for the confirmatory DNA PCR.***
- ***Breastfed babies with a negative DNA PCR at 6 weeks should have repeat HIV testing 6 weeks after cessation of breastfeeding, the type of HIV test performed depending upon the age of the patient. If DNA PCR is the test used and is positive, it should be repeated immediately, but do not wait for the confirmatory PCR to return before referring for HAART initiation.***
- ***When DNA PCR results are not readily available, HIV-exposed babies should be clinically evaluated monthly, since HIV-infected babies are at high risk of severe illness and death. The clinical evaluation should include WHO clinical staging.***
- ***Every HIV-exposed baby with WHO clinical stage 2, 3, or 4 condition(s), and whose DNA PCR is not available, must be discussed with a pediatric***

HIV Specialist for consideration of beginning HAART while a definitive diagnosis is pending.

- ***Adolescents must receive disclosure of their positive HIV status in a supportive environment.***
- ***An expedited algorithm for discordant HIV test results in pregnant women must be followed, as above.***
- ***Pregnant women who initially test HIV negative at ante-natal care registration should be retested either at 36 weeks gestation or at onset of labor, whichever comes first, in order to detect intercurrent HIV infection during pregnancy.***
- ***Clinicians must be alert to the signs and symptoms of the acute retroviral syndrome in a patient of unknown HIV status, especially if there has been recent high-risk exposure. Although acute HIV infection is not, in and of itself, an indication for HAART initiation in Botswana, a patient with severe symptoms of the acute retroviral syndrome should be discussed with an HIV Specialist for possible HAART initiation.***

3.0 CD4 and Clinical Screening: Preventive and Supportive Care

3.1 Determination of CD4 Cell Count/% and WHO Clinical Stage:

After diagnosing HIV infection, prompt patient referral for CD4 and clinical screening is mandatory, to determine the degree of immunologic deficiency and HIV-related disease, and to determine patient eligibility for HAART. This CD4 screening/monitoring visit is an opportunity for important preventive and supportive care, and to begin education about HIV disease and ARV therapy.

***CD4 and clinical screening entails more than just obtaining a CD4 cell count. Clinical staging by history and physical examination must be done for every patient referred for CD4 screening*.** Although CDC clinical staging has been used in the past, WHO staging is widely used worldwide, and is now recommended for classifying the clinical condition of the patient. WHO clinical staging categorizes patient symptoms and history into one of four stages, as outlined below for pediatric patients and for adult/adolescent patients:

PEDIATRIC WHO CLINICAL STAGING

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

ADULT/ADOLESCENT WHO CLINICAL STAGING

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, above:

i. 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 Preventive and Supportive Care:

The CD4 and clinical screening visit should also entail preventive and supportive care:

- 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 ARV adherence
- Frank and open discussion about safe sex, family planning, and future reproductive choices. Women must be encouraged to notify their practitioners if they become pregnant, or if they plan to become pregnant.
- When clinically indicated, initiation of CTX prophylaxis and/or IPT
- Annual PAP smears for women
- Patient education about HIV disease, the importance of adherence to medications and to scheduled appointments, and how ARV treatment is life-long and is not a cure
- Social service referral for evaluation of any assistance needed, 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 blood-letting
- Importance of regular exercise and adequate sleep
- When indicated and available, dental referral
- Assessment for evidence of 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
- Information about the referral processes for treatment and follow-up care, including specific appointments for HAART initiation or follow-up CD4 screening

As indicated, the above preventive and supportive care should also be provided at follow-up CD4 screening visits for patients who are not yet eligible for referral for HAART.

3.3 Special Pediatric and Adolescent Considerations:

Pediatric CD4 and clinical screening follows the same general principles as for adults. History and physical examination will determine the appropriate WHO staging for infants, children and adolescents. *Preventive and supportive care of pediatric*

patients must focus on both the child and the care-giver(s) and other family members. *HIV-infected adolescents (age 13 to 20 years) are not "small adults," and must be provided preventive and supportive care sensitive to the psychosocial aspects unique to this special population of HIV-infected patients*. (See Chapter 7).

3.4 Cotrimoxazole (CTX) Prophylaxis:

CTX prophylaxis must be given OD, not TIW, for all ages, in order to provide added protection against diarrheal and respiratory pathogens other than PCP.

CTX prophylaxis for infants and children, including HIV-*exposed* infants:

- CTX prophylaxis must be given to all HIV-*exposed* babies, starting at 6 weeks of age. Babies *not breastfed* and with a negative DNA PCR at 6 weeks of age may discontinue CTX. HIV-infected babies must continue CTX until at least 12 months of age, regardless of CD4 count/% and clinical condition. *At age 12 months, stopping or continuing CTX must be based on the infant's immunologic and clinical status*:
    - HIV-infected children between ages 1 and 5 years of age with **CD4 % < 25%** should receive CTX prophylaxis. *This threshold for CTX prophylaxis is higher than the previous CD4% threshold of < 15%.*
    - HIV-infected children over 5 years of age with either CD4% < 15% *or* absolute CD4 cell count < 200 cells/μL require CTX prophylaxis.
    - HIV-infected children with active, current WHO clinical stage 2, 3, or 4 disease should continue (or begin) CTX prophylaxis, until the clinical condition has resolved or been stable for at least 6 months.
- Other important clinical situations require CTX prophylaxis for pediatric patients:
    - HIV-*exposed* breastfeeding infants with negative DNA PCR at 6 weeks must continue CTX until HIV-infection is ruled out at least 6 weeks after complete cessation of breastfeeding.
    - Children of any age who qualify for HAART, but who are not currently receiving HAART for any reason, should be given CTX.
    - HIV-infected children on HAART who develop virologic failure should restart CTX until the viral load has re-suppressed and there are no other indications, as above, for CTX prophylaxis.

The standard pediatric dosing of CTX is 2.5-5.0 mg trimethoprim (TMP)/kg, to a maximum of 160mg/dose. *CTX must be given OD, and not TIW*. (For *documented, severe* sulfa allergy: dapsone 2mg/kg OD to a maximum of 100mg OD). Recommended simplified CTX dosing (as per WHO guidelines) is as below:

Age (and weight) of child	Recommended daily dose	Suspension (5ML syrup = 200 mg/40mg)	Child tablet (100mg/20mg)	Single strength adult tablet (400mg/80 mg)	Double strength adult tablet (800mg/160 mg)
6 weeks to 6 months (<5kg)	100mg SMX/ 20mg TMP	2.5ml	One tablet	-	-
6 months – 5 years (5-15kg)	200mg SMX / 40mg TMP	5ml	Two tablets	Half tablet	-
6 years to post-pubertal	400mg SMX / 80mg TMP	10ml	Four tablets	One tablet	Half tablet
Post-pubertal adoles-cents and adults	800mg SMX / 160mg TMP	-	-	Two tablets	One tablet

CTX prophylaxis for adolescents and adults:

- CTX prophylaxis must be given to all adults and adolescents with 1) severe immunosuppression, as evidenced by CD4 cell count < 200 cells/μL, *or* 2) 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 may be safely administered during breastfeeding, if clinically indicated as above.
- CTX must be given 960 mg OD (two 480mg single-strength tablets). For *documented* history of *severe* sulfa allergy, give dapsone 100 mg OD.
- When the CD4 count remains > 200 cells/uL for at least 3 months, CTX/dapsone may be stopped, but must be restarted if the CD4 count falls below 200 cells/μL.
- When the active WHO stage 3 or 4 condition has resolved or been stable for at least 6 months, CTX may be stopped.

CTX prophylaxis for patients with active TB:

- CTX prophylaxis, in OD dosing, should be administered to patients of all ages being treated for active TB, in the above 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.

Dapsone and history of "severe" sulfonamide allergy:

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

3.5 Nutritional Support for HIV-Infected Adults and Adolescents:

The following dietary recommendations should be made to all HIV-infected patients, regardless of immune and clinical status:

- 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, avoidance of raw/under-cooked meat, eggs, seafood
- Avoidance of *ingested* traditional medicines, which may adversely affect appetite and cause adverse drug interactions. 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.

Practitioners must identify and treat any conditions which might interfere with proper nutrition, such as oro-esophageal candidiasis, oral or esophageal ulcers, dental disease, and gastroenteritis. Patients must be discouraged from using so-called "immune boosters," which are of unproven benefit and are often very expensive.

3.6 Other Routine Interventions in HIV/AIDS Care:

- *At every visit there must be clinical screening for active TB infection*, i.e., inquiry into symptoms of active TB infection, with further investigations as indicated.
- Regardless of CD4 count, IPT per Botswana IPT protocol should be given to all HIV-infected adults, unless there are contraindications to IPT or a history of IPT or treated TB within the preceding 3 years. Ideally, 6 months of IPT should be given shortly after HIV diagnosis, to avoid potential overlapping toxicities with HAART (e.g., hepatitis), especially if the patient is not yet eligible for HAART. However, IPT may be safely administered with HAART in patients eligible for treatment. (See IPT protocol in Appendix).
    - In pregnancy, IPT initiation should be deferred until after delivery. However, if the patient becomes pregnant while having been on at least 3 months of IPT, then it may be continued to conclusion.
    - Prior to initiation of IPT, it is imperative to screen the patient for any clinical signs or symptoms of active TB, and, if any are present, to defer IPT until further investigations are made. Unless there are clinical symptoms of active TB, routine pre-IPT chest X-ray and sputum studies should be avoided. Clinical screening for active TB must be especially careful in patients with advanced immunodeficiency, since signs and symptoms of active TB may be subtle and difficult to detect in such patients. Nonetheless, IPT should be given to such patients, once active TB is believed not to be present.
    - If possible, avoid IPT initiation simultaneously with NNRTI-based HAART and/or CTX, in order to avoid diagnostic confusion if rash occurs, as well as to avoid increased risk of hepatitis. Nonetheless, IPT may be administered in patients on HAART and/or CTX.
    - Botswana TB guidelines currently do not provide for repeating IPT.
- Adolescents must receive any remaining routine immunizations.

- Advise boiling drinking water for 20 minutes when there is contamination of the water supply. Consider general CTX prophylaxis, until the outbreak has ended.
- Patients in areas with high prevalence of malaria should be encouraged to use treated bed nets at night. CTX prophylaxis should also be considered.
- HBV vaccination should be encouraged for all healthcare workers, especially those who are HIV-infected, and who handle blood and other body fluids.

KEY POINTS:

- ***WHO clinical and immunologic staging should be used for HIV-infected patients.***
- ***CD4 and clinical screening involves both determinations of CD4 cell count/% <u>and</u> targeted clinical history and physical examination, in order to properly determine the patient's WHO clinical stage.***
- ***The CD4 and clinical screening visit is an important opportunity for preventive and supportive care for the patient, including education about HIV disease, safe sex, and healthy lifestyle. Other important aspects of this visit include discussion of family planning and reproductive choices, assessment for psycho-social problems, initiation of CTX prophylaxis and IPT, as indicated, and referral for HAART initiation, if the patient is eligible.***
- ***The objectives of the CD4 and clinical screening visit for pediatric/adolescent patients are the same as that for adults, except that the child's care-giver(s) and other family members must be a part of the process, as well as the patient himself, as appropriate.***
- ***Adolescents require special attention during the CD4 and clinical screening visit (see Section 7.9.4).***
- ***CTX prophylaxis must be provided whenever clinically indicated, <u>especially in HIV-exposed and HIV-infected infants less than 12 months of age</u>.***
- ***Pregnancy is <u>not</u> a contraindication for CTX prophylaxis, when clinically indicated by clinical and immunological status.***
- ***CTX prophylaxis for all age groups of patients should be administered on an OD basis, in order to facilitate adherence, and to provide the full spectrum of benefit of this intervention, including protection against respiratory and diarrheal diseases.***
- ***IPT, routine immunizations, education about boiling drinking water during diarrheal outbreaks, and indicated malaria precautions must be routine aspects of HIV care.***
- ***If possible, avoid IPT initiation simultaneously with NNRTI-based HAART and/or CTX, in order to avoid diagnostic confusion if rash occurs, as well as to avoid increased risk of hepatitis.***
- ***Botswana IPT protocol must always be followed when administering IPT.***

4.0 Indications for Initiation of HAART:

4.1 Indications for HAART Initiation in Infants and Children:

- All HIV-infected infants under age 12 months require prompt initiation of HAART, regardless of immune and/or clinical status.
    - *Infants whose first DNA PCR is positive should immediately be referred for HAART initiation, without waiting for the confirmatory DNA PCR.*
    - *An HIV-exposed baby who has a WHO clinical condition 2, 3, or 4, and for whom the DNA-PCR is not available, should be discussed with an HIV Specialist for possible initiation of HAART, pending return of the DNA PCR, since such babies are at high risk for morbidity and mortality from HIV infection. Babies without WHO clinical stage condition(s) 2, 3, and 4, and for whom the DNA PCR is pending, must be followed on a monthly basis, with WHO staging at each visit, since HIV-infected babies are at high risk for clinical deterioration.*
- For HIV-infected infants and children over 12 months of age, either one of the following two instances requires initiation of HAART:
    - "Advanced" or "severe" symptoms—i.e., WHO clinical stage 3 or 4
    - "Advanced" or "severe" immunosuppression per WHO CD4-based definitions:

Simplified chart for WHO definitions of immune suppression in children over 12 months of age, based on CD4% and/or CD4 count and adjusted for patient age:

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

The table below, modified from WHO definitions, summarizes the clinical criteria for HAART eligibility in children.

Clinical criteria for commencement of HAART in children:

WHO clinical stage	<1 year	12-35 months	36-59 months	≥5 years
Mild (2)	Treat	No HAART	No HAART	No HAART
Advanced (3)	Treat	Treat	Treat	Treat
Severe (4)	Treat	Treat	Treat	Treat

4.2 Indications for HAART Initiation in Adolescents and Adults (pregnant and non-pregnant):

For all adults and adolescents, either one of the following requires HAART:

- WHO clinical stage 3 or 4, *or*
- Any CD4 cell count less than or equal to **250** cells/μL (previously < 200 cells/μL)

The increase in CD4 cell count threshold from 200 cells/μL to 250 cells/μL reflects international consensus that HAART should ideally be initiated *before* the CD4 cell count falls below 200 cells/μL.

For HAART initiation in both adult and pediatric patients:

- 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*: begin the patient on HAART on the basis of the patient's having a WHO clinical stage 3 or 4 condition and being in poor clinical condition. Likewise, do not delay CTX prophylaxis.
    - When beginning HAART in an adult/adolescent without a CD4 count, the possibility that the patient might have a high baseline CD4 count requires initiation with EFV- or LPV/r-based HAART instead of NVP, because of increased risk of NVP-induced hepatotoxicity with high baseline CD4 counts (see Section 5.2).
- There may arise other HIV-related conditions which may justify HAART in certain patients, as well as instances when severe WHO stage 2 conditions, e.g., severe dermatitis, merit HAART. In all such patients, and HIV Specialist should be consulted for possible HAART initiation.
    - A disproportionately low CD4% (< 15%) in an adult with absolute CD4 count > 250 cells/μL may also justify HAART.
    - Although acute HIV infection is not, in and of itself, an indication for HAART initiation, a patient with severe symptoms of the acute retroviral syndrome should be discussed with an HIV Specialist for possible HAART initiation.

4.3 Monitoring Patients Who Are Not Yet Eligible for HAART:

All patients who do not yet qualify for HAART must be periodically monitored, to assess disease progression, and to identify eventual eligibility for HAART initiation.

- For CD4 counts > 400 cells/μL, follow-up visits every 6 months
- For CD4 counts between 250 and 400 cells/μL, follow-up visits every 3 months
- Monitoring frequency should be increased if indicated by clinical condition, e.g., new WHO stage 2 condition.
- *Pediatric patients must be monitored at least every 3 months*, in order to assess CD4 count/% and clinical status, including growth and development.

During these follow-up visits, it is necessary to do more than just a CD4 cell count/% on the patient. As with the initial screening visit, there must also be evaluation for new symptoms and/or physical findings which may change the patient's WHO clinical staging, in which case referral for HAART initiation may be necessary. The preventive and supportive care given at the initial CD4/screening visit should also be provided.

KEY POINTS:

- ***Guidelines for initiation of HAART have been slightly liberalized from prior guidelines, to include all adults and adolescents with WHO clinical stage 3 or 4 conditions, and all adults and adolescents with CD4 cell count ≤ 250 cells/μL (previously < 200 cells/μL).***
- ***Recommended indications for HAART initiation in HIV-infected infants and children depend upon the child's age at time of assessment:***

    - ***All HIV-positive infants under age 12 months should begin HAART.***
    - ***HAART should be given to infants and children over 12 months of age with WHO clinical stage 3 or 4 conditions, or evidence of "advanced" or "severe" immune suppression per WHO age-adjusted CD4 count/% guidelines, as in Section 4.1, above.***
- ***Infants whose first DNA PCR is positive should immediately be referred for HAART initiation, without waiting for the confirmatory DNA PCR.***
- ***An HIV-exposed infant with a WHO clinical stage 2, 3, or 4 condition, and whose DNA-PCR is pending, should be discussed with an HIV Specialist for possible initiation of HAART, pending return of the test.***
- ***If an HIV-infected patient of any age has an active 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: <u>begin the patient on HAART</u> on the basis of the patient's having an active WHO clinical stage 3 or 4 condition and being in poor clinical condition.***
    - ***Before beginning HAART in an adult/adolescent without a CD4 count, consideration must be given to the possibility that the patient might have a high baseline CD4 count, and should be started on EFV- or LPV/r-based HAART and not NVP, because of increased risk of NVP-induced hepatotoxicity with high baseline CD4 count (see Section 5.2).***
- ***For patients not yet eligible for HAART, periodic CD4 and screening visits must entail the same laboratory and clinical evaluation performed in the initial screening visit, as well as indicated preventive care and support.***
    - ***Pediatric patients should be monitored at least every 3 months, in order to assess CD4 count/% and clinical status, including growth and development.***

5.0 HAART Initiation and Follow-Up

5.1 Baseline Evaluation and Preparation for HAART Initiation (Pediatric, Adolescent, and Adult Patients):

- Evaluation for any acute OIs or other serious medical conditions, which would require delay in HAART initiation until the condition has been addressed
- Evaluation of patient/care-giver readiness for HAART:
    - Patient/care-giver understanding and knowledge of HIV therapy
    - Adherence education for patient/care-giver
    - Patient/care-giver willingness to begin treatment
    - Patient willingness to include an adherence partner in treatment: patient disclosure of HIV infection to anyone outside of the clinic is a positive predictor of adherence. The patient should be *strongly* encouraged to bring an adherence partner at HAART initiation, and *the doctor and nurse must actively include the adherence partner in adherence discussions*. However, patient refusal to bring an adherence partner is *not* a reason to defer HAART, and ultimately, once every effort has been made to convince the patient to have an adherence partner, HAART must *not* be withheld in such circumstances. *If the patient fails HAART, re-involving the adherence partner in preparations for the next regimen is crucial for success.*
    - Only in rare instances should HAART initiation be indefinitely postponed in patients with severe neuro-cognitive impairment or psycho-social obstacles, for which family or friends are not available for adherence support. Always consult an experienced HIV clinician in such cases.
    - Refer to section 7.8.1 for further discussion of pediatric and adolescent adherence.
- *Women and children should be evaluated for any past history of sd-NVP for PMTCT.*
- Baseline laboratory tests:
    - ***No baseline viral load***
    - CD4 cell count/%. If the last CD4 count/% has made the patient eligible for HAART, do not repeat the CD4 count/%, unless clinically indicated.
    - FBC and chemistry, to include ALT/AST, urea, creatinine, glucose, electrolytes
    - PI-based HAART: total cholesterol (TC) and triglycerides (TG)
    - TDF-containing HAART: calculation of creatinine clearance, as below
    - Chest X-ray is not required, unless the patient has symptoms suggestive of respiratory disease, *in which case HAART initiation must be delayed*, pending investigations.
    - RPR (adults and adolescents), with indicated treatment and follow-up
    - Baseline PAP smears for all women, with indicated follow-up

Underlying principles and rationale of the 2008 revised first and second line regimens:

- Unless no other viable options exist, *d4T toxicities and side effects mandate that this ARV should no longer be routinely used for adults/adolescents*, both in past regimens under the 2005 guidelines and in the new 2008 regimens. Because of decreased frequency of toxicities in children, d4T may still be used for pediatric patients, but must be replaced at onset of adolescence.
- *Because of high risk of virologic failure when NVP-based HAART is introduced within 6 months of maternal sd-NVP, NNRTIs must not be initiated within 6 months of administration of sd-NVP to the woman, and LPV/r must be used instead.*
- *History of infant sd-NVP also requires avoidance of NNRTI-based HAART*.
- If possible, NVP should be avoided in patients with high baseline CD4 cell counts, as discussed below.
- The recommended second line regimen for pediatric patients has been changed, because of difficulties with adherence to ddI many pediatric patients have experienced.
- Because of risk of anemia, AZT should not routinely be part of any newly initiated first line adult regimen*, except for pregnant women*, and instead is now part of the new second line regimen for adults. AZT remains a first line ARV for all pediatric patients, pregnant women who are eligible for HAART, patients currently on AZT under prior guidelines, and when no other viable ARV options exist.
- Unboosted PIs, e.g., NFV, must be abandoned in favor of boosted PI's, e.g. LPV/r. *Patients of all age ranges who are still on NFV must be switched to LPV/r.*
- With regards to the new second line regimen for adults/adolescents, data from studies in Botswana show increased virologic failure with the NRTI backbone AZT + ddI in first line regimens. In addition, the cost of abacavir (ABC) is prohibitive for routine use in adults in the national program. Thus, it is noted that 3TC in the second line regimen may not exert full anti-HIV activity, while nonetheless having beneficial residual effects on viral load and viral fitness, as well as exerting anti-TAM effects. Moreover, inclusion of 3TC in second line regimen, when it (or FTC) had already been part of first line regimen, is supported in 2006 WHO recommendations for HAART regimens.
- Whether FTC or 3TC is used in adult regimens, below, will depend upon future cost, supply, and availability issues for the national program. FTC and 3TC are essentially interchangeable, and are listed as alternative options in the regimens below.

5.2 Recommended First and Second Line Regimens in Botswana:

For infants and children: Before initiating HAART, *it is essential to determine whether or not the patient received sd-NVP at birth*, since NVP resistance arising from sd-NVP can cause treatment failure with NNRTI-based HAART. *A history of maternal participation in PMTCT is a sufficient indicator of neonatal sd-NVP exposure*.

- First line regimen in treatment-naïve infants and children remains unchanged from the prior (2005) first line regimen, *except in cases where the infant received sd-NVP:*

    - AZT + 3TC + NVP or EFV, if there is no history of neonatal sd-NVP
    - If the child is less than 3 years of age, NVP should be used as the NNRTI, since EFV is not approved for use in children under the age of 3 years.
    - d4T should be used in place of AZT for baseline anemia (HgB < 7.0 gms/dL), for AZT-induced anemia, *or if the patient has symptoms attributable to anemia of any degree*.
    - *If the infant received sd-NVP at birth:*
        - *If under 6 months of age: consult a pediatric HIV Specialist before initiating HAART.*
        - *If over 6 months of age: AZT + 3TC + LPV/r.*
- Second line regimen for pediatric patients who fail the above first line regimen of AZT + 3TC + NNRTI:
    - ABC + d4T + LPV/r
        - If d4T had been used for first line regimen, then AZT should be used in its place in second line regimen. If AZT cannot be used because of persistent anemia, consult an HIV Specialist.
    - After switch to second line regimen, obtain follow-up viral load and CD4 cell count/% measurements at 3 and 6 months post-initiation of the new regimen. If 6 month viral load is < 400 copies/mL, then resume every 3 month viral load and every 6 month CD4 count/% monitoring. If viral load is not < 400 copies/mL at 6 months post-switch, then a pediatric HIV Specialist must be consulted.
- Pediatric patients who are already on prior second line regimen (d4T + ddI + LPV/r), who are virologically suppressed, and who are experiencing no adherence problems with taking ddI on an empty stomach (i.e., no food for the preceding 1-2 hours) and LPV/r at least 1 hour later with food, should continue their current second line regimen. Adherence problems with ddI require switching to ABC, with follow-up priority viral load in 6 weeks. However, onset of puberty requires replacement of d4T/ddI with TDF/FTC (or 3TC), to prevent d4T/ddI toxicities. Following this switch, a follow-up priority viral load should be done in 6 weeks, to ensure continued virologic suppression.
- Pediatric doses of ARVs should be simplified within the therapeutic range as much as possible, to allow for easy dosing and to improve adherence.
- WHO pediatric dosing guides (see Appendix) are the recommended method for determining correct ARV dosing, instead of previous dose calculations.

For adults and post-pubertal adolescents:

- Before initiating HAART in adults and adolescents, the following issues must be considered:
    - Evaluate women for any past history of sd-NVP for PMTCT. Studies have shown an increased risk of virologic failure when NNRTI-based HAART is initiated in women who have received sd-NVP in the past, *especially within 6 months of taking sd-NVP.*
    - Evaluate women for reproductive potential.
    - Determine CD4 cell count regarding risk for NVP hepatotoxicity with high *baseline* values. Avoid NVP if *baseline* CD4 cell count > 250 (women) or > 400 (men) cells/μL.
    - Use AZT-containing HAART for eligible pregnant women, if possible.

- First line regimens in *new* treatment-naïve patients:
    - TDF + FTC (or 3TC) + EFV or NVP, depending upon reproductive potential of female patients, and if the woman has not received sd-NVP within the prior 6 months
    - TDF + FTC (or 3TC) + LPV/r *for women who have received sd-NVP within the prior 6 months*
    - AZT + 3TC + NVP *for pregnant women* initiating HAART for their own HIV infection, and *who have CD4 cell count < 250 cells/μL*. After delivery, continue this AZT-based regimen, if there have been no AZT-associated side effects.
    - EFV or LPV/r must be used in place of NVP for women with *baseline* CD4 cell count > 250 cells/μL, and for men with *baseline* CD4 cell count > 400 cells/μL. As a rule, EFV will be an appropriate choice for such male patients, but should be avoided in pregnancy and in women with reproductive potential, in which cases LPV/r should be used instead.
- Second line regimen for patients who have failed the first line regimen of TDF + FTC (or 3TC) + EFV or NVP:
    - AZT + 3TC + LPV/r ("Kaletra" or "Aluvia")
    - After switch to second line regimen, obtain follow-up viral load and CD4 cell count measurements at 3 and 6 months post-initiation of the new regimen. If the viral load is < 400 copies/mL at 6 months, then every 6 month viral load and CD4 count monitoring can be resumed.
- Patients who are currently on previous first line regimens of AZT + 3TC + NNRTI *should be maintained on this regimen*, as long as it is fully suppressive, and as long as there are no AZT-related side effects, e.g., lipoatrophy, peripheral neuropathy.
    - Patients who eventually fail the prior first line regimen of AZT + 3TC + NNRTI, including women started on AZT-based HAART during pregnancy, should be switched to TDF + FTC (or 3TC) + LPV/r as their second line regimen. If failure of this first line regimen occurs during pregnancy, discuss use of TDF-based second line regimen with an HIV Specialist.
- 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 (or 3TC) + EFV or NVP.
    - If viral load has not been done within the prior 6 months (and < 400 copies/ ml), then first obtain priority viral load, and if < 400 copies/mL, proceed with the switch. If not < 400 copies/mL, then address treatment failure.
    - Obtain follow-up priority viral load 6 weeks after the switch to TDF + FTC. If viral load is < 400 copies/mL, then resume every 6 month determinations. If full viral suppression is not maintained, an HIV Specialist must be consulted.
    - For failure of this modified first line regimen (TDF + FTC [or 3TC] + EFV or NVP), the second line regimen should be AZT + 3TC + LPV/r, if the baseline anemia (or other AZT complications) has resolved. If not, then consult an HIV Specialist.
- Patients who are currently on a fully suppressive second line regimen of d4T + ddI + LPV/r *should be switched* to TDF + FTC (or 3TC) + LPV/r.

- If viral load has not been done within prior 6 months (and < 400 copies/ ml), then first obtain priority viral load, and if < 400 copies/mL, proceed with switch. If not < 400 copies/mL, then address treatment failure.
- Obtain follow-up priority viral load 6 weeks after the switch. If viral load is < 400 copies/mL, then resume every 6 month determinations. If full viral suppression is not maintained, an HIV Specialist must be consulted.

Patients whose *first* regimen must be LPV/r-based *and who eventually fail such a regimen*:

- Women, infants and children whose first regimen must be LPV/r-based because of prior sd-NVP, and who fail this regimen, should have a genotypic resistance assay performed, and must be promptly discussed with an HIV Specialist, since it is unclear whether NNRTI-based second line regimens will be effective in such patients. Do not wait for the assay to return before discussing the case with a 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 NVP- or EFV-based second line regimens, but with careful monitoring of AST/ALT for possible increased risk of hepatotoxicity. Although there are little data on this matter, EFV may be preferable to NVP in such instances, if possible. Patient education about hepatitis symptoms is necessary.

There are certain side effects, potential complications, and clinical caveats about these new regimens, with which the clinician must be familiar:

- TDF and potential for renal failure:
  - *Creatinine clearance must be calculated* and recorded at baseline, at the 3 and 6 month post-initiation visits, and, if stable, every 6 months thereafter. 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*. C_{creat} 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 creat.]
    - Females:1.037 x [(140 – age in yrs) x wt (kg)]/ [serum creat]
  - If baseline C_{creat} is < 60cc/minute, do not initiate TDF, and follow the algorithm, below. If C_{creat} becomes < 50cc/minute while on TDF, promptly consult an HIV Specialist.
    - Although some guidelines permit use of reduced TDF dosing intervals with baseline C_{Creat} < 60 cc/minute, this approach is not recommended in Botswana, because of the risk of adherence problems with every 48 or 72 hour TDF dosing schedules for renal insufficiency. TDF should not, as a rule, be initiated when baseline C_{Creat} is < 60 cc/minute.
- TDF, renal insufficiency, and calculation of creatinine clearance:
  1) When baseline creatinine clearance is < 60cc/minute:
     - *Recalculate the creatinine clearance 2-3 days later*, repeating the serum creatinine and patient weight, which should be verified with another set of scales. If the repeat clearance is still < 60cc/minute:

        - Initiate HAART with AZT, or, if there is significant baseline anemia, d4T. If already on d4T, continue d4T and do not switch to TDF.
            - Patients initiated on AZT should continue this ARV indefinitely, as long as there are no AZT side effects.
        - For patients initiated on d4T, or who have already been on d4T, monitor the creatinine clearance every 3 months, until it is > 60cc/minute, at which time switch to TDF can be done. Also, monitor the patient at every visit for any adverse effects of d4T.
        - If side effects from either AZT or d4T develop, and creatinine clearance remains < 60cc/minute, then consult an HIV Specialist.

    2) <u>When serum creatinine cannot be done:</u>

    - Proceed with TDF initiation or switch, <u>*unless*</u> 1) the patient is over 60 years of age, 2) the patient has a history of renal disease (insufficiency, chronic infection, stones), 3) there is greater than trace proteinuria on urinalysis, 4) serum urea is above the upper limit of normal range, <u>or</u> 5) the patient has conditions such as diabetes or uncontrolled hypertension, which might impair renal function. When serum creatinine can eventually be done, monitor creatinine clearance per usual laboratory schedules.
    - For patients who fall into one or more of the above five clinical situations, initiate HAART with AZT (or d4T, if there is anemia). If already on d4T, continue d4T and do not switch to TDF.
        - Patients initiated on AZT should continue this ARV indefinitely, as long as there are no AZT side effects.
        - Once serum creatinine can be done, monitor creatinine clearance every 3 months for patients on d4T, until it is > 60cc/minute, at which time switch to TDF can be done. Also, monitor the patient at every visit for any adverse effects of d4T.
        - If side effects from either AZT or d4T develop, then consult an HIV Specialist.

- When it is necessary to use d4T, as above, the adult dose should ideally be 30mg BD, regardless of weight, in order to minimize potential d4T side effects. However, the 40mg BD dose may be used, if the 30mg dose is not available.
- NVP-associated rash and hepatotoxicity: <u>*always educate patients/care-givers about symptoms of hepatitis*</u>.
    - The initial dose of NVP should be OD for two weeks for all age ranges.
    - After NVP initiation, follow-up in 2 weeks for evaluation for any side effects and for AST/ALT testing. If there are no apparent clinical signs or symptoms of side effects, increase NVP to BD, with follow-up in another 2 weeks, for repeat clinical evaluation and AST/ALT.
    - For benign rash within the first 2 weeks of NVP initiation, maintain OD dosing, and obtain AST/ALT, to rule out prodrome of hepatitis. When rash resolves, then dose-escalate to BD. If benign rash occurs after BD dose escalation, continue BD dose but monitor patient closely.

    - ***Do not use systemic steroids*** to prevent or to treat benign NVP/EFV-associated rash, since such use of steroids may cause severe SJS and death.
- NVP-associated hepatitis with high baseline CD4 cell counts:
    - NVP should be avoided 1) in women with *baseline* CD4 counts > 250 cells/μL, and 2) in men with *baseline* CD4 cell counts > 400 cells/μL (e.g., HAART initiation for WHO clinical stage 3 or 4 condition alone).
    - Alternative options include: 1) EFV in place of NVP (not in pregnancy or when the woman has reproductive potential), 2) LPV/r as the third ARV in the regimen, and 3) use NVP, but with close monitoring of AST/ALT and patient education regarding the symptoms of hepatitis.
    - The risk for hepatitis may not be increased in instances where the patient has been on fully suppressive non-NVP-based HAART, has a HAART-induced CD4 cell count increase to > 250 cells/μL (women) or > 400 cells/μL (men), and now has to be switched to NVP-based HAART (e.g., because of persistent CNS side effects of EFV, EFV-induced gynectomastia, or because a woman on EFV wishes to become pregnant). Such switching is probably safe, provided the viral load is undetectable and there is no hiatus between discontinuation of EFV and replacement with NVP. In such cases, dose escalation of NVP is *not* required, and the BD dose can be started. Monitor the patient for any NVP-induced hepatitis and educate the patient about signs and symptoms of hepatitis.
- EFV contraindications:
    - EFV should be avoided in women with reproductive potential. In those situations where EFV cannot be avoided (e.g., regimen switch due to NVP side effects), there must be counseling at each visit about consistent contraception and about notifying the practitioner if the patient wishes to become pregnant, of if pregnancy occurs.
    - EFV should be avoided in patients with severe acute or chronic psychiatric illnesses (e.g., psychosis, depression, bipolar disorder, schizophrenia), unless the potential benefits outweigh the risks.
    - EFV must not be used in children under 3 years of age.
    - Chronic, controlled seizure disorder is *not* a contraindication to EFV use, but because of adverse drug interactions, EFV should not be used with carbamazepine.
- "Truvada" is co-formulated TDF and FTC, is now available to the National Program, and dosed OD. "Atripla" is co-formulated TDF, FTC, and EFV, and is taken OD. It will available to the National Program by the end of 2008.
- TDF use in adolescents:
    - In order to reduce the chances of bone demineralization, TDF may be used only in adolescents at Tanner Stage 4 or higher (See Appendix for detailed Tanner staging). Nonetheless, TDF-associated bone demineralization is occasionally seen in children who are at Tanner 4 or higher, but at a lower frequency than is seen in younger children (Tanner 3 and lower). Clinicians should be aware of this possibility, if a child on TDF presents with frequent fractures.

- TDF use in pregnancy and theoretical effects on fetal bone mineral density:
    - There is no clear consensus concerning TDF use in pregnancy, with some recommendations allowing TDF use "with caution," if no other alternatives exist.
    - Pregnant women requiring HAART for their own HIV infection should be started on an NRTI backbone of AZT/3TC, to enhance PMTCT and to avoid the above concerns about TDF. If AZT cannot be used, e.g., due to anemia, then d4T should be used, but after delivery, d4T should be changed to TDF. If the woman has already failed an AZT- or d4T-based regimen, then an HIV Specialist should be consulted.
        - Pregnant women who have been initiated on AZT-based HAART should generally continue AZT after delivery, as long as there are no AZT-associated side effects.
        - When d4T must be used in place of AZT, monitor the patient's HgB, and if the anemia improves on HAART, then switch to AZT, with close follow-up of HgB.
    - It is advisable to switch pregnant patients already on TDF to AZT, both to avoid theoretical effects on fetal BMD and to provide additional PMTCT effect. After delivery, decisions about continuing AZT or switching back to TDF should be individualized and discussed with the patient.
    - *Women on TDF who have reproductive potential should be told to notify their practitioners if they wish to become pregnant, or if they become pregnant*.
    - Nonetheless, if no other alternatives exist, TDF may still be taken during pregnancy, pending further data to the contrary.
- Discontinuation of TDF/FTC (or 3TC) in patients with chronic HBV infection:
    - In patients with HBV infection, discontinuation of these ARVs, which have anti-HBV activity, may cause a "hepatitis flare". In patients who have chronic HBV infection, or whose HBV status is unknown, monitor AST/ALT 2 and 4 weeks post-discontinuation, with patient education about hepatitis symptoms. If hepatitis develops, then HBV surface antigen should be obtained, to clarify the cause of the hepatitis. Patients with suspected HBV flare should be managed in consultation with an HIV Specialist.
- NRTI doses in renal insufficiency:
    - As a rule, all NRTIs, excluding ABC, require dose-reduction with renal insufficiency, but there are sparse data on how best to address this subject for the African setting. At baseline, many African patients with advanced or severe immunodeficiency have mild to moderate renal insufficiency, *which usually improves significantly over time on HAART prescribed at standard ARV dosages*.
    - All patients with baseline C_{Creat} < 30 cc/minute, or who are on dialysis, must be discussed with an HIV Specialist before initiating NRTIs, excluding ABC.
    - *Patients with baseline C_{Creat} between 30 and 90 cc/minute may be initiated on standard doses of NRTIs, but require follow-up C_{Creat} in three months*. If follow-up C_{Creat} has not improved compared to

baseline, then an HIV Specialist must be consulted for possible dose reduction of the NRTIs.
    - If any NRTI is prescribed at a lower dose due to renal insufficiency, *it is imperative to monitor C_{Creat} at every three month intervals*, until the clearance has increased to > 50 cc/minute, *at which point the NRTI dose(s) must be increased to standard levels.* Failure to do so risks ARV under-dosing, with subsequent risk of treatment failure.
- LPV/r for adults should be dosed 400mg LPV/100mg RTV BD:
    - Kaletra capsules (133mg LPV/33mg RTV), dosed at *three* capsules BD, or
    - Aluvia tablets (200mg LPV/50mg RTV), dosed as *two* tablets BD
    - Unlike Kaletra, Aluvia is heat-stable and has no food requirements.
- NFV is no longer part of any recommended regimen, and should not be used, *including in pregnant women*, unless under the guidance of an HIV Specialist.

5.3 Third Line Regimens in Botswana:

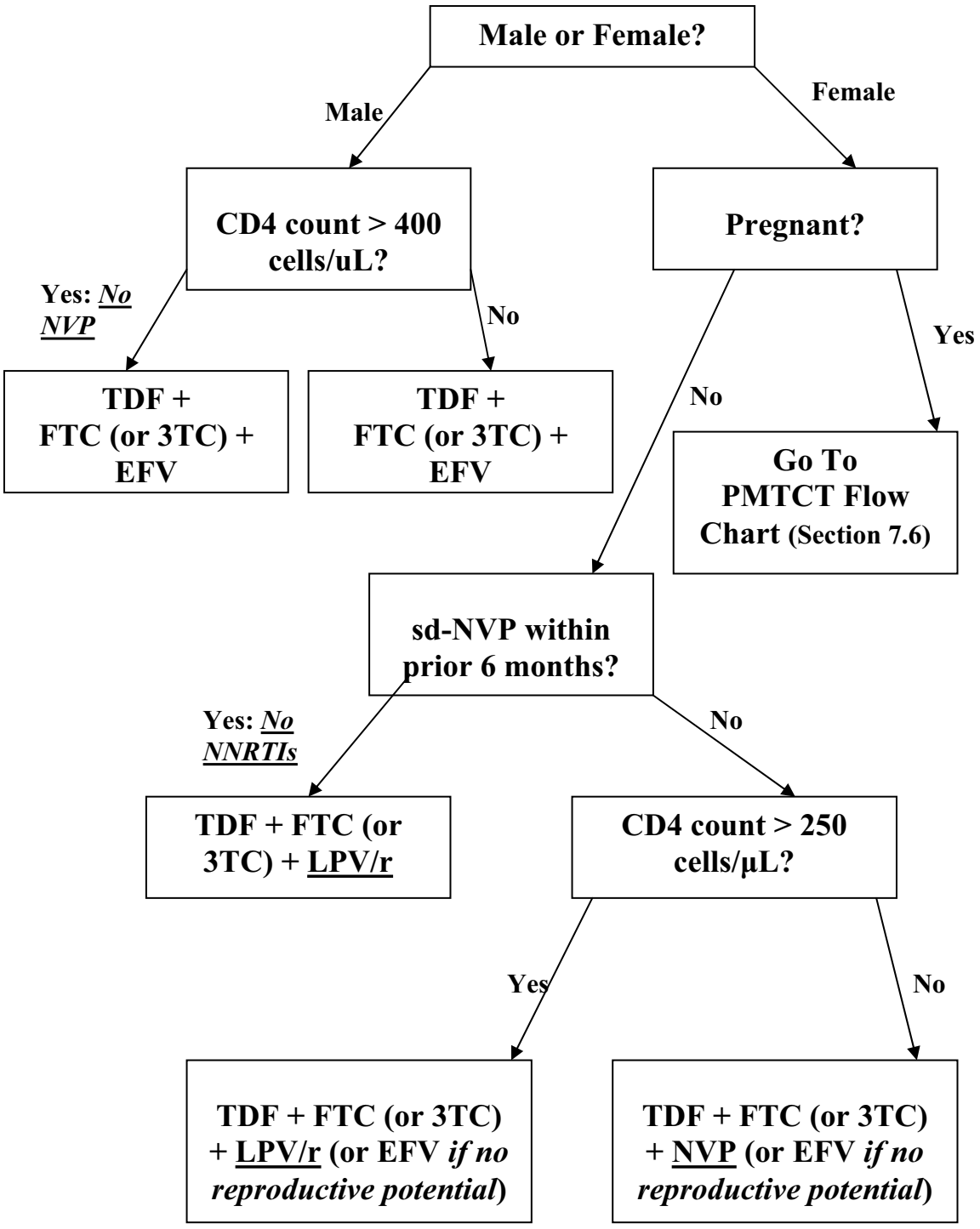
Patients who have failed both first and second line regimens require very close and intensive management.

- The patient must be referred to the clinic's Failure Management Team and Failure Management Clinic (See Chapter 8).
- A genotypic resistance assay must be obtained while the patient is still taking the failing second line regimen, or within 4 weeks of discontinuation of the failing regimen.
- *Do not wait for more than 4 weeks for the resistance assay to return.* If the resistance assay does not return within 4 weeks, the case must be discussed with an HIV Specialist for recommendations for prompt switching to an empiric third line regimen, pending eventual return of the resistance assay.
- *Intensive* psychosocial and adherence evaluation must be undertaken. *The patient's original adherence partner should be actively included in this intervention*. If the patient did not have an adherence partner at initiation of his first line regimen, then he must be *strongly encouraged* to include an adherence partner at this extremely critical stage of his care.
- Inquiries must be made into use of traditional/herbal medicines, as well as other drugs (prescription and over-the-counter), including alcohol and recreational drugs, to rule out drug-drug interactions and drug-related adherence lapses as causes of failure.
- Specifically inquire into whether the patient is on ATT, since patients may not report such treatment, which has significant drug interactions with PIs.
- Chronic gastroenteritis must be ruled out as a possible cause of regimen failure.
- Safe sex must be constantly reinforced, and the risk of transmitting ARV resistance to sexual partners must be stressed.
- Any indicated prophylaxis, e.g., CTX or fluconazole, must be continued or restarted.
- Once the third line regimen has been started, there must be intensive follow-up, with frequent clinic visits and home visits by clinic nurses and/or social workers.
- After switch to third line regimen, obtain follow-up viral load and CD4 cell count/% measurements at 3 and 6 months post-initiation of the new regimen.

If the viral load is < 400 copies/mL at 6 months, then every 6 month viral load monitoring should be done for adults (continue every 3 month monitoring for pediatric/adolescent patients). CD4/% monitoring can return to every 6 months for all ages.

- By late 2008, two new, highly potent ARVs will be available for use as "salvage" therapy for patients who have failed multiple ARV regimens, and who have significant resistance mutations. Darunavir (DRV) is a potent protease inhibitor, which is active against HIV with multiple PI resistance mutations. Raltegravir (RAL) is an integrase inhibitor which has shown great efficacy in highly treatment-experienced patients. A successful "salvage" regimen must contain *at least two fully active ARVs*, in order to prevent the eventual emergence of resistance due to *de facto* monotherapy. "Salvage" therapy consisting of DRV and RAL (plus optimized background therapy) is anticipated to be a highly potent regimen in Botswana, which, if used properly, should result in full virologic suppression in the majority of cases. Access to these two important ARVs will be controlled by the HIV Specialists comprising the Resistance Technical Working Group (TWG) of the Ministry of Health. A patient who may require such "salvage" HAART should be referred to an HIV Specialist, who will then discuss the case with the TWG. Clinicians should familiarize themselves with details of these two new ARVs, and listed below is a brief summary of essential points about their use:
    - DRV dosing (300mg tablets): 600mg BD *with 100mg RTV BD*, taken with food. Major side effects: diarrhea, hepatitis, rash (rare SJS). Metabolized by CYP450 3A4, and drug interactions are anticipated.
    - RAL dosing (400mg tablets): 400mg BD. No significant side effects or drug interactions have been reported to date.

SUMMARY: HAART INITIATION FOR *NEW*, ARV-NAÏVE PATIENTS:



5.4 Goals of ARV Therapy:

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

- The virologic goal of HAART initiation is achievement of viral load < 400 copies/mL by no later than 6 months after starting HAART.
- For the vast majority of *adult* patients initiated on HAART, the viral load obtained at 3 months post-initiation will be < 400 copies/mL. However, a minority of adults may require longer—i.e., up to 6 months—before viral load becomes undetectable. *For the adult patient whose viral load at 3 months is not < 400 copies/mL, there must be careful evaluation and monitoring for impending treatment failure, especially with regards to nonadherence*.
- All women who have received sd-NVP *any time in the past*, and who are initiated on NNRTI-based HAART, require close monitoring for virologic failure. *Any such woman whose viral load at 3 months after initiation of NVP or EFV is not < 400 copies/mL must promptly be discussed with an HIV Specialist*.
- Pediatric patients may require longer than 3 months to fully suppress viral load, but should nonetheless have viral load < 400 copies/mL no later than 6 months after HAART initiation. *Pediatric and adolescent patients who do not achieve a viral load < 400 copies/mL by 6 months after HAART initiation must be discussed with a pediatric HIV Specialist.*

Conversely, for both adult/adolescent and pediatric patients, virologic failure has occurred whenever one of the following two situations arises:

- Viral load is not < 400 copies/mL by 6 months after HAART initiation, or
- After initially being suppressed to < 400 copies/mL, viral load becomes detectable (i.e., > 400 copies/mL) at some later time in the future.

5.5 Recommended Schedule for Monitoring Patients on HAART:

- Clinical evaluation of patients on HAART:
  - During the first two years after HAART initiation, every patient should be seen on *at least a regular, every- 3-month basis*, and more often as clinically indicated.
  - If after two years of HAART an *adult* patient has remained clinically stable, has not had any treatment failure, is believed to be fully adherent, and has not developed ARV toxicity or other HIV-related complications, routine follow-up visits may then be decreased to every 6 months. *Pediatric and adolescent patients must continue to be followed at least every 3 months, until age 20 years.*
  - Clinical evaluation must include inquiry into possible ARV side effects, as well as any other patient signs and symptoms.
  - Every visit must include assessment of adherence and initiation of any interventions necessary to enhance adherence. Pharmacy staff should inform the practitioner if adherence < 90% is detected or suspected.
  - Safe sex, nutrition, and avoidance of smoking and ingested traditional medicines should be reinforced at every visit.
  - Family planning/reproductive choices should be reviewed every visit.
  - At every visit there must be clinical screening for active TB infection, i.e., inquiry into symptoms of active TB infection, with further investigations as indicated.

- Ongoing patient education about HIV is essential: e.g., *the patient/care-giver should eventually know the names and doses of the ARVs and other HIV-related medications.*
- All pediatric patients must be assessed for growth and development, with graphing of weight and height for all children, and head circumference measurements for patients under age 2 years of age.

- Laboratory monitoring of patients on HAART:

After obtaining baseline, pre-initiation laboratory tests (see Section 5.1), routine laboratory monitoring of patients initiated on HAART has been significantly streamlined from prior (2005) guidelines:

- CD4 cell count/%: 3 and 6 months post-initiation, then every 6 months (all ages)
- Viral load: 3 and 6 months post-initiation, then as follows:
  - Every 6 months for adults
  - Every 3 months for pediatric patients and adolescents
- FBC:
  - AZT-based HAART: at 4 and 12 weeks post-initiation, ***then annually only***, and as clinically indicated
  - If not on AZT-based HAART: ***annually only***, and as clinically indicated
- AST/ALT:
  - NVP-based HAART: 2, 4, and 12 weeks post-initiation, thereafter ***only as clinically indicated***
  - EFV-based HAART: 4 and 12 weeks post-initiation, thereafter ***only as clinically indicated***
  - PI-based HAART: only as clinically indicated
- Glucose and total cholesterol/triglycerides annually ***only if on PI-based HAART***
- Creatinine and creatinine clearance (C_{Creat}): 3 and 6 months post-initiation and then, if stable, every 6 months (TDF only)
- Chemistry: after baseline, only as indicated
- RPR: after baseline, only as indicated

New (2008) Adult 1st Line Regimen: TDF + FTC (or 3TC) + NVP or EFV

	Baseline	**2 weeks**	**1 month**	**3 months**	**6 months**	**12 months**	**Thereafter**
CD4 count	✓			✓	✓	✓	q6 months
Viral load	**NONE**			✓	✓	✓	q6 months
FBC	✓					✓	q12 months
Chemistry	✓						As indicated
AST/ALT	✓	✓ (NVP only)	✓	✓			As indicated
Creatinine & C_{Creat}	✓			✓	✓	✓	q6 months
RPR	✓						As indicated

New (2008) Adult 2nd Line Regimen: AZT + 3TC + LPV/r

	At switch	1 month	3 months	6 months	12 months	Thereafter
CD4 count			✓	✓	✓	q6 months
Viral load			✓	✓	✓	q6 months
FBC	If not done at baseline	✓	✓		✓	q12 months
Chemistry	As above					As indicated
AST/ALT	As above					As indicated
Glucose, TC/TG	If not done in prior 12 mos				✓	q12 months
RPR	If not done at baseline					As indicated

Prior (2005) and Pregnant Adult 1st Line Regimen (AZT + 3TC + NVP or EFV):*

	Baseline	2 weeks	1 month	3 months	6 months	12 months	Thereafter
CD4 count	✓			✓	✓	✓	q6 months
Viral load	(***NONE***)			✓	✓	✓	q6 months
FBC	✓		✓	✓		✓	q12 months
Chemistry	✓						As indicated
AST/ALT	✓	✓ (NVP only)	✓	✓			As indicated
RPR	✓						As indicated

***Note**: For patients already on prior 1st line regimen, start this monitoring schedule at whatever post-initiation stage of the regimen each individual patient is in at the time of release of these guidelines. Follow this schedule also for pregnant patients started on the above NVP-based regimen.

Prior (2005) Adult 1st Line Regimen d4T + 3TC + NVP/EFV: Change to TDF + FTC/3TC + NVP/EFV

Prior (2005) Adult 2nd Line Regimen d4T + ddI + LPV/r: Change to TDF + FTC/3TC + LPV/r

	At time of switch	**6 weeks**	**3 months**	**6 months**	**12 months**	**Thereafter**
CD4 count	If not done within prior 6 months			✓	✓	q6 months
Viral load	If not done within prior 6 months **and < 400 copies/mL**	✓		✓	✓	q6 months
FBC	If not done within prior 12 months					q12 months
Chemistry	If not done at baseline					As indicated
AST/ALT	If not done in first 3 mos of ART (NNRTI only)					As indicated
Glucose, TC/TG	If not done within prior 12 months				✓	q12 months
Creatinine & C_{Creat}	✓		✓	✓	✓	q6 months
RPR	If not done at baseline					As indicated

Pediatric 1st Line Regimen (*Unchanged*): AZT + 3TC + NVP or EFV

	Baseline	**2 weeks**	**1 month**	**3 mos**	**6 mos**	**9 mos**	**12 months**	**Thereafter**
CD4 count/%	✓			✓	✓		✓	q6 months
Viral load	**NONE**			✓	✓	✓	✓	*q3 months*
FBC	✓		✓	✓			✓	q12 months
Chemistry	✓							As indicated
AST/ALT	✓	✓ (NVP only)	✓	✓				As indicated
Growth & development	✓		Weight only	✓	✓	✓	✓	*q3 months*

New (2008) and Prior (2005) Pediatric 2nd Line Regimen: ABC (or ddI*) + d4T + LPV/r

	At switch	6 weeks	3 months	6 months	9 months	12 months	Thereafter
CD4 count/%	If not done in prior 6 months		✓	✓		✓	q6 months
Viral load	If not done in prior 3 mos **and < 400 copies/mL** (for ddI switch to ABC only)	✓ (For switch of ddI to ABC)	✓	✓	✓	✓	*q3 months*
FBC	If not done in prior year					✓	q12 months
Chemistry	As with FBC						As indicated
AST/ALT	As with FBC						As indicated
Glucose, TC/TG	✓					✓	q12 months
Growth & development	✓	Weight only	✓	✓	✓	✓	*q3 months*

* If no adherence problems with ddI, continue prior (2005) 2nd line regimen (d4T + ddI + LPV/r) and follow this laboratory schedule. If adherence problems with ddI, switch from ddI to ABC, obtain 6 week viral load, and then follow above laboratory schedule.

New Pediatric 1st Line Regimen Modified for Exposure to sd-NVP: AZT + 3TC + LPV/r

	Baseline	1 month	3 months	6 months	9 months	12 months	Thereafter
CD4 count/%	✓		✓	✓		✓	q6 months
Viral load	**(NONE)**		✓	✓	✓	✓	*q3 months*
FBC	✓	✓	✓			✓	q12 months
Chemistry	✓						As indicated
AST/ALT	✓						As indicated
Glucose, TC/TG	✓					✓	q12 months
Growth and development	✓		✓	✓	✓	✓	*q3 months*

Notes on laboratory testing:

- Certain viral load and CD4 count determinations require *priority* designation:
  - Viral loads on all patients < 20 years of age
  - Confirmation of virologic failure in a patient on HAART
  - Follow-up 6 week VL to confirm continued virologic suppression after switching from suppressive 2nd line adult and pediatric regimens (2005 guidelines) to the new 2nd line regimens under these guidelines

    - Follow-up 6 week VL after restarting/continuing HAART after completed interventions for treatment failure due to non-adherence, drug interactions, inappropriate ARV dose, and gastroenteritis
    - Follow-up 6 week VL after ARV switch for side effects or toxicity, when there had previously been full virologic suppression prior to the switch
    - VL done prior to switching from a prior adult or pediatric regimen containing d4T and/or ddI, when there has been no viral load performed within the previous 6 months
    - *CD4 cell count for any pregnant woman who is not yet on HAART, in order to determine her eligibility for HAART.*
    - On the relevant laboratory forms, priority tests should be marked "priority," along with the reason for this designation. This protocol will be monitored for any abuse.
- "Chemistry" testing should include glucose, electrolytes, urea, and creatinine.
- "As indicated" does not imply routine testing, and instead means testing only if clinically indicated for an individual patient situation. ***Do not "routinely" order FBC, AST/ALT, CD4 cell count/%, and viral load every three months: follow the above schedules.***
- If the CD4 cell count/% response at 12 months after HAART initiation has been adequate (CD4 increase > 25-50 cells/μL for adults and adolescents, or CD4% increase > 5 percentage points above baseline for pediatric patients), CD4 cell count/% should be monitored only every 6 months.
- Any change in HAART for treatment failure requires follow-up viral load and CD4 cell count/% measurements at 3 and 6 months post-initiation of the new regimen. If the viral load is < 400 copies/mL at 6 months, then every 6 month viral load monitoring should be done for adults (continue every 3 month monitoring for pediatric/adolescent patients). CD4 cell count/% monitoring can return to every 6 months for all ages.
- Any change in HAART regimen for toxicity or side effects requires repeat priority viral load 6 weeks after the switch, to ensure continued virologic suppression. If this 6 week viral load remains < 400 copies/mL, then resume normal viral load monitoring, according to whether the patient is adult or pediatric/adolescent. CD4 cell count/% monitoring can remain at every 6 month intervals.
- *For pediatric and adolescent patients: viral load every 3 months until age 20 years.*
- CD4 cell count/% measurements should return to every three month frequency (or more often as clinically indicated) whenever any of the following situations arises:
    - Any new WHO stage 3 or 4 clinical condition or symptom
    - Whenever a previously suppressed viral load becomes detectable
    - Any time the patient's HAART regimen is changed for treatment failure
    - Any time non-adherence is suspected
    - Whenever 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/% determinations may return to every 6 months.

- Once a patient's CD4 cell count/% 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.
- A significant elevation of AST/ALT has occurred when it is greater than five times the upper limits of normal for each test.
- When ATT is initiated in a patient on HAART, or *vice-versa,* AST/ALT should be monitored monthly for the first 3 months, or more frequently as indicated.
- On a case-by-case basis, practitioners may have the discretion to decrease frequency of pediatric and adolescent viral load testing to every 6 months, but only 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.
- HBsAg should be obtained when hepatitis occurs soon after discontinuation of ARVs with anti-HBV activity (see Section 5.2)
- Certain clinical situations—e.g., chemotherapy for KS—may merit closer monitoring of certain laboratory tests.
- The above laboratory and clinical evaluations should also apply to patients who are continued on prior HAART regimens.
- Whenever DNA PCR tests, resistance assays, CD4 cell counts, and viral loads are delayed, determine from the referral laboratory an estimated "time line" 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.*

5.6 Switching ARVs for Toxicity or Severe Side Effects:

- Symptomatic lactic acidosis is a life-threatening complication, and all ARVs must be stopped immediately, in spite of the long half-lives of NNRTIs.
- SJS usually obligates cessation of all ARVs, to permit recovery from the SJS. However, certain clinical distinctions and strategies may preserve NNRTI treatment options after the SJS resolves:
    - 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 all ARVs must be stopped simultaneously.
    - Some patients may initially have mild symptoms of early SJS due to NVP, and may not appear seriously ill, e.g., minimal mucous membrane involvement, lip swelling alone, or fever only. In these patients it may be possible to stop the NVP, while continuing the two N[t]RTIs for 3-5 days before stopping them, to save EFV as an alternative ARV option once the early SJS has resolved.
- In patients taking NNRTI-based HAART, significant hepatitis (AST/ALT > 5 times the ULN) generally requires discontinuation of all drugs, including ARVs. However, if the AST/ALT elevations are not > 10 times the ULN, and if the patient does not have jaundice, fever, or vomiting, and appears non-toxic, it may be possible to discontinue NVP while continuing the two N[t]RTIs for 3-5 days, to preserve EFV as a possible future treatment option after the hepatitis resolves. However, if one of the NRTIs is ABC, which is metabolized by the liver, then all ARVs must be stopped simultaneously.

- For mild hepatitis or early SJS which is 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. However, for EFV-associated hepatitis or SJS, 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*.
- Because of up to 50% cross-reactivity between NVP and EFV, any substitution of EFV for NVP-associated toxicity must entail careful patient education and clinical/laboratory follow-up. If there is any concern that replacement of NVP with EFV may risk recurrence of the toxicity, then LPV/r should be used instead.

5.7 ARV-Related Hyperlipidemia and Its Management

All classes of ARVs in the Botswana National Program can cause elevated total cholesterol (TC) and triglycerides (TGs), which, if not addressed, may lead to long-term, serious cardiovascular and/or cerebrovascular disease. In addition, elevated TGs can cause pancreatitis. *Because patients are living longer on HAART, lipid-related mortality and morbidity due to ARV therapy must be addressed promptly*, including modification of other vascular risk factors such as smoking, hypertension, and diabetes. Elevated lipids can appear within the first several months of ARV therapy. The most significant lipid abnormalities occur with d4T and PIs, including LPV/r, whereas NNRTIs cause relatively minor increases in cholesterol. Prior to initiation of PI-based HAART, baseline TC and TGs should be done, and, if elevated, appropriate management and follow-up are necessary. Patients on PI-based HAART 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 the presence of known vascular risk factors or disease:

- For known vascular disease or diabetes, LDL should be < 2.5 mmol/L
- For 2 or more cardiac risk factors, LDL should be < 3.3 mmol/L
- For no cardiovascular risk factors, LDL should be < 4.0 mmol/L
- As a rule, TGs should be < 4.5 mmol/L

Any increased LDL (per above) and/or TG > 4.5 mmol/L requires the following stepwise 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, then drug therapy:
    - Pravastatin 10-20 mg OD
    - For increased TGs, bezafibrate 200mg BD
- Follow-up lipids every 3 months until normal, and thereafter annually
- Consultation with an HIV Specialist if the above interventions are unsuccessful.

KEY POINTS:

- ***Baseline viral load must no longer be done.***

- ***Only in rare instances should HAART initiation be indefinitely postponed in patients with severe neuro-cognitive impairment or psycho-social obstacles, for which family or friends are not available for support.***
- ***Before initiating HAART in adults and adolescents, the following issues must be considered:***
    - ***Evaluate women for any past history of sd-NVP for PMTCT within the previous 6 months.***
    - ***Evaluate women for reproductive potential.***
    - ***Determine baseline CD4 cell count regarding risk for NVP hepatotoxicity with high baseline values. Avoid NVP if baseline CD4 cell count > 250 (women) or > 400 (men) cells/μL.***
    - ***Use AZT-containing HAART for eligible pregnant women, if possible.***
- ***Recommended first and second line HAART regimens for <u>new</u> adult and adolescent patients remain NNRTI- and PI-based, respectively, and only the N[t]RTI backbone has been changed:***
    - ***The first line N[t]RTI backbone for <u>new</u> adult/adolescent patients (non-pregnant) is TDF + FTC (or 3TC). NVP and EFV remain the preferred NNRTIs in first line regimen.***
    - ***The second line NRTI backbone for patients failing the above new first line regimen is AZT + 3TC. LPV/r (Kaletra or Aluvia) remains the preferred PI in the second line.***
- ***First line regimens in <u>new</u> treatment-naïve adult/adolescent patients:***
    - ***TDF + FTC (or 3TC) + EFV or NVP, depending upon reproductive potential of female patients***
    - ***TDF + FTC (or 3TC) + LPV/r <u>for women who have received sd-NVP within the prior 6 months</u>***
    - ***AZT + 3TC + NVP <u>for pregnant women</u> initiating HAART for their own HIV infection, and who have CD4 cell count < 250 cells/μL. After delivery, continue this AZT-based regimen, if there have been no AZT-associated side effects.***
    - ***EFV or LPV/r must be used in place of NVP for women with baseline CD4 cell count > 250 cells/μL, and for men with baseline CD4 cell count > 400 cells/μL. As a rule, EFV will be an appropriate choice for such male patients, but should be avoided in pregnancy and in women with reproductive potential, in which cases LPV/r should be used instead.***
- ***Second line regimen for patients who have failed the first line regimen of TDF + FTC (or 3TC) + EFV or NVP:***
    - ***AZT + 3TC + LPV/r ("Kaletra" or "Aluvia")***
- ***For adult and adolescent patients already on previous (2005) first and second line HAART regimens:***
    - ***If on AZT + 3TC + NVP/EFV, continue the regimen, if fully suppressive and there are no AZT side effects, e.g. lipoatrophy, peripheral neuropathy. If these patients eventually fail this regimen, then their second line regimen should be TDF + FTC (or 3TC) + LPV/r.***
    - ***If on d4T + 3TC + NVP/EFV, switch to TDF + FTC + NVP/EFV, even if the d4T-based regimen is fully suppressive.***

- ***If on previous second line regimen of d4T + ddI + LPV/r, switch to TDF + FTC fully (or 3TC) + LPV/r, even if the d4T/ddI-based regimen has been fully suppressive.***

- ***For pediatric patients:***
  - ***The recommended first line HAART regimen remains unchanged:***
    - ***AZT (or d4T, if severe anemia is present) + 3TC + NVP/EFV (no EFV if under 3 years of age).***
  - ***It is essential to determine whether a pediatric patient received sd-NVP at birth, since subsequent NVP resistance may compromise NNRTI-based HAART.***
    - ***Infants under 6 months of age with history of sd-NVP exposure must be discussed with a pediatric HIV specialist before HAART initiation.***
    - ***Infants and children over 6 months of age with history of sd-NVP should be initiated on LPV/r-based HAART, not NNRTI-based HAART.***
  - ***Recommended second line regimen for pediatric patients has been changed:***
    - ***ABC + d4T (or AZT, if d4T already used in first line regimen) + LPV/r.***
  - ***Pediatric patients already on the previous second line regimen of d4T + ddI + LPV/r should continue this regimen, if it is fully suppressive and the patient is not having adherence problems taking ddI. If there are adherence problems with ddI, then it should be switched to ABC. At onset of puberty, d4T/ddI should be discontinued and replaced with TDF + FTC (or 3TC), to prevent development of d4T toxicities, which are more common in adults.***
  - ***WHO pediatric dosing guides (see Appendix) are the recommended method for determining correct pediatric ARV dosing, instead of previous dose calculations.***
- ***Women, infants, and children whose first HAART regimen was LPV/r-based because of prior sd-NVP, and who fail this first regimen, should have a genotypic resistance assay performed, and must be promptly discussed with an HIV Specialist, since it is unclear whether NNRTI-based second line regimens will be effective.***
- ***Do NOT use systemic steroids to prevent or to treat benign NVP/EFV-associated rash.***
- ***Hepatitis B "flares" can occur with discontinuation of TDF, FTC, and/or 3TC.***
- ***All cases of second line regimen failures must be discussed with an HIV Specialist. By late 2008, darunavir and raltegravir will be available for "salvage therapy," under Specialist approval and supervision.***
  - ***A resistance assay must be done for all second line failures, while the patient is still on the failing regimen, or within 4 weeks of discontinuing the regimen.***
  - ***Do not wait for more than 4 weeks for the resistance assay to return before changing to an empiric third line regimen, under Specialist guidance.***

- ***By 6 months after HAART initiation, the viral load must be < 400 copies/mL for all age ranges. If not, then treatment failure has occurred and appropriate management must be initiated (see Chapter 8).***
    - ***Adults who do not suppress viral load to < 400 copies/mL by 3 months after HAART initiation may be at increased risk for treatment failure at 6 months, and should undergo intensive adherence intervention and other evaluation for possible causes of treatment failure. Pediatric patients often require up to 6 months to achieve full virologic suppression.***
    - ***All women who have received sd-NVP <u>any time in the past</u>, and who are initiated on NNRTI-based HAART, require close monitoring for virologic failure. <u>Any such woman whose viral load at 3 months after initiation of NVP or EFV is not < 400 copies/mL must promptly be discussed with an HIV Specialist</u>.***
- ***Clinical monitoring of patients on HAART should continue to be scheduled at least every 3 months, or more often as needed. Adult patients who have remained completely stable for two years may be followed every 6 months.***
- ***TDF-containing HAART requires determination of creatinine clearance at baseline, 3 and 6 months post-initiation, and, if stable, every 6 months thereafter.***
- ***TDF, renal insufficiency, and calculation of creatinine clearance:***
  1) When baseline creatinine clearance is < 60cc/minute:
    - ***Recalculate the creatinine clearance 2-3 days later, repeating the serum creatinine and patient weight, which should be verified with another set of scales. If the repeat clearance is still < 60cc/minute:***
        - ***Initiate HAART with AZT, or, if there is significant baseline anemia, d4T. If already on d4T, continue d4T and do not switch to TDF.***
            - ***Patients initiated on AZT should continue this ARV indefinitely, as long as there are no AZT side effects.***
        - ***For patients initiated on d4T, or who have already been on d4T, monitor the creatinine clearance every 3 months, until it is > 60cc/minute, at which time switch to TDF can be done. Also, monitor the patient at every visit for any adverse effects of d4T.***
        - ***If side effects from either AZT or d4T develop, and creatinine clearance remains < 60cc/minute, then consult an HIV Specialist.***

  2) When serum creatinine cannot be done:
    - ***Proceed with TDF initiation or switch, unless 1) the patient is over 60 years of age, 2) the patient has a history of renal disease (insufficiency, chronic infection, stones), 3) there is greater than trace proteinuria on urinalysis, 4) serum urea is above the upper limit of normal range, <u>or</u> 5) the patient has conditions such as diabetes or uncontrolled hypertension, which might impair renal function. When serum creatinine can eventually be done, monitor creatinine clearance per usual laboratory schedules.***
    - ***For patients who fall into one or more of the above five clinical situations, initiate HAART with AZT (or d4T, if there is anemia). If already on d4T, continue d4T and do not switch to TDF.***

        - ***Patients initiated on AZT should continue this ARV indefinitely, as long as there are no AZT side effects.***
        - ***Once serum creatinine can be done, monitor creatinine clearance every 3 months for patients on d4T, until it is > 60cc/minute, at which time switch to TDF can be done. Also, monitor the patient at every visit for any adverse effects of d4T.***
        - ***If side effects from either AZT or d4T develop, then consult an HIV Specialist.***
- ***Women on TDF and EFV, and who have reproductive potential, should be told to notify their practitioners if they wish to become pregnant, or if they become pregnant.***
- ***For all age groups, CD4 cell count/% should be performed at 3, 6, and 12 months post-initiation of HAART. Thereafter, if immune response has been adequate, CD4 count/% should be done at every 6 month intervals.***
- ***For all age groups, viral load should be done at 3 and 6 months post-initiation of HAART.***
    - ***If viral load at 6 months is < 400 copies/mL, then for adults every 6 month viral load measurements are recommended.***
    - ***Pediatric and adolescent patients, however, require every 3 month viral load measurements indefinitely.***
- ***Switching an ARV for toxicity, or to replace d4T with TDF, requires follow-up priority viral load 6 weeks after the switch, to ensure continued virologic suppression.***
- ***Any change in HAART for treatment failure requires follow-up viral load and CD4 cell count/% measurements at 3 and 6 months post-initiation of the new regimen. If the viral load is < 400 copies/mL at 6 months, then every 6 month viral load monitoring should be done for adults (continue every 3 month monitoring for pediatric/adolescent patients). CD4 cell count/% monitoring can return to every 6 months for all ages.***
- ***Whenever DNA PCR tests, resistance assays, CD4 counts, and viral loads are delayed, determine from the referral laboratory an estimated "time line" for return of these results. Do not automatically repeat pending tests, since such repeat determinations will only further delay return of results.***
- ***For NNRTI-based HAART, AST/ALT should not be routinely done if they have been stable during the first 3 months of monitoring after HAART initiation.***
- ***If the clinical condition of the patient permits, e.g., early SJS or mild hepatitis, discontinuation of ARVs for certain toxicities should take into account the long half-lives of NNRTIs. In some cases it may be possible to continue a 3-5 day N[t]RTI "tail" to prevent the development of NNRTI resistance and thus preserve future treatment options.***
- ***Hyperlipidemia can be an important side effect of ARV therapy, and can lead to serious, potentially fatal vascular complications. Baseline total cholesterol and TGs must be obtained on patients before initiating PI-based HAART, and must be monitored annually in patients on PI-based therapy. Any increases in total cholesterol and/or TGs must be addressed and managed appropriately, with non-drug interventions initiated before considering drug treatment.***

6.0 TB/HIV Co-Infection: (See also Section 10.2)

Co-infection with TB and HIV markedly increases the mortality and morbidity of both diseases, and represents an ongoing public health crisis in Botswana. Active pulmonary TB and extra-pulmonary TB are WHO clinical stage 3 and 4 conditions, respectively. (Pulmonary *and lymph node* TB are WHO stage 3 conditions for pediatric patients). At every visit there must be clinical screening for active TB infection, i.e., inquiry into the presence of symptoms of active TB infection, with further investigations as indicated.

6.1 HAART Initiation in TB/HIV Co-infection:

- Patients who are already on HAART, and who develop active TB, should continue HAART 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 (see Section 10.14).
- For HIV-infected patients who have active TB, and who are not yet on HAART, treat the TB first. *Decisions about when to initiate HAART after initiation of ATT must be individualized*, taking into consideration both immunologic and clinical status:
    - Patients with CD4 cell counts > 250 cells/μL should, as a rule, complete ATT before beginning HAART, unless there are other clinical indications for earlier HAART initiation:
        - All TB patients with CD4 cell counts > 250 cells/μL, and who have another active WHO stage 3 or 4 condition, should be started on HAART at 2 months after ATT initiation. If the WHO stage 3 or 4 condition is life-threatening, HAART should be initiated much sooner after ATT initiation, the exact timing of HAART initiation depending upon the seriousness of the patient's medical condition.
        - All MDR-TB patients with CD4 cell counts > 250 cells/μL should be started on HAART at 2 months after ATT initiation, with close monitoring for additive drug toxicities, especially hepatitis.
    - If the CD4 cell count is < 100 cells/μL, HAART can be started as early as 1-2 weeks after initiation of ATT, if the patient's condition is desperate.
    - If CD4 cell count is between 100 and 250 cells/μL, HAART can be started within 2-4 weeks after initiation of ATT. If the patient's clinical condition is fair or good, HAART can be delayed until ATT is in its continuation phase. Patients with other serious manifestations of HIV disease may be started on HAART as soon as 2 weeks after ATT initiation, but *great care must be taken to monitor the patient for hepatitis and worsening of TB due to IRIS.*
- *All patients of all ages with active TB must be started on CTX prophylaxis, given OD*. Once ATT has been completed, decisions about discontinuing CTX must be based on clinical and immunological criteria discussed in Section 3.4.
- When ATT is initiated in a patient on HAART, or *vice-versa,* AST/ALT should be monitored monthly for the first 3 months, or more frequently as

indicated. There must also be patient/care-giver education about the signs and symptoms of hepatitis, with instructions to return immediately if any occur.

6.2 Drug Interactions between ATT and ARVs:

- The first line regimens, which are EFV- and NVP-based, do *not* require dose modification with ATT. The standard EFV dose of 600 mg should be used.
- *The effect of rifampicin on PI levels is significant. LPV/r cannot be used in standard doses with rifampicin*. Acceptable dosing options include:
    - Double the standard dosing of LPV/r to 800 mg/200 mg BD (i.e., 6 Kaletra capsules BD, or 4 Aluvia tablets BD)
    - Continue the standard LPV/r dose (400 mg/100 mg BD) and add extra RTV boosting with 300 mg RTV BD, i.e., 1:1 ratio of LPV and RTV, with standard doses of LPV.
    - RTV 400mg/SQV 400 mg BD can be substituted for LPV/r. This combination may be associated with significant risk of hepatotoxicity, and an HIV Specialist must be consulted prior to use.
    - Ideal dose adjustment of LPV/r in pediatric TB patients remains unclear. At the time of this revised edition, recent studies in South Africa showed suboptimal LPV levels in pediatric TB patients when the standard LPV/r dose was doubled, whereas therapeutic levels were documented when extra RTV was given in 1:1 ratio (with standard LPV doses). Although further studies are necessary, it may be advisable to use the latter dosing strategy in such patients.
    - Post-ATT, LPV/r should be changed back to pre-ATT doses.

6.3 Management of ATT/HAART-Induced Hepatitis

The development of hepatotoxicity (transaminases > 5X ULN) is a potentially life-threatening complication of early initiation of HAART during the first 2 months of ATT.

- *All* medications with any potential to cause hepatotoxicity must be immediately discontinued, including HAART, ATT, and CTX. If AST/ALT are < 10X the ULN, the HAART is NVP-based, and the patient appears non-toxic (no jaundice, rash, fever, or vomiting), then a 3-5 day "tail" of the two N[t]RTIs (but not ABC) can be considered, to prevent development of NNRTI resistance and thereby preserve EFV as a future treatment option, once the hepatitis has resolved.
- Supportive measures should be undertaken: adequate rest and nutrition (with vitamins) and avoidance of alcohol, traditional medicines, and over-the-counter medications, e.g., paracetamol. If significant nausea and vomiting develop, then hospitalization is necessary for IV fluids and closer clinical monitoring.
- AST/ALT must be monitored at least weekly until a significant downward trajectory has been established.
- Switching patients to "second line," "non-hepatotoxic" ATT drugs (e.g. streptomycin or ciprofloxacin) as a temporizing measure should, as a rule, not be done, unless under HIV Specialist guidance.
- Once AST/ALT have dropped below 2.5 times the upper limit of normal and the patient's clinical condition has improved, then gradually re-introduce ATT first, as in the following schedule:

Schedule for reintroduction of TB Drugs

Day	Drug and dose
1	INH 25 mg
2	INH 50 mg
3	INH 100 mg
4	INH 200 mg
5	INH 300 mg*
6	INH 300 mg + R 150 mg
7	INH 300 mg + R 300 mg
8	INH 300 mg + R 450 mg
9	INH 300 mg + R 600 mg*
10	INH 300 mg + R 600 mg + E 400 mg
11	INH 300 mg + R 600 mg + E 800 mg
12	INH 300 mg + R 600 mg + E 1200 mg*
13	INH 300 mg + R 600 mg + E 1200 mg + Z 500 mg
14	INH 300 mg + R 600 mg + E 1200 mg + Z 1000 mg
15	INH 300 mg + R 600 mg + E 1200 mg + Z 1500 mg
16	INH 300 mg + R 600 mg + E 1200 mg + Z 2000 mg*

* All doses are weight dependant, and the highest dose might not be indicated for low-weight patients and children

- During the gradual phase-in of ATT, AST/ALT should be monitored on at least a weekly basis. The patient/care-giver must be educated about the signs and symptoms of hepatitis. Any increase in AST/ALT or recurrence of symptoms must be addressed promptly with consultation with an HIV Specialist.
- If clinical and laboratory parameters remain stable for 1-2 months after reinitiating ATT, then HAART can be restarted. The decision whether to replace NVP with either EFV or LPV/r must take into account the clinical and laboratory severity of the patient's hepatitis.
- CTX should be restarted once the patient is believed stable.
- If severe hepatitis recurs, all medications must again be stopped, and the patient must be discussed with an HIV Specialist.

KEY POINTS:

- ***Decisions about HAART initiation after starting ATT must be individualized, and must take into account both the patient's clinical and immunological condition, as well as the risks of early HAART initiation. Even the most seriously immune-compromised patient should not start HAART until at least 2 weeks after ATT initiation. Patients started on HAART during the first two months of ATT require very close monitoring for hepatotoxicity and IRIS-related TB.***
- ***All TB patients with CD4 cell counts > 250 cells/µL, and who have another active WHO stage 3 or 4 condition, should be started on HAART at 2 months after ATT initiation. If the WHO stage 3 or 4 condition is life-threatening, HAART should be initiated much sooner after ATT initiation, the exact timing of HAART initiation depending upon the seriousness of the patient's medical condition.***

- ***All MDR-TB patients with CD4 cell counts > 250 cells/µL should be started on HAART at 2 months after ATT initiation, with close monitoring for additive drug toxicities, especially hepatitis.***
- ***For all patients on both EFV and rifampicin, the recommended EFV dose is 600 mg dose, regardless of patient weight.***
- ***The interaction between rifampicin and all PIs, including boosted PIs, is highly significant, and mandates alternative PI options or dosing.***
- ***All patients of all ages with active TB must be started on CTX prophylaxis, given OD. Once ATT has been completed, decisions about discontinuing CTX must be based on criteria discussed in Section 3.4.***
- ***ATT/HAART-induced hepatotoxicity requires complete cessation of all drugs with any potential hepatotoxicity, supportive therapy, and close monitoring of clinical and laboratory parameters. After the hepatitis resolves, ATT should be restarted first, followed later by HAART, and finally CTX.***

7.0 Clinical Care of HIV-Infected Women (Non-Pregnant and Pregnant), HIV-Exposed Infants, and HIV-Infected Infants, Children, and Adolescents

7.1 General Clinical Care of HIV-Infected Women:

- *Annual PAP smears must be done, with gynecologic follow-up of any abnormalities.*
- STI evaluation must be carried out, using a syndromic approach.
- RPR must be done at baseline visit, with indicated treatment and contact tracing if positive.
- The unique challenges facing HIV-infected women must be considered: child-care demands, disclosure issues, stigma, domestic violence, social ostracism.
- ARVs may adversely affect the efficacy of oral contraceptives and/or increase their side effects, and alternative methods of contraception should be used, e.g., depo-medroxyprogesterone. The safety and efficacy of intra-uterine devices in this context remains controversial.

7.2 ARV-Related Clinical Care of Non-Pregnant HIV-Infected Women: (See also Section 5.2)

- EFV use in a woman with reproductive potential mandates reminding her *at every visit* to return immediately if she becomes pregnant, or wishes to become pregnant.
- Women who received sd-NVP within the prior 6 months have greater risk of virologic failure with NNRTI-based HAART, and LPV/r should be used instead.
- Every non-pregnant woman on TDF should be advised to immediately inform her clinician if she becomes pregnant, or if she desires to become pregnant. In either of these instances, switching TDF to AZT is advisable.
- Lactic acidosis due to NRTIs is more common in women, especially when BMI is > 28 kg/m^2 (usually with weight > 75kg).
- Hepatotoxicity due to NVP is more common in women, especially when BMI is < 18.5 kg/m^2, and/or when *baseline* CD4 count is > 250 cell/μL.

7.3 Reproductive Choices in the Setting of HIV Infection:

HIV-infected couples, both discordant and concordant with regards to their HIV infection(s), may wish to have children. Such couples should be counseled about adoption. However, for a couple wishing to have their own biological child, they should be advised to confine unprotected intercourse only to the woman's fertile period and, if at all possible, while the infected partner's viral load is undetectable. It is very important that neither partner has any genital ulcer disease, and that "dry" or "rough" sex not be performed. Both for the viability of the pregnancy and for her own health, an HIV-infected woman should be counseled to defer pregnancy until her condition has improved on HAART, with ongoing virologic suppression, high CD4 count, and good nutritional status. The potential risks of unprotected intercourse must be carefully explained to both partners, especially the HIV-negative partner. (Such situations are not indication for post-sexual exposure prophylaxis). In all cases, the patient/couple should be encouraged to discuss the matter with their clinician.

7.4 Clinical Care of Pregnant HIV-Infected Women and Prevention of Mother-to-Child Transmission:

- *Discordant HIV test results in a pregnant woman require priority evaluation*, as discussed in Section 2.1.
- Pregnant women who test HIV-negative must receive ongoing counseling regarding safe sex, in order to avoid undetected HIV infection during pregnancy, which could be transmitted to the baby. Such women should be advised to have repeat HIV testing if they have possible exposure to HIV infection during pregnancy.
- Pregnant women who initially test HIV negative at ante-natal care registration should be retested either at 36 weeks gestation or at onset of labor, whichever comes first, in order to detect intercurrent HIV infection during pregnancy.
- HAART eligibility for pregnant women is the same as that for all other adults (Section 4.2).
    - ***In all cases, pregnant women not yet on HAART must receive priority scheduling for CD4 and clinical screening.*** *Baseline CD4 cell count must receive priority status*, and when the CD4 cell count does not return within 2 weeks of initial screening, the head of the relevant laboratory must be contacted to expedite its return. When the CD4 cell count is still not forthcoming, then an HIV Specialist must be consulted for possible HAART initiation.
- Those pregnant women who are eligible for HAART for their own HIV infection (per criteria in Section 4.2) *must be given priority scheduling for HAART, without exception.* If the woman's immune status is poor, HAART must not be deferred until the second trimester. When a PMTCT site refers such patients to a site providing HAART, the referrals must be recorded in the Obstetrics Record Book.
    - First line regimen for eligible pregnant women should, if possible, be AZT-based, and the regimen should be continued after delivery if there are no AZT-associated side effects.
    - Pregnant women with *baseline* CD4 cell count > 250 cells/μL, but who qualify for HAART because of WHO clinical stage 3 or 4 conditions, should not be initiated on NVP-based HAART and instead should receive LPV/r-based HAART.
        - A pregnant woman with active WHO stage 3 or 4 condition(s), and for whom there is a > 2 week delay in return of priority CD4 count (e.g., due to unavoidable laboratory problems) should be promptly initiated on LPV/r-based HAART, not NVP-based HAART.
    - *Any pregnant woman presenting for care at 28 weeks gestation or beyond must immediately be started on AZT 300 mg BD*, with expedited CD4 and clinical screening to determine whether or not she is eligible for HAART initiation.
- For pregnant women who are not yet eligible for HAART initiation, the following PMTCT interventions are mandatory:
    - At 28 weeks gestation (*or immediately at presentation, if > 28 weeks gestation*), begin AZT 300mg po BD, until the onset of labor.

- At the onset of labor, *use of sd-NVP during labor will depend upon the duration of AZT therapy prior to labor:*
  - If the woman has received **4 weeks or more of AZT** prior to labor:
    - ***Do not give sd-NVP***
    - Administer supplemental AZT 300mg po every 3 hours until delivery (to a maximum of 1500mg)
  - If the woman has received **< 4 weeks of AZT** prior to delivery:
    - ***sd-NVP 200mg po*** at the beginning of labor (do *not* repeat)
    - Administer supplemental AZT 300mg po every 3 hours until delivery (to a maximum of 1500mg).
  - If at labor the patient *and* her medical records are uncertain or unclear as to whether or not she has received AZT for at least 4 weeks, *administer sd-NVP*, as well as AZT 300mg po every 3 hours until delivery (to a maximum of 1500mg).

- Women who are first identified HIV-positive only at onset of labor must receive the following PMTCT interventions:
  - sd-NVP 200mg po at the beginning of labor (do *not* repeat),
  - Supplemental AZT 300mg po every 3 hours until delivery (to a maximum of 1500mg)
  - After delivery, prompt referral for CD4 and clinical screening
- For pregnant women who are eligible for HAART for their own HIV infection, the principles of ARV treatment, including dosages, lab monitoring, and criteria for treatment success or failure, are unchanged from other adults.
  - Even late in pregnancy, HAART should be started if the patient is eligible and is believed ready. *Unless active labor has started, there is no stage in a pregnancy where it is too late to begin HAART for women who meet general adult eligibility criteria per Section 4.2.*
  - ***At the onset of labor, women on HAART must still receive high-dose AZT*:**
    - At onset of labor, supplemental AZT 300mg po every 3 hours until delivery, to a maximum of 1500mg.
    - ***sd-NVP should not be administered.***
    - If the woman is on d4T-containing HAART at the time of labor, one of two options should be chosen:
      - Discontinue d4T and begin AZT 300mg po every 3 hours until delivery, to a maximum of 1500mg, with transfusion support as needed. This approach is preferred, if the patient is able to tolerate AZT.
      - Continue d4T and do not administer AZT.
- If oral AZT cannot be tolerated for any of the above clinical scenarios, then give intravenous AZT: 2mg/kg IV loading dose over 1 hour, followed by infusion of 1mg/kg every hour until delivery.
- For false labor, do not repeat any administered sd-NVP. When labor resumes, restart AZT 300mg po 3h until delivery. If the interval between false labor and its resumption is > 24 hours, the 1500mg AZT maximum should be calculated from the resumption of labor.

Other issues concerning HAART, pregnancy, and PMTCT:

- Pregnant women who are already on HAART should continue treatment, with any necessary modifications to the regimen as indicated below.
- *Regardless of stage of pregnancy, CTX prophylaxis must be given during pregnancy if the woman's CD4 count is < 200 cells/uL, or if she has an active, current WHO clinical stage 3 or 4 condition*.
- Although 2006 WHO guidelines permit continuation of TDF during pregnancy, it is advisable to switch pregnant patients on TDF to AZT, if possible, both to avoid theoretical effects on fetal BMD and to provide additional PMTCT effect (see also Section 5.2).
- First trimester exposure to EFV is not a medical indication for abortion, since the risks of teratogenicity are very small. Because the risks of EFV during the second and third trimesters are unknown, it generally should not be used, unless benefits clearly outweigh possible risks, and only after Specialist consultation.
- Anemia during pregnancy may complicate use of AZT for PMTCT, both with HAART and with short-course prophylaxis begun at 28 weeks gestation. Such anemia can occur at baseline or after initiation of AZT.
    - Every effort should be made to use AZT, because of its demonstrated PMTCT efficacy. Both for the viability of the pregnancy and for allowing use of AZT for PMTCT, transfuse the patient as needed.
    - If transfusion is not possible, sustainable, or effective, then promptly switch to *full d4T-containing HAART* (both for women on AZT-containing HAART *and for women on short-course AZT prophylaxis*). For those women switched from short-course AZT prophylaxis to full d4T-containing HAART, baseline CD4 cell count must determine whether the HAART is NVP- or LPV/r-based (see Section 5.2). If anemia improves on d4T-containing HAART, consider switching to AZT-based HAART, with close monitoring of HgB. If AZT cannot be used pre-partum, then still try to use it during labor (300mg po q3 hours until delivery, to maximum of 1500mg), stopping d4T and continuing the other two ARVs in the HAART regimen, with transfusion support as needed. If AZT cannot be used during delivery, then continue the d4T-containing HAART.
    - After delivery, women initially not eligible for HAART should be discussed with an HIV Specialist as to whether HAART should be continued or stopped. Those women who were initially eligible for HAART, and who were switched from AZT-containing HAART to d4T-containing HAART because of anemia, should have d4T replaced with TDF.
- Because of increased risk of pancreatitis and lactic acidosis, d4T + ddI should not be used during pregnancy, unless there are no other ARV options.
- Because of potentially carcinogenic and teratogenic impurities, NFV should not be used in pregnancy.

- IPT is a non-urgent preventative intervention that should be deferred until after delivery. However, if the patient becomes pregnant while having been on at least 3 months of IPT, then it may be continued to conclusion.
- Nausea and vomiting secondary to pregnancy must be addressed promptly and intensively, to minimize non-adherence and/or decreased absorption of ARVs.
- HAART for all pregnant women is an intervention which may be taken in the private sector.
- The Ministry of Health will soon conduct a pilot project at selected ARV sites to study the feasibility of HAART for all pregnant women, regardless of baseline CD4 cell count and WHO clinical stage.

7.5 Neonatal ARV Interventions for PMTCT:

Short-course ARVs to the infant:

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

- NVP syrup 6mg po as a single dose *as soon as possible after delivery*, but no later than 72 hours after birth. Preterm (< 35 weeks gestation) and low birth weight (< 2.5 kg) babies should receive 2mg/kg NVP po.
- AZT 4mg/kg po every 12 hours for 4 weeks. If preterm or low birth weight, the AZT dose is 2mg/kg po every 12 hours for the first 2 weeks, *which is then increased to 2mg/kg dose po every 8 hours (TDS) for the final 2 weeks*.
- HIV-exposed infants brought in > 72 hours after birth should not receive sd-NVP or AZT prophylaxis.

7.6 Non-ARV Interventions for PMTCT:

1) Evaluation and treatment of sexually transmitted infections (see Section 1.3 and Appendix):

- There must be counseling at every visit on the importance of using condoms during the pregnancy.
- Routine syphilis serology must be monitored, and positive results addressed.
- Any episode of genital HSV during the pregnancy must be aggressively treated with acyclovir. If necessary, obtain Specialist approval for use of acyclovir for this indication.

2) Obstetric measures to reduce MTCT:

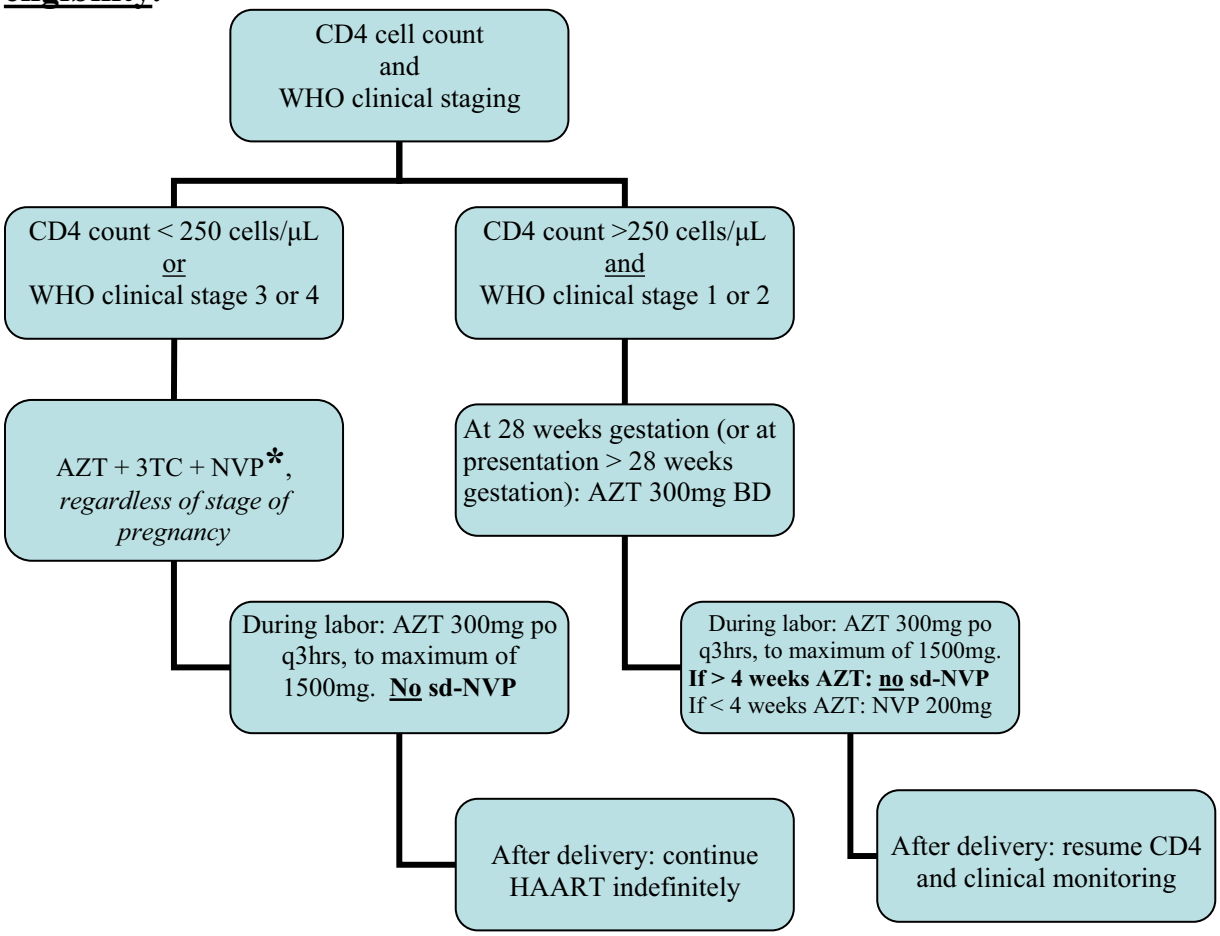
- Avoidance of artificial rupture of membranes
- Avoidance of routine episiotomies
- When assisted vaginal delivery is indicated, use of non-traumatizing suction cups on vacuum extractors, where possible
- Avoidance of fetal scalp puncture
- Consideration of labor induction beyond 4 hours after rupture of membranes
- In settings with the capacity to do so, *elective* caesarean section has been shown to reduce MTCT when maternal viral load is > 1000 copies/mL. This intervention, which can be associated with morbidity and mortality (up to 60% incidence), 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 rare 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 600mg po should be given 3 hours before the elective C-section.

3) Modification of infant feeding Practices: see Section 7.7, below

SUMMARY: 2008 PMTCT GUIDELINES

All HIV-infected pregnant women who are not on HAART must have priority CD4 and clinical screening, to determine HAART eligibility.



***If CD4 cell count > 250 cells/µL, LPV/r instead of NVP.**

WOMEN FIRST IDENTIFIED HIV-INFECTED AT ONSET OF LABOR

- ***sd-NVP 200mg po at start of labor (do not repeat)***
- ***AZT 300mg po every 3 hours, to a maximum of 1500mg***
- ***After delivery, prompt referral for screening for HAART eligibility***

ALL NEWBORNS, REGARDLESS OF MATERNAL PMTCT INTERVETIONS

- ***sd-NVP syrup 6mg as soon as possible after delivery, no later than 72 hours. If < 35 weeks gestation or low birth weight (< 2.5 kg): 2mg/kg sd-NVP.***
- ***AZT 4mg/kg q12 hours for 4 weeks.***
  - ***If < 35 weeks gestation or weight < 2.5 kg: AZT 2mg/kg q12 hours for 2 weeks, then increase to 2mg/kg q8 hours (TDS) for the final 2 weeks.***

7.7 Care of HIV-Exposed Infants: (see also Sections 2.2 and 3.4)

Age	Test or Intervention
Birth	**-STAT dose of NVP** **-give AZT for 4 weeks** **-infant feeding counseling (see Section 7.7, below)** **-routine baby care, including vaccinations** **-counseling regarding early infant HIV testing**
4-6 weeks	**-HIV DNA PCR testing for early infant diagnosis**
6 weeks	**-begin CTX (see Section 3.4)**
6 weeks after weaning for breastfed babies initially tested DNA PCR negative	**-repeat HIV DNA PCR or rapid test, depending upon the patient's age**

Immunizations:
Healthy HIV-exposed babies should receive all vaccinations which are currently recommended for HIV-negative children. However, live vaccines (e.g., 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.

- BCG Vaccine:
    - Because of the increased risk of disseminated BCG disease, known HIV-positive babies and babies of unknown HIV status who have signs or symptoms of HIV infection at birth should *not* receive BCG vaccine. All healthy-appearing newborns should be vaccinated with BCG at birth. The following table from the national TB guidelines summarizes these situations:

Give BCG vaccine	Do not give BCG vaccine
Known HIV negative children	*Known HIV positive* children with or without signs or symptoms of HIV infection
Children of *unknown HIV status* without signs or symptoms of HIV infection, regardless of the HIV status of mother	Children of *unknown HIV status* with signs or symptoms of HIV infection present, regardless of the HIV status of mother

    - Although usually given at birth, BCG vaccination should be postponed if the mother has sputum-positive TB at delivery, and the infant should first be given 6 months of INH (5mg/kg OD). After 6 months, BCG should be administered, but *only if the child is HIV negative*.
    - Children whose BCG vaccination was delayed at birth for other reasons should first be HIV-tested prior to vaccination. Those infants and children diagnosed HIV-positive, or who have signs/symptoms of HIV infection, should *not* be given BCG.
- Measles Vaccine:
    - *Babies in Botswana who are known to be HIV-positive should undergo CD4% monitoring prior to measles vaccination.* If severe immune suppression is present (CD4% < 15%), vaccination may be delayed

until HAART has allowed for immune recovery (CD4% > 15%), if the risk of vaccine-related illness is deemed higher than the risk of becoming sick from measles.

7.8 Modification of Infant Feeding Practices:

To achieve the goals of Vision 2016 for an AIDS-free generation, the recommended policy is the complete avoidance of exposure to HIV-infected breast milk, with the provision of adequate education, clean and readily available water, unhindered access to formula, and ongoing psycho-social support for the mother. All women, regardless of HIV status, should be provided with infant feeding information and counseling during antenatal care, according to Botswana's infant feeding guidelines, as below, to ensure that they understand the recommended methods of feeding, and to assist them in making their decisions.

Patient Situation	Feeding recommended from 0-6 months	Feeding recommended from 6-24 months
HIV-negative women	Exclusive breastfeeding (no added foods or liquids, including plain water)	Breastfeeding until at least 2 years, plus complementary foods
HIV-positive women for whom formula feeding is AFASS*	Exclusive formula feeding (no added foods or liquids, including plain water)	Formula until 1 year, plus complementary foods
HIV-positive women for whom formula feeding is <u>not</u> AFASS*	Exclusive breastfeeding (no added foods or liquids, including plain water)	Early cessation of breastfeeding at six months with transition to formula feeding, plus complementary foods
Women of unknown HIV status (should be strongly encouraged to be tested.)	Exclusive breastfeeding (no added foods or liquids, including plain water)	Breastfeeding until at least 2 years, plus complementary foods

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

- **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 has adequate time, knowledge, skills, social/family support, and resources to obtain formula regularly, to prepare feeds, and to feed the infant.
- **Affordable**: The mother and family, with available community and/or health system support, can pay for the costs of the replacement feeds – including formula, fuel (to boil water), and clean water – without compromising the family's health and nutrition spending.
- **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 and using clean utensils, preferably by cups.

Important points for women considering formula feeding:

- *Women deciding to use formula must be taught how to use formula safely; <u>women should not simply be given formula and told to use it</u>.*

- If refrigeration is available, prepared formula can be stored prior to use for up to 24 hours, after which time it should be discarded. However, if refrigeration is not available, each feed must be made fresh, to be used *within 1 hour of preparation*.
- Bottles should be avoided, but if a woman decides to use a bottle, then both bottle and teat should be cleaned using soap and boiling water, giving particular attention to the teat, where bacteria can collect. The bottle and the teat should be immersed in boiling water for 10 minutes before each use.
- Refer to 2006 Botswana PMTCT Guidelines, Section 2.6.4, for further details.
- *Because monthly formula requirements often exceed standardized guideline "averages," **clinics which dispense formula must not turn away a mother who requests additional formula for her baby, and must provide additional formula.*** However, follow-up home visits should be done to access proper formula use.

7.9 Special Aspects of Care of HIV-Infected Infants, Children, and Adolescents:

7.9.1 Preparation of caregivers and children for HAART initiation:

All caregivers of an HIV-infected child must know about the child's HIV status, and be prepared to actively participate in the ongoing care and treatment of the child. For HIV-infected children, adherence problems often occur when only a single caregiver is fully aware of the child's medical needs, including the importance of strict adherence. Prior to commencement of HAART, healthcare providers must 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. The healthcare providers must 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*. The following specific points must be assessed prior to the initiation of HAART in a pediatric patient:

- Who will be primarily responsible for giving the child medications and supervising adherence? If there are multiple caregivers, how will coordination between these caregivers be achieved?
- What is the caregivers' 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 ARV 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?

7.9.2 Growth and development *must* be monitored at each clinic visit:

- Evaluation by a doctor and/or pediatric-trained nurse at least every 3 months, *more frequently (at least monthly) if the child is not improving*
- Review of systems, with special attention to possible ARV side effects, which may be more subtle in a child, e.g., declining school performance as a primary manifestation of neuro-psychiatric side effects of EFV

- Measuring and plotting of growth at every visit (height and weight for all children; head circumference for children under 2 years of age)
    - A trained practitioner should review the growth curves at every visit, in order to determine if growth failure is occurring.
- Assessment of developmental milestones: loss of milestones must prompt neurological examination and review of causes of clinical failure.
- Physical examination, with attention to areas likely to reveal HIV-related pathology, e.g., the mouth and skin, the lungs, and lymph nodes
- Assessment of adherence, including both qualitative (questioning the patient and caregiver) and quantitative (pill counts) measures

7.9.3 Disclosure of HIV status to children and adolescents:

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:

- Truth-telling: Clinic staff should never tell lies to children about their medical care, and families should be encouraged to always be truthful with children when discussing their medical needs. Children beginning HAART should not be told that they are taking ARVs for transient conditions such as coughs or rashes. Instead, children can be told 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, to develop a positive outlook regarding HIV infection.
- Simplification of messages for children: Families should be counseled regarding age-appropriate ways to communicate with children about their illness. Very young children do not need to use "adult words" such as "HIV" and "ARVs." But they should learn early on that the medications will help to make them strong and healthy, and that it is important never to miss medication doses. Further truthful details about the illness should be added as the child ages, and as the family becomes ready for more full disclosure.
- Positive messages: HIV-infected children have the potential to be healthy and productive adult members of society. Healthcare workers must counter false and negative messages regarding HIV-infected people.
- Continuous validation and encouragement of the child: Healthcare providers should provide positive reinforcement for HIV-related knowledge and clinical improvement achieved by their pediatric patients.

Disclosure of HIV status to children should be considered a process rather than a one-time event. At each visit for follow-up care, the child should learn and reinforce facts about his care, including positive messages. Counseling must be tailored to the individual child and family:

- Young children should learn that they take their medicines because the medicines help them stay strong and healthy.
- Young children should learn how their medicines are taken (what time, how much).
- School-aged children should be responsible for reminding their caregivers when it is time to take medicines, and for ensuring that the appropriate doses are given (*adult supervision is still required*, and the ultimate responsibility for ensuring adherence remains with the adult).

- School-aged children should learn the names of their medicines.
- Children should be taught that their medicines help them stay healthy by helping their CD4 cells ("soldiers of the body") remain strong and numerous.
    - Children should learn that as long as they continue to take their medicines correctly, they can achieve all that they want in life.
- Older children whose families are not yet ready for full disclosure of the HIV status should learn that their "soldiers" were weak because a "bad guy" was attacking them. The medicines keep the "bad guy" sleeping. Older children should learn that consistent adherence to HAART is necessary to avoid the "bad guys" waking up and escaping from the medicines.
- Older children and adolescents should be taught "adult" terminology. When the term "HIV" is first used in the context of the child's condition*, all of the previously taught positive messages are reinforced, dispelling misconceptions*.
- Continuous reinforcement of positive messages and assessments of understanding should occur throughout all childhood and adolescent visits.

7.9.4 Special issues during adolescence require attention:

- ARV dosing:
    - Pharmacokinetics of ARVs during the adolescent period are unpredictable, with increased risk of treatment failure. Viral loads must be measured every 3 months, and not every 6 months as with adults.
    - ARVs should be dosed according to Tanner Stage (see chart in Appendix). Children and adolescents who are tanner stage 1 or 2 (pre-pubertal and early pubertal) should be dosed according to pediatric guidelines. When tanner stage 5 has been reached, adult dosing should be used. Tanner stages 3 and 4 are periods of rapid growth for most adolescents. In most cases, pediatric dosing will be appropriate until the growth spurt is complete.
- Intensified, clinic-based psychosocial support:
    - Most HIV-infected adolescents have special psychosocial issues which 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 ARVs
        - Distrust of family, practitioners, and the healthcare system
        - Low self-esteem and unstructured, chaotic lifestyles
        - Limited familial and social support

The most critical aspect of providing appropriate care to HIV-infected adolescents is closely monitoring psychosocial health. All ARV clinics should identify staff with interest in adolescent care, who can provide continuity of care with 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 remain involved with the care of all adolescents*. 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. Due to stigma, it is often difficult for adolescents to disclose their HIV status to peers without fear of rejection. 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.

Discontinuation of therapy due to non-adherence is another major challenge in adolescent care. Due to their reliance on adult caregivers and the unique challenges of adolescence, it is sometimes necessary to temporarily discontinue HAART in pediatric and adolescent patients who are unable to take their medications reliably. This step is taken in order to preserve future treatment options. (Whenever possible, the long half lives of NNRTIs should be taken into account: see Section 8.4). *Discontinuation of HAART should never be considered a punitive measure, nor should it ever be presented to the patient and family as such.* The clinician must carefully and sympathetically explain to the patient and family the reasons for temporary treatment discontinuation. At the time of temporary treatment discontinuation, a plan for preparing the patient to safely restart therapy should be formulated and implemented. Prior to temporary treatment discontinuation, a comprehensive evaluation of the factors leading to non-adherence must be undertaken, and all available resources must be marshaled to address those factors. For patients with severe or advanced immune suppression or disease, the short-term risks of treatment interruption will often outweigh the potential long-term benefits, and a pediatric HIV Specialist should be consulted in these cases. *Patients who discontinue HAART should be started on CTX prophylaxis* and a multivitamin, regardless of immunologic and clinical status. They should also be scheduled frequently for clinical monitoring and counseling, in order to determine when HAART can be safely restarted. CTX and multivitamins can preserve the patient's health, and should also be used to re-establish the habit of good medication adherence, which can be monitored with CTX and multivitamin pill counts at each visit.

KEY POINTS:

- ***PAP smear must be provided annually to every HIV-infected woman, with prompt follow-up of any abnormalities.***
- ***Discordant HIV test results in a pregnant woman require priority evaluation, as discussed in Section 2.1.***
- ***Women must be empowered to make their own reproductive decisions.***
- ***Discordant and HIV positive couples wishing to have their own children should confine unprotected intercourse to the fertile period.***
- ***Maternal sd-NVP is associated with higher rates of treatment failure, if NNRTI-based HAART is begun within 6 months after the sd-NVP. LPV/r-based HAART should be used in these women.***
- ***Regardless of stage of pregnancy, CTX prophylaxis must be administered to all pregnant women with CD4 cell counts < 200 cells/μL, or with active WHO stage 3 or 4 conditions.***
- ***In all cases, pregnant women not yet on HAART must receive priority scheduling for CD4 and clinical screening. If the CD4 cell count does not return within 2 weeks of initial screening, the head of the relevant***

laboratory must be contacted, to expedite its return. When the CD4 cell count is still not forthcoming, then an HIV Specialist must be consulted for possible HAART initiation.

- ***Any pregnant woman not on HAART who presents for care at 28 weeks gestation or beyond must <u>immediately</u> be started on AZT 300 mg BD, <u>with expedited CD4 screening to determine whether or not she is eligible for HAART initiation</u>.***
- ***HAART eligibility in pregnancy is the same as that for other adults.***
    - ***Even late in pregnancy, HAART should be started if the patient is eligible and is believed ready. <u>Unless active labor has started, it is never too late to begin HAART</u>.***
    - ***If possible, first line HAART should be AZT-based. This regimen should be continued after delivery, if there are no AZT-associated side effects.***
    - ***<u>At the onset of labor, women on HAART must still receive high-dose AZT per standard PMTCT protocol (up to 1500mg dose)</u>, but should <u>not</u> be given sd-NVP.***
    - ***Pregnant women with <u>baseline</u> CD4 cell count > 250 cells/μL, but who qualify for HAART because of active WHO clinical stage 3 or 4 conditions should <u>not</u> be initiated on NVP-based HAART and instead should receive LPV/r-based HAART.***
    - ***Whether TDF should be avoided during pregnancy remains unresolved, and if possible, AZT-based HAART should be used in this circumstance.***
- ***For pregnant women who are not yet eligible for HAART initiation:***
    - ***At 28 weeks gestation (or <u>immediately at presentation</u>, if > 28 weeks gestation), begin AZT 300mg po BD until the onset of labor.***
    - ***At the onset of labor, <u>use of sd-NVP during labor will depend upon the duration of AZT therapy prior to labor</u>:***
        - ***If the woman has received <u>4 or more weeks of AZT</u> prior to labor:***
            - ***<u>Do not give sd-NVP</u>***
            - ***Administer supplemental AZT 300mg po every 3 hours until delivery (to a maximum of 1500mg)***
        - ***If the woman has received <u>less than 4 weeks of AZT</u> prior to delivery:***
            - ***sd-NVP 200mg po at the beginning of labor (do not repeat)***
            - ***Administer supplemental AZT 300mg po every 3 hours until delivery (to a maximum of 1500mg).***
        - ***If at labor the patient and her medical records are uncertain or unclear as to whether or not she has received AZT for at least 4 weeks, <u>administer sd-NVP 200mg po</u>, as well as AZT 300mg po every 3 hours until delivery (to a maximum of 1500mg).***
- ***Anemia during pregnancy may complicate use of AZT for PMTCT, both with HAART and with short-course prophylaxis. <u>If transfusion cannot resolve AZT-associated anemia, then d4T-containing HAART should be used</u>, including for those women only on short-course AZT prophylaxis***

(Section 7.4). After delivery, women initially not eligible for HAART should be discussed with an HIV Specialist as to whether HAART should be continued or stopped.

- ***The Ministry of Health will conduct a pilot project at selected ARV sites to study the feasibility of HAART for all pregnant women, regardless of baseline CD4 cell count or WHO clinical stage.***
- ***Short-course ARVs to the newborn infant:***
    - ***NVP syrup 6mg po as a single dose as soon as possible after delivery, but no later than 72 hours after birth. Preterm (< 35 weeks gestation) and low birth weight (< 2.5 kg) babies: 2mg/kg NVP po.***
    - ***AZT 4mg/kg po every 12 hours for 4 weeks. If preterm or low birth weight, 2mg/kg po every 12 hours for 2 weeks, which is then increased to 2mg/kg dose po every 8 hours (TDS) for the final 2 weeks.***
- ***If at labor the patient and her medical records are uncertain or unclear as to whether or not she has received AZT for at least 4 weeks, administer sd-NVP, as well as AZT 300mg po every 3 hours until delivery (to a maximum of 1500mg).***
- ***Live vaccines (e.g., BCG, measles), should be avoided whenever possible in severely immune-suppressed children.***
- ***Women deciding to use formula must be taught how to use formula safely; women should not simply be given formula and told to use it.***
- ***Because monthly formula requirements often exceed standardized guideline "averages," clinics which dispense formula must not turn away a mother who requests additional formula for her baby, and must provide additional formula. However, follow-up home visits should be done to access proper formula use.***
- ***Children are reliant on adult caregivers for adherence to medical therapies. All caregivers for each HIV-infected child must be thoroughly counseled and prepared for HAART initiation, with continued ongoing counseling.***
- ***Clinical monitoring of children on HAART must include routine physical exams and ongoing assessment of growth and development.***
- ***Disclosure of HIV status to children should be considered a process rather than a one-time event.***
- ***Developmentally-appropriate discussion and disclosure to the child about his medical care, including supportive disclosure of HIV status, is an essential component of comprehensive clinical care, and, in coordination with family and other clinic staff is the responsibility of the treating practitioner.***
- ***The most critical aspect of providing appropriate care to HIV-infected adolescents is closely monitoring psychosocial health. All ARV clinics should identify staff with interest in adolescent care, who can provide continuity of care with HIV-infected adolescents.***

8.0 Pediatric, Adolescent, and Adult Treatment Failure and Its Management

For all age ranges, there are three types of treatment failure:
1) Virologic Failure: Viral load is never fully suppressed to < 400 copies/mL by 6 months after initiation of HAART, *or* after initial suppression to < 400 copies/mL, the viral load becomes > 400 copies/mL any time in the future.

- After initiation of HAART, pediatric patients may require longer than 6 months for viral load to become undetectable. *When viral load in a pediatric patient is not < 400 copies/ml by 6 months after HAART initiation, a pediatric HIV Specialist must be consulted.*
- For most adolescent and adult patients, viral load is usually < 400 copies/mL by 3 months after HAART initiation, although a few may require up to 6 months for viral load to become fully suppressed. Nonetheless, if the 3 month viral load is not <400 copies/mL, the patient must be evaluated very closely for possible development of eventual treatment failure at 6 months, with special emphasis on adherence, as well as other non-resistance causes of failure, as below.
    - Studies have shown an increased risk of virologic failure when NNRT-based HAART is initiated in women who have received sd-NVP in the past, especially within 6 months of taking sd-NVP. Current guidelines permit initiation of NNRTI-based HAART in women who have received sd-NVP more than 6 months in the past, but these patients require close monitoring for virologic failure. *Any such woman whose viral load at 3 months after initiation of NVP or EFV is not < 400 copies/mL must promptly be discussed with an HIV Specialist.*
- A detectable viral load on HAART should always be repeated as a "priority" viral load, to confirm the presence of virologic failure and to detect any possible laboratory error in the initial determination. However, while waiting for the return of the confirmatory viral load, begin evaluation for treatment failure. If the repeat viral load does not return within 2 weeks, then proceed with any indicated intervention, *without delay,* and under HIV Specialist guidance if necessary.

2) Immunologic Failure:

- For pediatric patients, when one of the following situations arises:
    - Development of age-related severe immunodeficiency after initial immune recovery
    - A persistent decline of 5 percentage points or more in CD4%
    - Failure to increase CD4% by at least 5 percentage points above baseline during the first year of therapy
- For adolescent and adult patients, when one of the following situations arises:
    - The CD4 cell count persistently falls below the baseline CD4 cell count
    - The CD4 cell count fails to increase by more than 25-50 cells/μL after one year of treatment
    - There is a > 50% decline in CD4 cell count from its highest level on HAART

Immunologic failure in the presence of full virologic suppression and clinical improvement usually does not merit a treatment change.

3) Clinical Failure:
   - For pediatric patients, when one of the following situations arises:
     - Recurrence or persistence of AIDS-defining conditions or serious infections, excluding IRIS
     - Progressive neuro-developmental deterioration or failure to reach expected neuro-developmental milestones
     - Growth failure, i.e., a persistent decline in weight-growth velocity despite adequate nutrition and without other explanation
   - For adolescent and adult patients, when the patient has a new AIDS-defining illness—i.e., a new WHO stage 3 or 4 condition--after initiation of HAART, excluding IRIS (see 10.13).

Clinical failure in the presence of full virologic suppression may or may not justify a change in HAART, and an HIV Specialist must be consulted.

8.1 Causes of Treatment Failure:

As a rule, "treatment failure" usually means "virologic failure." The causes of virologic failure fall into two general categories: 1) resistance and 2) non-resistance causes related to sub-therapeutic levels of ARVs. Treatment failure does not necessarily mean that resistance has yet developed. However, *if non-resistance causes of treatment failure are not promptly addressed, and if ongoing viremia due to these non-resistance causes persists in the presence of ARVs, then resistance will eventually develop*.

1) ARV resistance can be primary and/or acquired:
   - Primary or transmitted resistance: initial infection with resistant HIV
   - Acquired resistance: viral replication in the presence of suboptimal ARV levels. It is unknown how long viremia must occur before resistance finally develops, but it probably varies among ARVs and among patients.

2) Non-resistance causes of treatment failure: suboptimal ARV levels
   - Non-adherence, the most common non-resistance cause
   - Incorrect dose of ARV (e.g., pediatric dose determinations, ddI dose in adults)
   - Adverse drug-drug interactions (e.g., rifampicin and LPV/r)
   - Variable absorption (e.g., food requirements of ARV, gastroenteritis)
   - Lack of regimen potency and/or durability (e.g., mono/dual therapy)
   - Incorrect storage (e.g., inconsistent refrigeration for liquid d4T)

8.2 Clinical Approach to Treatment Failure:

1) Identify the presence of treatment failure:
   a. ***Review viral load results on a timely basis as soon as the results return from the laboratory. All viral loads that are not < 400 copies/uL must be acted upon promptly.***
   b. Monitor CD4 cell count/% in comparison to baseline and prior values
   c. Monitor clinical condition for new HIV-related disease(s)
2) Determine the type of treatment failure: virologic, immunologic, or clinical
   a. *Immunologic and/or clinical failure in the presence of full virological suppression must be discussed with an HIV Specialist, since change in HAART regimen may not be necessary.*

3) Determine the cause(s) of treatment failure:
    a. Non-resistance causes, due to suboptimal ARV levels, as above
    b. ARV resistance: if non-resistance causes cannot be identified, then assume that resistance has developed.
4) If after careful evaluation, a non-resistance cause of failure cannot be identified, then assume that resistance has developed, and change the entire regimen, as below.
5) If non-resistance cause has been identified:
    a. Address and correct the underlying problem(s).
    b. Decide whether to discontinue the present regimen while the non-resistance cause of failure is being addressed, always in consultation with a senior HIV clinician. Severe gastroenteritis or significant non-adherence may justify temporary discontinuation of HAART. Drug interactions, incorrect ARV dose, minor nonadherence and/or minor gastroenteritis may not require HAART discontinuation, if addressed promptly.
    c. After successfully addressing the suspected non-resistance cause of treatment failure and restarting/continuing HAART, repeat *priority* viral load in 6 weeks. If the viral load has not suppressed to < 400 copies/mL (adults), then resistance has developed, and the entire regimen must be changed. (See also Section 8.4, below)

8.3 Switching Antiretroviral Therapy for Treatment Failure:

- For a patient with complete viral suppression, never change the regimen for immunologic and/or clinical failure without first consulting an HIV Specialist.
- For virologic failure, always obtain a repeat *priority* viral load to confirm viremia: do not change a regimen on the basis of only one viral load. Intensive adherence counseling and evaluation for other non-resistance causes of treatment failure must be undertaken while awaiting the confirmatory viral load. *If the repeat viral load does not return within 2 weeks, then proceed with any indicated action without delay*, including change in HAART regimen and discussion with an HIV Specialist, as needed.
- For first line regimen failures, change to the second-line regimen, while continuing intensive adherence counseling and support. Specialist consultation is no longer required for permission for straightforward switching to second line regimen for first line failures, unless there are unusual clinical circumstances.
- For second line regimen failures:
    - Genotypic resistance testing while the patient is still on the failing regimen (or no more than 4 weeks after discontinuation of the failing regimen)
    - Intensive adherence counseling, reinvolvement of adherence partner
    - Consideration of possible adverse drug interactions and poor absorption of ARVs
    - *Do not wait for more than 4 weeks for the resistance assay to return* before changing to an empiric third line regimen, *under Specialist guidance,* pending eventual return of the resistance assay.
- For second line regimen failures, the subsequent regimen must contain at least two new ARVs to which the patient's HIV is most likely susceptible.

    - For patients who have failed multiple regimens, and for whom there are no viable ARV choices left, the HIV Specialist Panel, below, should determine an appropriate "salvage" regimen. Pending such evaluation, do *not* stop HAART: maintain the patient on the current failing regimen.
- Any change in HAART for treatment failure requires follow-up viral load and CD4 cell count/% measurements at 3 and 6 months post-initiation of the new regimen. If the viral load is < 400 copies/mL at 6 months, then every 6 month viral load monitoring should be done for adults (continue every 3 month monitoring for pediatric/adolescent patients). CD4/% monitoring can return to every 6 months for all ages.

8.4 Special Considerations in Treatment Failure:

"Viral blips:"

- A "viral blip" is a *transient* increase in viral load from < 400 copies/mL to no more than 1000 copies/mL*, with follow-up viral load returning to < 400 copies/mL.* The cause of "blips" is unknown, but they are probably not of clinical significance. *Sustained* viremia with viral loads >400 copies/mL do not constitute "viral blips," and should always be considered significant.

Transient viremia secondary to intercurrent infections and immunizations:

- Any acute, intercurrent infection (e.g., viral upper respiratory infection, HSV, TB, malaria) can elevated 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/mL, and treatment failure has not occurred. As a rule, routine viral load determinations should be deferred whenever there is an intercurrent infection or recent vaccination.

Nonadherence:

- Nonadherence and resistance are the two 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 nonadherence, and must always be taken seriously. Pill counts, pharmacy refill data, and whether the patient has disclosed his HIV status to anyone outside of the clinic are important indicators of adherence. Clinician assessment of adherence is a poor predictor, as are patient educational level, sex, and socio-economic status. Barriers to adherence in children are often complex (see Section 7.8 for discussion of pediatric adherence).
- *When nonadherence is suspected or confirmed, bringing back the patient's adherence partner for further support for the patient may be an effective intervention.*

Discontinuation of HAART:

- Whenever NNRTI-based HAART is discontinued—e.g., for toxicity, side effects, severe nonadherence, 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 optimal length for this N[t]RTI "tail" is unknown, but 3-5 days is advised for patients with severe NVP-induced toxicities, and 7 days for non-life-threatening situations. Another alternative would be to use a boosted PI, i.e., LPV/r, along with the 2 N[t]RTIs for 7 days.

- For treatment failure due to non-adherence, decisions about continuation or discontinuation of the current regimen must be made with great care. Although HAART discontinuation may be necessary in certain instances, these are usually infrequent. As a rule, HAART should not be stopped *without first consulting an experienced HIV clinician*.
    - Patients with only intermittent non-adherence should be maintained on their current regimen, while the non-adherence is being addressed. Patients with very poor adherence—e.g., missing doses for several days at a time over the prior 2 weeks--or who have already stopped their ARVs, should not be restarted on the current regimen until the non-adherence has been successfully dealt with. Once the non-adherence has been addressed, the current regimen can be restarted (or continued, if HAART was not discontinued during adherence interventions), and a follow-up *priority* viral load should be obtained in 6 weeks:
        - If full viral suppression has been achieved 6 weeks after adherence intervention, then follow-up viral load should be done in 3 months, after which, if viral load remains < 400 copies/mL, every 6 month monitoring can be resumed for adults, with every 3 month viral load monitoring continued for pediatric and adolescent patients.
        - If the viral load 6 weeks after adherence intervention is not < 400 copies/mL *in an adult patient*, then reassess for any correctable causes of failure. If so identified, address the correctable causes and continue HAART, with repeat *priority* viral load in another 6 weeks. If no correctable cause of failure is found, or if the repeat 6 week viral load is not < 400 copies/mL, then assume that resistance has developed and change the regimen accordingly. If the repeat viral load is < 400 copies/mL, then follow-up viral load should be done in 3 months, after which, if viral load remains < 400 copies/mL, every 6 month monitoring can be resumed.
        - *Pediatric* patients may require longer time for complete virologic suppression. If the viral load 6 weeks after the adherence intervention is not < 400 copies/mL, then reassess the patient for any correctable causes of failure, and address them. Regardless of whether or not correctable causes of failure have been identified, continue HAART, and repeat *priority* viral load in another 6 weeks. If this viral load is not < 400 copies/mL, a pediatric HIV Specialist must be consulted.
    - Treatment failure due to mild to moderate gastroenteritis may not require regimen discontinuation while the gastroenteritis is being treated. However, severe gastroenteritis—e.g., protracted vomiting and/or frequent voluminous diarrhea, not controlled by standard therapy--may require temporary cessation of ARVs until the gastroenteritis has resolved. Management and follow-up of *priority* viral load 6 weeks after resolution of the gastroenteritis is otherwise the same as with severe non-adherence, as detailed above.

The patient who has defaulted from therapy, or who has been lost to follow-up:

- Patients who either have defaulted from therapy or have been lost to follow-up are at very high risk for subsequent treatment failure once HAART is restarted. Accordingly, HAART should not be restarted in such patients until the reasons for the defaulting and/or missing clinic appointments have been identified and addressed. However*, indicated OI prophylaxis (e.g., CTX, fluconazole) should be continued.*

8.5 Clinical Review of Detectable Viral Loads:

Since baseline viral loads must no longer be performed, every viral load result will be from a patient on HAART, and thus must be < 400 copies/mL. (Refer to discussion of 3 months post-initiation viral load at beginning of this chapter). It is the responsibility of the practitioner to review viral load results as soon as they return from the laboratory, and to act upon any abnormal results promptly. Failure to address treatment failure promptly—i.e., within a week after monitoring labs return—is a serious breach of standards of care, since delay in addressing treatment failure will eventually lead to resistance and/or will result in accumulation of resistance mutations, which could limit future treatment options for the patient. A patient must not be maintained on a failing regimen for more than a maximum of 4 weeks after treatment failure has been identified. Every ARV clinic must have an ongoing and sustainable system for reviewing monitoring laboratory results within no more than 48 hours after their return to the clinic. Waiting to review monitoring lab results until the patient returns for the follow-up 3 month appointment is not acceptable, and is a serious dereliction of professional responsibility*.***

8.6 Recognition and Management of Treatment Failure When Monitoring Laboratory Results Are Not Available:

- When viral load and/or CD4 cell count/% is not available, it may be necessary to evaluate possible treatment failure using only clinical criteria. 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*.
- In the absence of a recent viral load, either or both of the following 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 HAART initiation.
    - Any drop in CD4 cell count/% to below baseline value, or a 50% decline in CD4 cell count/% from the highest on-treatment value. If possible, a confirmatory CD4 cell count/% should be done.
    - The likelihood of treatment failure is increased when both clinical and immunologic deterioration are present simultaneously.
- In the absence of both a recent viral load and CD4 cell count/%, evaluation for treatment failure must rely 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 HAART. Diagnosing treatment failure within the first 3-6 months of HAART initiation on the basis of clinical deterioration must consider the possibility of IRIS, which does not denote treatment failure.

8.7 HIV Specialist Panel (revised November 1, 2008):

Adult and General HIV/AIDS care:

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Pediatric and Adolescent HIV/AIDS care :

Dr. R. Phelps	**71321718**	**messageforryan@gmail.com**
Dr. S. Musa-Aisien	**72108312**	**musaaisien@yahoo.com**
Dr. H. Jibril	**71838264**	**hjibril@gov.bw**
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PMTCT and Women's Health:

Dr. D. Ramogala **72687480** **doreen@botsnet.bw**

All other Specialists listed above

Laboratory Issues:

Dr. M. Mine **71307122** **mmine@bhp.org.bw**

All other Specialists listed above

This list will be updated as needed: refer to www.moh.gov.bw, Masa webpage. If necessary, messages for Specialist assistance can be left at the toll-free number 0 800 600 691.

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 are as follows:

- Infants whose DNA PCR results are pending, and who have WHO clinical stage 2, 3, or 4 conditions
- Special indications for HAART initiation, e.g., severe WHO stage 2 condition(s), disproportionately low adult CD4% (< 15%) with absolute CD4 count > 250 cells/μL, severe symptoms of the antiretroviral syndrome
- HAART initiation in infants < 6 months of age who had received sd-NVP at birth
- First line regimen failure in women and children initiated on LPV/r-based HAART because of history of sd-NVP
- Second-line regimen failure and all subsequent regimen failures
- Interpretation of genotypic and phenotypic resistance assays
- Immunologic and/or clinical failure with full virologic suppression
- Failure of viral load to be < 400 copies/mL in a pediatric patient after 6 months on therapy

- Post-delivery decisions about continuing or stopping HAART begun during pregnancy for women not initially eligible for HAART, but who, because of intractable anemia secondary to short-course AZT prophylaxis, had been put on full d4T-containing HAART
- Evaluation of treatment failure in the absence of monitoring laboratory results
- Difficult decisions regarding indications for PEP
- Any other HIV/AIDS-related clinical questions requiring clinical expertise
- Approval for ARVs and other HIV-related drugs not included in routine first- and second-line HAART regimens (refer to Appendix for protocol for "Special Order" drugs)

8.8 Failure Management Clinics and Teams:

Management of treatment failure must, of necessity, be a "team effort," involving many different staff and clinical cadres in the ARV clinic, both for direct intervention for patients failing therapy and for discussion of treatment strategies and options. Accordingly, within three months of the release of these revised guidelines, *every ARV clinic must have an established, ongoing Failure Management Clinic and a corollary Failure Management Team,* to address failure management in a comprehensive, methodical manner. Each ARV clinic must have a designated focal nurse, who is responsible for ensuring that 1) the Failure Management Clinic and Team are assembled under the terms listed below, and 2) the responsibilities of the Failure Management Team and Clinic, as outlined below, are carried out. The head of the Failure Management Team and Clinic should be the director of the ARV clinic and/or the most experienced doctor/medical officer in the clinic. Members of the Failure Management Team should include the following:

- The director of the ARV clinic and/or the most experienced doctor/medical officer in the clinic
- Clinic doctors who have the greatest HIV/AIDS experience
- The clinic's focal ARV nurse
- Adherence educator(s)
- Clinic social worker(s)
- Lay counselors
- Clinic pharmacist(s) or pharmacy technician(s)
- In addition, treating practitioners and other clinic staff should attend those Team meetings at which there will be discussion about patients with whose care they are directly involved.

Responsibilities of the Failure Management Team:

- The Failure Management Team must meet no less often than every 2 weeks, to discuss all patients currently failing therapy, including first line regimen failures, and to review and/or plan individual interventions for addressing their treatment failure. *However, switching a patient from a failing first line regimen must not be delayed if the Failure Management Team does not meet within 2 weeks of the diagnosis of treatment failure, nor should any necessary HIV Specialist consultation be similarly delayed.*
- The agenda of meetings of the Failure Management Team should include discussion of new patients referred for possible treatment failure and follow-up discussion of previously referred patients. Once a patient's treatment failure has been successfully addressed, and the viral load has been fully

suppressed, it is not necessary to review the patient any longer, unless clinically indicated.

- Any difficult cases for which there is no Team consensus should be discussed with an HIV Specialist, with the consultation reviewed at subsequent meetings, and recorded in the patient's Failure Management Registry Form (see below). However, such Team review must not delay any indicated empiric changes in a patient's HAART regimen, under HIV Specialist guidance.
- As the first order of business after its formation, the Failure Management Team must establish and implement *on a continuous and ongoing basis* a protocol for timely, contemporaneous review of abnormal laboratory results of all patients treated at the ARV clinic, including viral load results, as mandated in Section 8.5, above. The Team is responsible for ensuring that this laboratory review is maintained. The following abnormalities require immediate follow-up, to include prompt clinical evaluation:
    - Hemoglobin < 7gms%
    - Platelets < 60,000/μL
    - Transaminase elevation > 5 times the upper limit of normal value(s)
    - *Any viral load not < 400 copies/mL*
- The Failure Management Team must keep a Failure Management Registry, which must be recorded on a standardized form. A copy of this registry is included in the Appendix. It is the responsibility of the ARV clinic focal nurse to ensure the timely and accurate updating of patient information on these registry forms, including:
    - Patient name, date of birth, sex, Masa and clinic number, and Omang.
    - Baseline CD4 cell count/%
    - Chronological listing of past and current ARV regimens, including date of initiation, date of discontinuation, and reason(s) for any switch.
    - Date and results of resistance assay(s), if any
    - A section for adherence review, to include the following aspects of adherence:
        - Adherence partner and/or patient care-giver(s)
        - Substance abuse
        - Drug-drug interactions
        - Depression or other mental illness
        - Dementia
        - Other illnesses affecting adherence
        - Any TB treatment
        - Dates of specialized adherence intervention(s)
    - A section for notation of any other relevant patient information, including any consultations with an HIV Specialist
- The Failure Management Team must report to an HIV Specialist any of the following:
    - Any consistent pattern of specific causes of treatment failure
    - The association of certain HAART regimens and/or ARVs with an increased incidence of treatment failure, adverse side effects/toxicity, and/or non-adherence
    - Any other unusual occurrences or patterns which fall outside of normal clinical experience

Responsibilities of the Failure Management Clinic:

- The Failure Management Clinic must be scheduled no less often than every two weeks, depending upon the number of patients currently with treatment failure.
- Whenever a patient is referred to the Failure Management Clinic, the patient's contact information must be updated in the clinic chart.
- Patients who must be referred to the Failure Management Clinic, and who must be discussed in the meetings of the Failure Management Team, are the following:
    - Patients with virologic, immunologic, and/or clinical failure
    - Patients who do not suppress viral load to < 400 copies/mL at 3 months post-initiation of HAART, since these patients, while not yet meeting criteria for treatment failure, may be at increased risk for eventual treatment failure at 6 months
    - Patients who experience severe, potentially life-threatening treatment toxicity, and who require a new ARV regimen
- Once a patient's treatment failure has been successfully addressed, and the viral load is fully suppressed, it is no longer necessary for the patient to be seen in the Failure Management Clinic. However, more frequent follow-up and monitoring in the regular ARV clinic may still be necessary.
- The Failure Management Clinic must follow a standardized protocol for prompt follow-up of treatment failure, which should include the following interventions:
    - Comprehensive adherence assessment, to include:
        - Patient motivation and understanding of importance of adherence
        - Involvement of adherence partner and/or care-giver(s)
        - Any side effects which might interfere with adherence
        - Inconvenience of regimen
        - Depression or other mental illness
        - Substance abuse or alcohol abuse
        - Problems with stigma or disclosure, which might adversely impact adherence
        - Presence of any illness which might adversely affect adherence
    - Review of potential drug-drug interactions
    - Any medical conditions interfering with oral intake or ARV absorption
    - Any intercurrent infections which might elevate viral load
- 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 require more frequent clinic visits (e.g., every 1-2 weeks), and should not be relegated to the standard every-three-month schedule of visits.

KEY POINTS:

- ***Treatment failure requires immediate evaluation and proper management, in order to preserve future treatment options, and to prevent ultimate clinical deterioration.***

- ***Virologic failure has occurred when viral load does not suppress to < 400 copies/mL by 6 months after HAART initiation, or when, after initial virologic suppression to < 400 copies/mL, viral load again becomes detectable anytime in the future.***
- ***As a rule, immunologic failure in the presence of full virologic suppression and clinical improvement does not merit a change in HAART.***
- ***An HIV Specialist must be consulted for any patient with full virologic suppression, but with immunologic and/or clinical failure.***
- ***Possible causes of virologic failure must be investigated in a step-by-step, methodical manner.***
- ***Virologic failure can be due to resistance and/or non-resistance causes, but if nonresistance causes of failure persist, ARV resistance will ultimately develop.***
- ***An HIV Specialist Panel has been established as an ongoing clinical resource for practitioners.***
- ***When nonadherence is suspected or confirmed, bringing back the patient's adherence partner for further support for the patient may be an effective intervention.***
- ***All ARV clinics must establish and implement an ongoing Failure Management Clinic and Failure Management Team, to address treatment failure in a methodical and comprehensive manner.***
- ***Every ARV clinic must have an ongoing and sustainable system for reviewing monitoring laboratory results—especially returning viral loads--within no more than 48 hours after their return to the clinic. Waiting to review monitoring lab results until the patient returns for the follow-up 3 month appointment is not acceptable.***

9.0 Post-Exposure Prophylaxis (PEP)

9.1 PEP for Occupational Exposure to HIV

Ideally, *PEP should be initiated within 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) 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 counseling 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) Body fluids and their HIV infectiousness:
   - 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. Examples of infectious fluids include 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) Type and extent of exposure:
   - 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) Exposure management (unproven efficacy):
   - 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 exposed site with these agents.

4) Estimation of the HIV risk of the specific exposure:
   - Needle stick injury is associated with an average, aggregated transmission risk of 0.3% (3 transmissions per 1000 events), which is greater if there was a hollow-bore needle, if the needle was in the source patient's artery or vein, if there was visible source patient blood or other infectious fluid on the needle, if the injury was deep, and if the source patient's viral load was high.
   - Mucous membrane exposure has been estimated to have a 0.09% risk of HIV transmission, but many specialists believe that the risk is much lower. 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 known to already be HIV-infected, PEP is not indicated, but HBV vaccination should be considered if the HCW has not already received it.
- To facilitate necessary evaluation and intervention, the rapid test should be used if available.
- If the HCW refuses HIV testing, then PEP should not be given.
- If the HCW tests HIV-positive, then PEP is not indicated, and necessary reassurance and emotional support must be provided to the HCW, 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 he refuses HIV testing, then an HIV (rapid) test will be obtained, but the results will 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-positive*. 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, but 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 healthcare worker.*
- For mucosal exposure to HIV-infected fluid, 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.

- PEP may be indicated in instances where non-intact skin has been exposed to HIV-infected fluid (e.g., chronic dermatitis or eczema, or a recent break in skin integrity). As with mucosal exposure, decisions regarding PEP may depend upon the length of exposure, whether or not cleansing of skin occurred promptly, the degree of skin breakdown, and the HIV test result of the source patient.
- 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 trash or elsewhere merit PEP.
- It is imperative that the medical practitioner makes decisions concerning PEP initiation free from any pressure from the exposed HCW.

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 4 hours after exposure, but no later than 72 hours.

- For adolescents and adults: co-formulated AZT 300 mg/ 3TC 150 mg BD for 28 days. (Children starting PEP require determination of AZT and 3TC doses according to the WHO pediatric dosing guide, as well as active involvement of family care-givers, as discussed in Chapter 7). The HCW must understand the importance of completing the entire 28 day regimen. Supportive care and management of AZT-associated side effects are necessary.
- The HCW should be seen for follow-up 2 weeks after PEP initiation, both for evaluation for possible side effects and to provide adherence counseling and emotional support. Routine laboratory monitoring of HCWs on PEP must be individualized according to the HCW's medical history, e.g., a woman with a past history of anemia may merit baseline and follow-up HgB. In many 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 of the incident*.
- Pregnancy is not a contraindication to PEP.
- If the HCW cannot tolerate AZT, then an HIV Specialist must be consulted immediately.
- The HCW must be counseled to practice safe sex during the period of PEP and until repeat HIV testing is negative. Women who are breastfeeding must be counseled regarding the risks of breastfeeding following an HIV exposure, and should be advised to abstain from breastfeeding. Finally, the HCW must be educated about the signs and symptoms of the acute retroviral syndrome, with instructions to return immediately if they 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 had ceased breastfeeding on PEP, a negative 6 week HIV test can be confirmed with a *priority* viral load or DNA PCR, 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.

9.2 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 great caution, because of the very real risk that the rapist is in the "window period."* Thus, as a rule, if the rape victim tests HIV negative, PEP should be offered, unless there are compelling reasons and circumstances to the contrary.

- The PEP protocol for such victims, *including infants and children*, is exactly as that for HCWs, above, *including the need for baseline HIV testing*.
- Violent rape, with obvious genital/rectal trauma (hymeneal/labial/vaginal/rectal tearing, bleeding, bruising, lacerations) may justify PEP with 3 ARVs, and should be discussed with an HIV Specialist. However, *such consultation must not delay prompt initiation of PEP with at least AZT and 3TC*, pending further discussion with a Specialist.
- It is essential that police understand that PEP must be started *immediately* for victims of sexual violence. *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, nor should he be 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 care, both medical and psychosocial. 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 screening pregnancy test, consideration should be given to offering emergency contraception to prevent pregnancy.
    - The patient/caregiver should receive education about signs and symptoms of STIs, including the importance of ongoing safe sex for adult victims.
    - 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 test, and if positive, indicated 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 initial visit, such interventions must be ongoing at follow-up visits, and always conducted within a safe, supportive, and confidential environment.*

9.3 Pre- and Post-Sexual Prophylaxis

- Until further information is available, *pre-exposure sexual prophylaxis must not be provided.*

- 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, abandonment of safe sex practices, and contradictory public health messages regarding HIV prevention and safe sex. Accordingly, except for victims of rape/defilement, as above, *post-sexual prophylaxis should not be administered.*

9.4 HIV and Occupational Health

In addition to PEP, other health interventions can reduce the frequency of workplace injury and illness:

- Hepatitis B vaccination, which is made available to HCWs by the government, is safe and effective, and will reduce the incidence of occupationally acquired hepatitis B, which can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma.
- Appropriate respiratory precautions when caring for patients with active TB will reduce the risk of occupationally acquired TB, which is a serious hazard for all HCWs, but especially those who are HIV-infected.

9.5 Surgery and Medically Invasive Procedures on HIV-Infected Patients:

As HAART extends patient life-expectancy to that of non-infected persons, the need for surgical or invasive medical procedures on HIV-infected patients will increase. An extensive meta-analysis of 114 studies of this subject (AIDS, Vol. 12 [17], November 1998) noted important deficiencies of prior studies, and concluded that "the ultimate outcome of HIV-infected patients is most likely dependent upon many independent variables and not just the underlying [HIV] infection and disease stage." In particular, 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. Delay or postponement of surgery or other invasive medical procedures cannot be justified by asserting that the HIV-infected patient has a "terminal illness," since HAART has increased life expectancy for many patients to a normal life span. Emergency surgery in an HIV-infected patient must not be delayed simply because of HIV status, or because of a low CD4 cell count or high viral load. *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 contra-indicate surgery, or other invasive medical procedures. 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 HAART 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, stage 4 malignancies, which are in remission or are resolving (e.g., KS responding to therapy), are *not* contra-

indications 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 South Africa 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) if on HAART, the patient has not demonstrated significant non-adherence and has not defaulted from treatment or clinic appointments, 4) the patient's over-all operative/medical risk for the proposed surgery or medical intervention is considered good, and 5) *the medical and/or surgical facility and the physicians/surgeons in South Africa accepting the patient in referral verify that they do not regard stable, asymptomatic HIV infection as contraindication to the proposed surgery or medical intervention*. If these five conditions are met, then eligibility for medical/surgical referral to South Africa 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 over-all surgical risk. This policy, however, does not apply to routine opt-out HIV testing of hospitalized patients of unknown HIV sero-status, which must be encouraged.

KEY POINTS:

- ***To ensure its efficacy, PEP should ideally be administered within 4 hours of the exposure, and no later than 72 hours.***
- ***Some exposures to HIV-infected fluids always require PEP—e.g., a needle stick injury involving infectious body fluid from an HIV-infected source patient. Other exposures may or may not require PEP, and clinical evaluation of the nature and extent of the exposure is necessary. Difficult cases require consultation with an HIV Specialist, but do not delay PEP initiation for more than 4 hours.***
- ***Decisions regarding PEP initiation must take into account the possibility that a source patient, whose HIV test result is negative, may be in the "window period" of early HIV infection.***
- ***The source patient does not ultimately have the right to refuse HIV testing in the PEP protocol. If the source patient refuses to be tested, then an HIV test should be obtained and the patient not informed about the result.***
- ***Three-drug PEP may be indicated with certain high-risk exposures, e.g., rape with significant genital-rectal injury, but only after consultation with an HIV Specialist. However, do not delay initiation of AZT/3TC.***
- ***Victims of sexual violence who present for care within 72 hours of the assault should be offered PEP. Victims of sexual violence must first be brought to the hospital for PEP evaluation, before a detailed police interrogation is initiated. The practitioner must not wait for a police report,***

and must not be bound by the findings of such a report. A patient history of penetrative sexual violence is sufficient for PEP initiation.

- ***Victims of sexual violence, especially children, require special and ongoing care, both medical and psychosocial. This care must be provided regardless of whether or not the patient received PEP.***

- ***Pre- and post-exposure sexual prophylaxis is of unproven benefit, and must not be administered.***
- ***Hepatitis B vaccination for healthcare workers is provided by the government, is safe and effective, and will reduce the incidence of occupationally acquired hepatitis B, which can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma.***
- ***Appropriate respiratory precautions when caring for patients with active TB will reduce the risk of occupationally acquired TB, which is a serious hazard for all HCWs, but especially those who are HIV-infected.***
- ***HIV infection itself is not a contraindication to surgery or other invasive medical procedures, and indicated interventions in such patients must not be delayed, unless there is a medically valid reason independent of HIV infection.***
- ***Preoperative surgical evaluation of the HIV-infected patient must focus on the same standard anesthetic and medical risks used for HIV-uninfected patients, and not on the presence of HIV infection.***

10.0 Management of Opportunistic Infections and Other HIV-Related Conditions in Botswana

10.1 Cryptococcal Meningitis:

Diagnosis: Disease onset is often subtle, and classic meningeal signs are absent in up to 50% of patients. Chronic headache, often initially of low-grade severity, is common, and should raise suspicion of the diagnosis, as should progressive deterioration of mental status, visual disturbances, and/or unexplained fevers in any HIV-infected patient with a low CD4 cell count (< 100 cell/μL) or low CD4% (< 15%).

- The lumbar puncture is the cornerstone of diagnosis, and, if performed promptly, is also therapeutic and potentially life-saving. LPs are safe, and cause serious complications only very rarely, *if at all*. Nonetheless, to ensure patient safety, a neurological examination must be performed before performing an LP. Defer an LP until after an urgent non-contrast head CT scan has been done *only* if a patient has focal neurological findings (unequal/irregular pupils, hemiparesis), focal seizures, or clinical signs of impending brainstem herniation (pupil changes, abnormal respiratory pattern). When CT scanning is not immediately available for the above clinical situations, and the suspicion of meningitis is high, *the potential benefits of an LP outweigh any theoretical risks*: proceed with the LP, using a 20-24 gauge needle, if available. An HIV Specialist should be consulted for any difficult cases, but *obtaining a CT scan or consulting an HIV Specialist must not significantly delay the LP and subsequent initiation of treatment*. In all cases, reasons for not doing an LP must be valid and well documented, *and casual, poorly founded reasons for initiating "empiric" treatment without ever performing an LP are not acceptable.*
- The LP must be regarded as part of general medical evaluation, akin to obtaining a chest X-ray or an FBC. *The LP should be presented to the patient as an "opt out" procedure, which does not require explicit consent*. If the patient cannot acknowledge implied permission for having an LP, e.g., due to altered mental status, then the LP should be performed at once, since delay in performing this diagnostic/therapeutic procedure can be life-threatening. *Gathering the entire family for consent is unnecessary and should not be done.*
- Typically, CSF analysis will reveal a lymphocytic pleocytosis, with elevation of protein and moderate lowering of glucose. *A normal CSF profile does not rule out cryptococcal meningitis*, and can be present in up to 50% of cases. The India ink test of CSF is the diagnostic method of choice. In instances where the India ink test is negative and clinical suspicion is still high for cryptococcal meningitis, CSF or serum cryptococcal antigen and empiric treatment are indicated. In instances where the patient refuses a spinal tap, or when equipment for an LP is not available, a serum cryptococcal antigen should be obtained, and treatment initiated promptly, pending the return of the result from the laboratory. Empiric treatment for cryptococcal meningitis should be initiated whenever clinical suspicion is high, especially when the LP reveals high CSF pressure and the patient is severely immunosuppressed. *Delay in return of laboratory results must not delay initiation of treatment.*

Treatment: The proper treatment of cryptococcal meningitis entails the prompt administration of antifungal agents *and* the judicious management of increased intracranial pressure (ICP):

- Induction therapy: Once the diagnosis of cryptococcal meningitis is made, initiate IV amphotericin B (0.7mg-1.0 mg/kg/day) for at least 2 weeks.
    - Pre-hydrate the patient before each dose of amphotericin B with one liter of 0.9% saline or lactated Ringer's solution. For children, 20ml/kg of 0.9% saline or lactated Ringer's solution should be used.
    - *Vigorous* IV hydration with 0.9% saline at rates of 100-150cc/hour is necessary to reduce the risk of serious amphotericin-induced renal failure.
    - Two common infusion-related side effects often require symptomatic management: pethidine is effective in the management of rigors, and paracetamol can lessen fever.
    - Nephrotoxicity and hypokalemia are other important side effects of amphotericin B. All patients should have urea, creatinine and serum potassium monitored at least twice weekly. For patients who do not tolerate amphotericin B (or who are completely alert and without other neurological signs or symptoms), or in situations where amphotericin B is not available, an alternative treatment is high dose fluconazole (800mg OD for 3 days, followed by 400mg OD for at least 2 weeks *prior to the consolidation phase*, as below).
- Consolidation therapy: After completing the induction phase with amphotericin, begin fluconazole 400 mg OD for 8-10 weeks. (For adults treated solely with fluconazole for 2 weeks of induction therapy, as above, continue 400mg OD fluconazole for *an additional* 8-10 weeks.). Children should receive fluconazole 6-12 mg/kg OD for 8 weeks during the consolidation phase.
- Maintenance therapy: Fluconazole must be continued at 200 mg OD as secondary prophylaxis, until HAART has increased the patient's CD4 cell count to more than 200 cells/uL for at least 6 months. Fluconazole for secondary prophylaxis in children should be continued indefinitely at 6mg/kg OD.

ICP Management: *The proper management of cryptococcal meningitis involves the management of increased intra-cranial pressure*. Opening and closing pressure of CSF must be measured each time an LP is performed. (Normal CSF opening pressure is < 15 cm water). *Increased ICP is the major cause of mortality and morbidity of this disease*. When the initial opening pressure is > 20cm of H_2O, drain any excess CSF until the closing pressure is < 15 cm of H_2O. *It is imperative to perform daily lumbar punctures until the opening pressure is consistently below 15 cm of H_2O*. For those patients without increased ICP on presentation, *perform a repeat lumbar puncture to assess for elevated pressure if the patient is not improving on amphotericin B, or if the patient initially improves, but then subsequently deteriorates*. Persistent or increasing headache, visual changes, and diminished level of consciousness are indicators of increased ICP. In the absence of a manometer, CSF pressure can be assessed by measuring the height of the column of CSF in IV tubing affixed to the spinal needle.

10.2 Tuberculosis: (See also Chapter 6).

Diagnosis of Pulmonary TB:

- Sputum microscopy is the single most important test in TB diagnosis. At least three sputum samples for AFB should be obtained in symptomatic patients, with at least one of these specimens being an early morning sputum. Although

culture is the absolute standard for diagnosing TB, this test is not routinely done in Botswana for new TB cases.

- *Active TB cases in which TB culture with antimicrobial sensitivities should always be obtained include the following*: 1) patients who have had TB treatment in the past, 2) patients who remain smear-positive at the end of the initial phase and/or the end of the continuation phase of ATT, 3) active TB which develops while the patient has been on IPT, 4) TB diagnosis in the setting of repeatedly smear-negative microscopy, 5) contacts of MDR-TB, 6) TB in laboratory and other healthcare workers, 7) TB diagnosis from non-sputum sources such as urine, abscesses, CSF, and gastric, pericardial, and pleural fluids, 8) children in whom the diagnosis of TB is uncertain, and 9) TB IRIS or suspected TB IRIS.
- TB can also be cultured from blood, an investigation which is useful if there is clinical suspicion of cryptogenic (disseminated) TB. Special TB blood culture bottles can be ordered from the National Health Laboratory in Gaborone.

Diagnosis of Extra-Pulmonary TB:

- TB lymphadenitis commonly affects cervical lymph nodes and can often be diagnosed with examination and culture of a fine needle aspirate.
- Pleural TB has an exudative effusion, which can be bloody, with high protein, low PH, and low or normal glucose. Effusion cytology may also be diagnostic for TB.
- TB meningitis:
    - Symptoms of greater than 5 days duration
    - Headache
    - Confusion and/or diminished level of consciousness
    - Cranial nerve findings
    - CSF may appear initially clear, but on standing often develops a delicate fibrin clot suspended in the fluid.
    - CSF white blood count < 1000 cells/μL
    - CSF lymphocyte % > 30%
    - CSF protein > 100mg/dL
    - CSF glucose is usually below normal range, but not as low as that commonly seen in other pyogenic meningitides.
    - Negative India ink stain
- TB pericarditis: Echocardiogram may show fibrinous strands and pericardial thickening.

Treatment of TB in HIV-Infected Patients:

- New cases of pulmonary TB: for adults, the standard 6-month regimen of 2 months of HRZE followed by 4 months of HR. For children, uncomplicated pulmonary TB is treated with 2 months of HRZ followed by 4 months of HR. Children with severe TB (excluding TB meningitis) should be treated with 2 months of HRZE followed by 4 months of HR *under the supervision of a pediatric specialist.* Streptomycin should replace ethambutol in the treatment of TB meningitis. "Severe" childhood TB includes meningitis, miliary disease, spinal TB, adenitis with compressive complications, and pericarditis with effusion and tamponade.
- Sputum smears on patients on ATT should be done at 2 months and at 5-6 months of treatment. *Positive smears at or after 5 months indicate treatment failure, and require sputum culture with drug susceptibility tests* and an

immediate switch to the category II ("retreatment") regimen: 2 months of HRZES, followed by one month of HRZE, followed by 5 months of HRE.

- CTX prophylaxis, regardless of CD4 cell count, should be given OD to all patients being treated for active TB.
- Severe cases of extra-pulmonary TB--TB meningitis, TB pericarditis, disseminated TB, and spinal disease with neurological complications-- should be treated with at least 8 months of ATT, i.e., 2HRZE/6HR.
- Adjunctive steroids should be given to all patients with TB meningitis and for TB pericarditis: prednisone 1-2 mg/kg/day, with a maximum dose of 60 mg/day for 1 month, with tapering over the next 2 months.
- Post-ATT chest X-ray often lags behind clinical improvement, and can thus often be misleading. As a rule, it should not be done.
- Multi-drug resistant (MDR) TB is largely manmade, and is due to faulty ATT management: non-adherence, adding one drug to a failing ATT regimen, using drugs of low potency, and failure to recognize existing drug resistance. ***It is imperative to obtain TB cultures with drug susceptibility testing for any of the indications listed above, in order to detect early cases of MDR TB.***
- Common side effects of ATT drugs:
    - Isoniazid: hepatitis and peripheral neuropathy
    - Pyrazinamide: nausea, abdominal pain, arthralgias, gouty arthritis, and hyperuricemia (asymptomatic hyperuricemia does not require treatment).
    - Ethambutol: optic neuritis, which is rare and sometimes reversible (also a potential complication of ddI).
    - Rash and autoimmune thrombocytopenia due to ATT is usually due to rifampicin.
- Patients developing active TB while on IPT must be discussed with an HIV Specialist, and must have relevant specimens sent for culture and drug susceptibility testing.

10.3 Kaposi's Sarcoma (KS):

- Diagnosis of KS in Botswana is usually made clinically.
- Chest X-ray should be done to rule out pulmonary KS.
- A few KS lesions confined to the skin can be treated with HAART alone, sometimes along with local chemotherapy injections. A careful physical examination, including inspection of the oral cavity and a chest x-ray, must be done to rule out concomitant extra-cutaneous KS.
- Indications for systemic chemotherapy for KS: pulmonary involvement, extensive skin disease, severe pain, lower leg edema, impending upper airway obstruction from oral and/or neck edema.
    - IRIS (see 10.14) may worsen KS. Patients with pulmonary disease, massive cervical and/or hilar adenopathy, and large oropharyngeal lesions must be monitored closely after HAART initiation for possible life-threatening upper or lower respiratory complications due to IRIS. In such cases, chemo/radiotherapy should be considered at the time of HAART initiation, or even prior to initiation.
- Radiotherapy may decrease tumor size and lessen pain, and may be of benefit for extensive, severe leg edema and neck edema with impending upper airway obstruction. Radiotherapy can be arranged by the oncologist at Princess Marina Hospital.

- In general, HAART and chemotherapy will prevent progression and decrease tumor burden. However, complete resolution of KS lesions is often very slow, and sometimes is never achieved.
- The treatment of pediatric KS has been favorable in Botswana, with a number of children with extensive disease having achieved remission following chemotherapy and immune reconstitution.

10.4 Neurological Disease:

10.4.1 Peripheral Neuropathy:

Peripheral neuropathy can result from either drug toxicity (INH, d4T, ddI, AZT) or HIV itself. All HIV-infected patients receiving INH should routinely receive pyridoxine 25mg OD to prevent peripheral neuropathy. Patients with suspected INH-induced peripheral neuropathy may require higher doses of pyridoxine, often up to 100mg OD. Symptomatic treatment of HIV/ARV-related peripheral neuropathy should begin with amitriptyline or imipramine, in increasing doses as needed: increase by 25 mg weekly until sufficient benefit is reached, anti-cholinergic effects appear, or the maximum recommended dose is attained (75-100mg). *A common management error is not aggressively increasing the dose until symptomatic relief is obtained.* Although not part of the national formulary, gabapentin can be especially effective. Carbamazepine is another therapeutic alternative (avoid with EFV due to adverse drug interactions). Switching the offending ARV to an agent less commonly associated with neuropathy, e.g., ABC or TDF, may be helpful. HIV-associated neuropathy will often improve on HAART.

10.4.2 AIDS Dementia Complex/HIV Encephalopathy:

- 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. HIV encephalopathy should be considered in all children with loss of developmental milestones.
- Fully suppressive HAART usually improves AIDS dementia complex.

10.4.3 Spinal Cord Disease and Myelopathy:

- 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 HAART

10.5 Herpes Simplex Virus (HSV):

- *Symptomatic HSV infection (> 30 days duration or any visceral site) is a WHO stage 4 condition*.

- Genital HSV, both symptomatic disease and asymptomatic shedding, increases the risk of HIV acquisition and transmission, and HSV shedding has been implicated in MTCT.
- Treatment for HSV oralis/genitalis: acyclovir 400mg po TDS for 10 days (for children 40-80 mg/kg/day divided into 3-4 doses each day) for an initial episode. Recurrent episodes must be discussed with an HIV Specialist regarding the need for acyclovir prophylaxis.

10.6 Varicella-Zoster Virus (VZV):

- Recurrent mono-dermatomal VZV, ophthalmic VZV, and multi-dermatomal VZV (one episode) are Botswana-specific "WHO clinical stage 3" conditions.
- Treatment for multi-dermatomal VZV (if diagnosed within 72hrs of onset) and for ophthalmic VZV: acyclovir **800** mg by mouth *five times per day* for 7-10 days. (40-80 mg/kg/day divided into 3-4 doses each day for children). *Lower doses of acyclovir for these manifestations of VZV are ineffective, and should not be used*.
- Treatment for disseminated VZV: IV acyclovir 10 mg/kg every 8 hrs 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/m^2 (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 is a medical emergency*, and should be treated as early as possible with oral acyclovir in the same 800mg dose schedule used for multi-dermatomal zoster, as above. *Urgent ophthalmologic consultation is mandatory*. When such consultation is not immediately available, treat with topical steroids and scopolamine 0.25%, 1 drop in affected eye TDS. Topical acyclovir eye ointment is of little value in ophthalmic zoster, and is not recommended.
- In Botswana, acyclovir is not authorized for single dermatomal zoster, but may be indicated for severe presentations, e.g., with bacterial superinfection. Discuss with an HIV Specialist for permission to treat with acyclovir in such circumstances.

10.7 CMV Retinitis:

- Diagnosis: funduscopic findings of white retinal patches and retinal hemorrhages, vasculitis, and retinal necrosis and 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*.

10.8 Mucocutaneous Candidiasis/Oral Candidiasis:

- Oral candidiasis is common in patients with HIV infection: 1) pseudo-membranous candidiasis (white removable plaques on the palate and other oropharyngeal surfaces), 2) erythematous candidiasis (smooth red areas on the

hard palate or dorsal tongue), and 3) angular cheilitis (fissures at the corners of the mouth). Persistent oral candidiasis is a WHO stage 3 condition (after age 6 weeks in infants).

- For all cases of oral candidiasis, esophageal involvement must be ruled out by inquiring about the presence of odynophagia (painful swallowing of liquids and/or solids) and/or dysphagia. If esophageal symptoms are present, empiric therapy with systemic antifungal therapy should be initiated: fluconazole 200 mgs OD for 10-14 days. For children, 6 mg/kg should be given once, followed by 3 mg/kg OD for esophageal candidiasis.
- If Candida is limited to the oropharyngeal cavity *and is symptomatic*, only topical antifungals are required: miconazole gel, clotrimazole troches/pessaries, and/or nystatin swish/spit. Thrush usually resolves promptly with HAART.
- Esophagitis can also be caused by CMV, HSV, and probably HIV itself. If odynophagia persists despite a 2 week course of fluconazole, start empiric acyclovir for HSV. If this therapy fails, consider referral for diagnostic upper endoscopy.
- Prolonged fluconazole use (> 2-3 weeks) should be discouraged, since Candida resistance to azoles is apt to occur. (This precaution does not apply to fluconazole use for cryptococcal treatment and prophylaxis).

10.9 Bacterial Pneumonia:

Severe bacterial pneumonia is a WHO stage 3 condition, and recurrent severe bacterial pneumonia is a stage 4 condition.

- Differential diagnosis of severe community-acquired pneumonia in patients with known HIV infection:
  - Children < 1 year of age: *Pneumocystis jiroveci* (PCP) pneumonia
  - All age groups: *Streptococcus pneumoniae, g*ram negative pneumonia (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Hemophilus influenzae*), *Mycobacteriae tuberculosis* (drug-sensitive and MDR/XDR)
- Diagnosis:
  - History and physical examination
  - Chest x-ray
  - Oxygen saturation (when available)
  - Sputum gram stain and culture
  - Sputum smears for AFB x 3
  - Blood cultures, if available
- Management of severe community-acquired pneumonia:
  - Empiric broad spectrum IV antibiotics (10-14 days total): high-dose IV penicillin or IV cefotaxime *plus* IV or p.o. erythromycin or po doxycycline. Recommended regimen: IV cefotaxime (1-2 grams IV q 6-8 hours) plus doxycycline 100mg po BD
    - Consider empiric high dose oral CTX, if CD4 count < 200 cells/μL and/or child < 1 year of age and/or classic chest X-ray findings for PCP (diffuse bilateral interstitial infiltrates)
    - Consider empiric ATT, if no significant improvement with above treatment and/or with clinical symptoms suggestive of TB and/or classic chest X-ray findings (upper lobe cavitary disease or military pattern). However, *a "trial" of ATT should*

never be done, since 1) rifampicin has anti-bacterial activity and 2) pulmonary TB may require several months for any observed clinical response, both of which situations can result in confusion if clinical response to a "trial" of ATT is used as a diagnostic indicator.

- Duration of any antibiotic treatment should be *at least 10 days*, or longer if required by clinical condition and/or response to treatment. *Quinolones, e.g., ciprofloxacin, and aminoglycoside antibiotics, e.g., amikacin, should be avoided as empiric antibiotic therapy, except for infections documented to be resistant to conventional therapy and sensitive to quinolones/aminoglycosides, because of potential compromise of these important second-line ATT drugs if the patient has undetected active TB instead of other bacterial infections.*
- Follow-up chest X-ray may require several months, even longer, before showing radiographic resolution of pneumonia, and clinical response to treatment is the best way of monitoring the patient.

10.10 Pneumocystis Jiroveci Pneumonia (formerly pneumocystis carinii pneumonia, PCP):

Diagnosis: subacute onset of fever, dry cough, increasing dyspnea in patient with CD4 cell count < 200 cells/μL and chest X-ray finding of *bilateral* interstitial infiltrates (definitive diagnosis via bronchoscopy is not routinely available in Botswana). The chest X-ray can be variable and occasionally normal. An important clue to clinical diagnosis is low oxygen saturation, which can often be detected when the patient has evidence of oxygen desaturation with minimal exercise/walking (e.g., cyanosis, significant dyspnea).

Treatment:

- For adults:
  - 15-20mg/kg trimethoprim (TMP)/day + 75-100mg/kg/day sulfamethoxazole (SMX) po or IV in 3 or 4 divided doses for 21 days
  - Alternative: if < 50kg, 3 SS [single strength] CTX tablets TDS; if > 50kg, 4 SS CTX tablets TDS (each dose X 21 days).
- For children: 15mg TMP/75mg SMX per kg/day po or IV in 3-4 doses.
- If oxygen saturation is < 90%, or if there is clinical evidence of oxygen desaturation, administer high-dose steroids, with gradual tapering over 21 days (prednisolone 40mg BD X 5 days, then 40mg OD X 5 days, then 20mg OD X 11 days; alternative regimen: prednisolone 1mg/kg BD X 5 days, then taper over next 16 days). *If arterial blood gases or pulse oximetry is unavailable, clinical symptoms of increasing respiratory distress merit empiric high-dose steroids and oxygen therapy.*
- Chest X-ray may initially worsen in spite of clinical improvement.
- Paradoxical worsening of symptoms can sometimes occur during the first week or so of high-dose CTX therapy.

Prevention: Ault secondary CTX prophylaxis with 960mg (2 SS CTX tablets) OD, until CD4 cell count increases to > 200 cells/mL for at least 3 months and there are no active, current WHO stage 3 or 4 conditions. For pediatric patients, secondary CTX prophylaxis with 2.5-5.0 mg/kg TMP OD, to maximum 160mg dose, until CD4 cell %/count are > 25% and 350 cells/uL, respectively.

10.11 Lymphoid Interstitial Pneumonitis (LIP):

LIP is a common lymphoproliferative pulmonary disorder in HIV-infection, especially in pediatric HIV infection, with a spectrum of disorders involving lymphocytic infiltration of the lungs and hyperplasia of bronchus-associated lymphoid tissue. 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. 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 HAART.

Diagnosis: the diagnosis of LIP is made on the basis of clinical history, physical examination, and chest X-ray, with exclusion of treatable lung diseases.

Treatment: HAART, antibiotics. For children with significant pulmonary compromise, inhaled beta-agonists and steroids may be helpful.

10.12 Chronic Diarrhea:

"Chronic unexplained diarrhea" for > 30 days in adults and "unexplained persistent diarrhea" for > 14 days in pediatric patients are WHO stage 3 conditions.

Diagnosis: stool for culture, ova and parasites (*repeat studies are often necessary* to make the diagnosis). Common causes in immune-compromised patients: Cryptosporidium parvum, Isospora, Microsporidia, Giardia lamblia, mycobacteria, e.g., TB. Also, consider antibiotic-associated diarrhea, e.g., C. difficile. Chronic unexplained diarrhea > 30 days in adults and unexplained persistent diarrhea > 14 days in children are with stage 3.

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.
- Empiric CTX and metronidazole, either sequentially or simultaneously. CTX should be administered as 1 DS tablet QID for 10 days, followed by BD dosing for 21 days. For children, 5 mg/kg TMP BD.
- For *documented* microsporidia infection: albendazole 400mg BD until the CD4 cell count is > 200 cells/μL. Laboratories are strongly encouraged to gain necessary capacity to identify microsporidia infection, but when the laboratory is not able to screen stool specimens for this specific pathogen, empiric albendazole can be used for a 21 day trial, after several courses of empiric CTX and metronidazole have proven ineffective.
- Loperamide, calcium *carbonate*, avoidance of milk and milk products. *Because of serious adverse events, loperamide must not be used for children who are < 3 years of age, moderately or severely dehydrated, systemically ill, or with bloody diarrhea*.

10.13 Immune Reconstitution Inflammatory Syndrome (IRIS):

- IRIS is a potential complication that can occur following the initiation of HAART, when improvement in immune function is accompanied by the worsening of a current opportunistic infection or the unmasking of a latent or previous one. IRIS presents as a paradoxical worsening of clinical status despite "favorable" CD4 and viral load responses.
- IRIS most commonly occurs in the setting of underlying mycobacterial infections (e.g., TB), cryptococcal infection, and herpes virus infections

(HSV, VZV, CMV, KS). Almost all other OIs have been associated with IRIS.
    - Usually occurring in the first 2 weeks of HAART initiation, TB IRIS is an especially common complication of HAART initiation in many African countries, and is a reason to avoid HAART initiation soon after ATT initiation, unless the patient's condition is desperate (see Chapter 6).
- Baseline CD4 count < 50 cells/μL, rapid viral load decline, and robust immune reconstitution with HAART are associated with IRIS.
- The interval between initiation of HAART and onset of IRIS is variable, ranging from < 1 week to many months, usually in the first 3-6 months of therapy.
- Specific treatment directed against the IRIS-related OI should be initiated.
- No formal guidelines are in place for HAART discontinuation with IRIS. The general practice is to discontinue HAART only if: 1) the inflammatory responses are life-threatening (e.g., impending upper airway obstruction, severe hypoxemia), 2) the responses are not amenable to steroids, or 3) the pathogens are not controllable by specific antimicrobial therapy.
- Systemic steroids are often given when inflammatory damage at a site of involvement severely impairs organ function and becomes life-threatening, e.g., upper respiratory obstruction from lymphadenopathy due to TB or KS.

KEY POINTS:

- ***The LP must be regarded as part of the general medical evaluation, akin to obtaining a chest X-ray or an FBC. <u>The LP should be presented to the patient as an "opt out" procedure, which does not require explicit consent</u>. If the patient cannot acknowledge implied permission for having an LP, e.g., due to altered mental status, then the LP should be performed at once, since delay in performing this diagnostic/therapeutic procedure can be life-threatening. <u>Gathering the entire family for consent is unnecessary and should not be done.</u>***
- ***In up to half the patients with cryptococcal meningitis, the CSF can be normal and/or meningeal signs can be absent on physical examination.***
- ***Amphotericin therapy for cryptococcal meningitis mandates <u>vigorous IV fluid hydration</u>, to prevent renal failure, and at least twice-weekly monitoring of serum potassium, urea, and creatinine.***
- ***<u>The proper management of cryptococcal meningitis involves the management of increased intra-cranial pressure</u>. Perform a repeat lumbar puncture to assess for elevated pressure if the patient is not improving on amphotericin, if headache worsens or cranial nerve signs (e.g., visual changes) develop, or if the patient initially improves but then subsequently deteriorates.***
- ***<u>It is imperative to obtain TB cultures with drug susceptibility testing for any of the indications listed in 10.2, above, in order to detect early cases of MDR TB.</u>***
- ***Certain severe forms of extra-pulmonary TB--TB meningitis, TB pericarditis, disseminated TB, and spinal disease with neurological complications-- should be treated with <u>8 months of ATT</u>, i.e., 2HRZE/6HR.***
- ***Adjunctive steroids should be given to all patients with TB meningitis and with TB pericarditis.***
- ***Post-ATT chest X-ray often lags behind clinical improvement, and can thus often be misleading. As a rule, it should not be done.***
- ***<u>A "trial" of ATT should never be done</u>.***

- ***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.***
- ***Treatment for multi-dermatomal VZV (if diagnosed within 72hrs of onset) and for ophthalmic VZV: acyclovir <u>800</u> mg by mouth five times per day for 7-10 days. (40-80 mg/kg/day divided into 3-4 doses each day for children). <u>Lower doses of acyclovir for these manifestations of VZV are ineffective, and should not be used</u>.***
- ***Quinolones, e.g., ciprofloxacin, and aminoglycoside antibiotics, e.g., amikacin, should be avoided as empiric antibiotic therapy, except for infections documented to be resistant to conventional therapy and sensitive to quinolones/aminoglycosides, because of potential compromise of these second-line ATT drugs if the patient has undetected active TB instead of other bacterial infections.***
- ***To detect CMV retinitis as early as possible, patients with very low CD4 cell counts should be counseled to return immediately if any visual symptoms develop.***
- ***Management of IRIS should be done under the guidance of an experienced HIV clinician or HIV Specialist.***

Appendix:

1. Protocol for "Special Order" ARV Drugs
    a) Procedure for Approval of "Special Order" ARV Drugs
    b) Procedure to Ensure Availability of ARV Drugs
2. STI Algorithms
3. IPT Algorithm
4. WHO Pediatric Dosing Charts
5. Table of ARVs for Adults, Their Dosages and Common Side Effect/Toxicities
6. Tanner Staging
7. Failure Management Registry

Protocol for "Special Order" ARV Drugs:

I. Procedure for Approval of "Special Order" ARV Drugs
II. Procedure to Ensure Availability of ARV Drugs

I. Procedure for Approval of "Special Order" ARV Drugs

ARV drugs have been divided into the following two categories:

Category 1: First and second line drugs, *which can be prescribed by all government doctors, without HIV Specialist approval*.

a) TDF + FTC (Truvada)
b) EFV
c) NVP
d) AZT + 3TC (Combivir/Lamzid)
e) 3TC
f) LPV/r (Kaletra, Aluvia)
g) d4T
h) ddI
i) ABC (for 2nd line therapy in pediatric patients only)

Category 2: "Special Order" drugs*, which can be prescribed only by, or authorized by, an HIV Specialist on the HIV Specialist Panel, as designated by the Ministry of Health and NASCOD*.

a) Indinavir
b) Saquinavir
c) Ritonavir
d) Nelfinavir
e) ABC (for adults)
f) Raltegravir
g) Darunavir
h) Any other ARV drug(s) which might become registered in Botswana in the future.

Ministry of Health HIV Specialists authorized to approve Category 2 ("Special Order") drugs are all of those listed in Section 8.7, HIV Specialist Panel. "Special Order" drugs will be available in both referral hospitals and other facilities which have been approved for drug storage, *provided there are facility patients who have*

been prescribed the particular drug. Because these drugs require authorization by an accredited HIV Specialist, the following steps are necessary:

1. When an HIV Specialist in a facility prescribes the drug and signs the prescription himself, the pharmacy will dispense the drug as prescribed.
2. When a non-specialist clinician prescribes the drug, and there is an HIV Specialist available at the facility, the Specialist must approve use of the drug and then counter-sign the prescription. The drug will then be dispensed as prescribed.
3. When a non-specialist clinician prescribes the drug, and there is no HIV Specialist available at the facility to approve and sign the prescription, the non-specialist clinician must phone any Specialist from the above list to discuss the case with the Specialist. If the non-specialist has insufficient cell phone units, a land line toll-free number [0 800 600 691] may be used to contact the PEPFAR office in Gaborone, which will immediately contact and request a Specialist to phone the clinician. Once the Specialist verbally approves the drug over the phone, the non-specialist practitioner must then complete the standard "Special Order" form, listing the following minimum clinical details:

    - Patient name, age, gender, Omang, and clinic chart number
    - Brief ARV history, including current regimen and reason(s) why the change is necessary
    - Current VL and CD4 count
    - Full final regimen as agreed upon with the Specialist
    - The name of the Specialist approving the drug

    The completed form should then be faxed to the PEPFAR office at 3903577. If this fax is not working, the form should be faxed to Marina's superintendent's office at 3973776, from which it will be delivered to the PEPFAR office. The PEPFAR office will arrange for the authorizing HIV Specialist to sign the form, immediately after which it will be faxed back to the non-specialist clinician, who must then forward it to the dispensing pharmacy.

    To avoid unnecessary delays in dispensing the drug, the non-specialist clinician should give the patient the original special order form, on which has been recorded the telephonic approval given by the Specialist. The patient should take the form, along with the prescription for the new drug(s) to the pharmacy, for collection of the drugs.

    To ensure the integrity and necessary oversight of the above procedure, the special order forms received by the PEPFAR office and those received by the pharmacy will be forwarded to the BEDAP office in the Ministry of Health on a monthly basis, for review and verification.

II. <u>Procedure to Ensure Availability of ARV Drugs</u>:

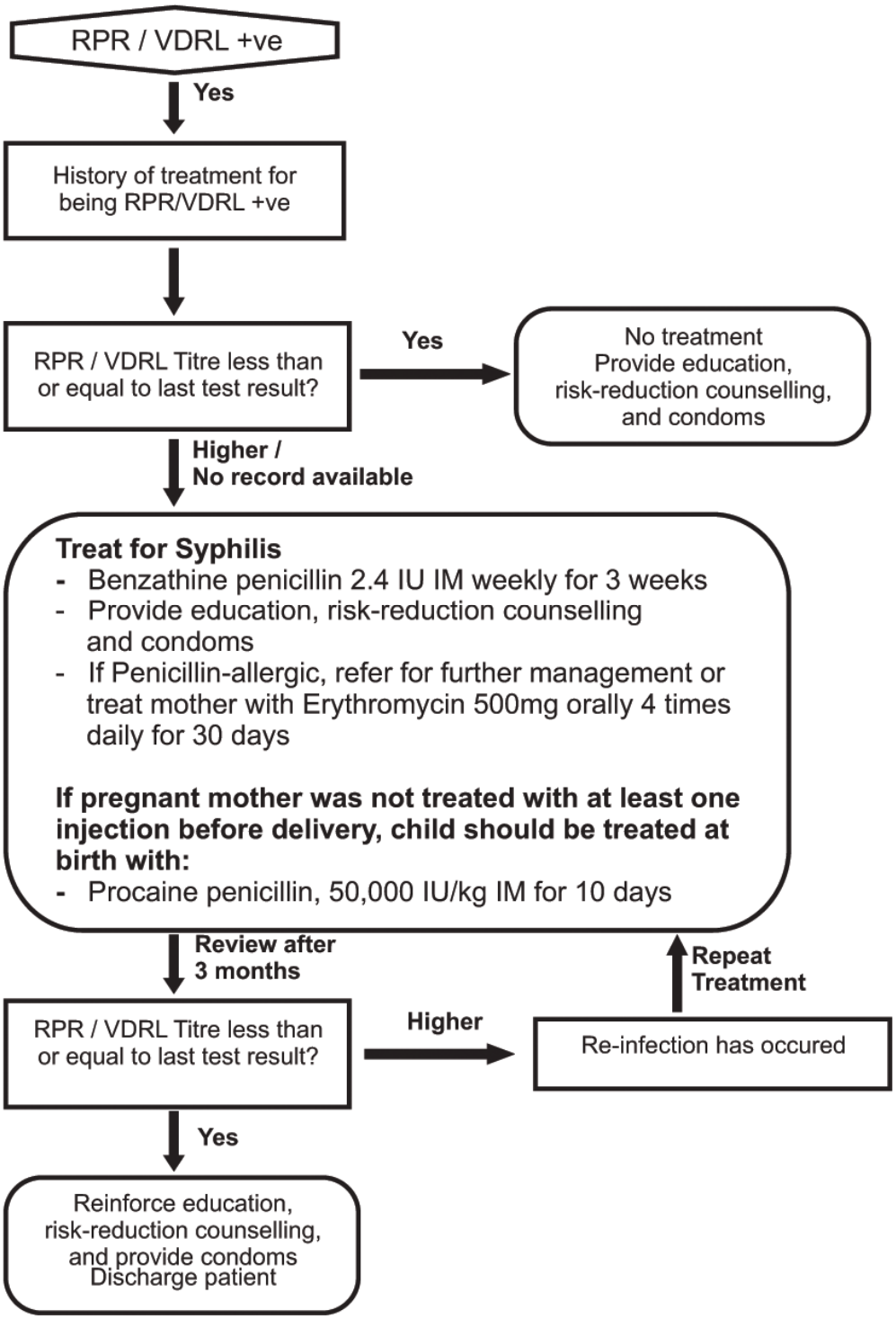
1. ARV sites which have been approved for drug storage should keep in stock at all times sufficient quantities of the first and second line ARV drugs as listed in Category 1, above, provided that there are patients currently receiving the

particular drugs from that site. These drugs are ordered from CMS through the standard ordering system and can be prescribed by any government doctor.

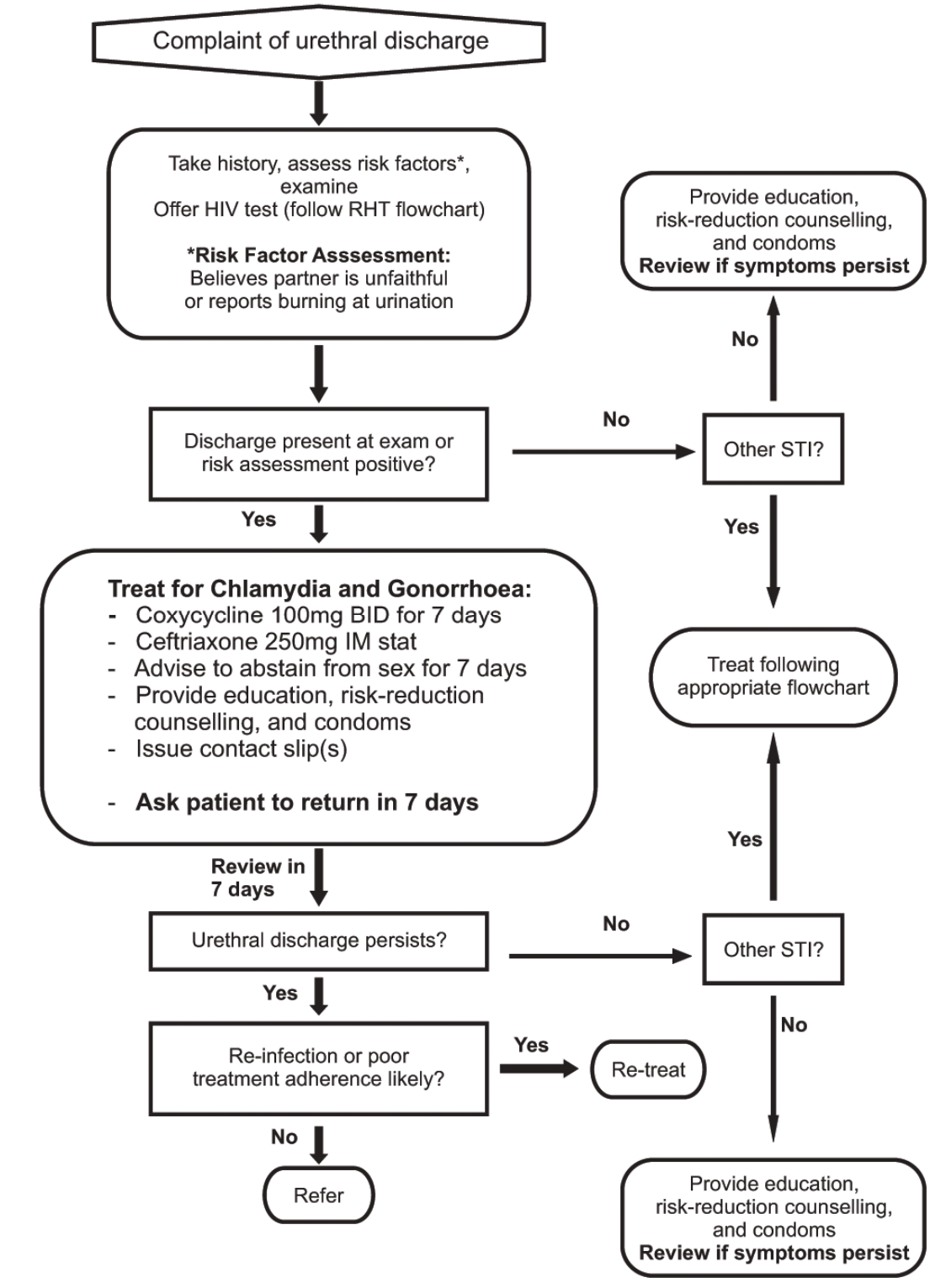
2. Facilities which are not approved for drug storage will continue to be supplied from their nearest government health facility pharmacy, as in the past.
3. Smaller facilities which have been approved for drug storage should only order specific second line drugs as stock items once they have patients who have been prescribed these drugs. Therefore, at the first time a patient is prescribed a second line drug(s) in that facility, the patient will need to either collect the medication from the nearest hospital or wait until the order for the drug from CMS has been received and the drug has been received at the facility where the drug was prescribed. Thereafter, the facility will be expected to keep a sufficient stock of the drug(s) for that patient, as well as for any other patients subsequently prescribed the drug.
4. Pharmacy personnel will also be expected to review the stock supplies of second line ARV drugs each month to ensure that:
    a. there are sufficient stocks for those patients in the pharmacy register who have been prescribed the drugs, and
    b. if individual drugs accumulate due to their no longer being dispensed, the drugs are returned to CMS, to avoid the unnecessary expiration of expensive drugs.

STI Treatment Algorithms:

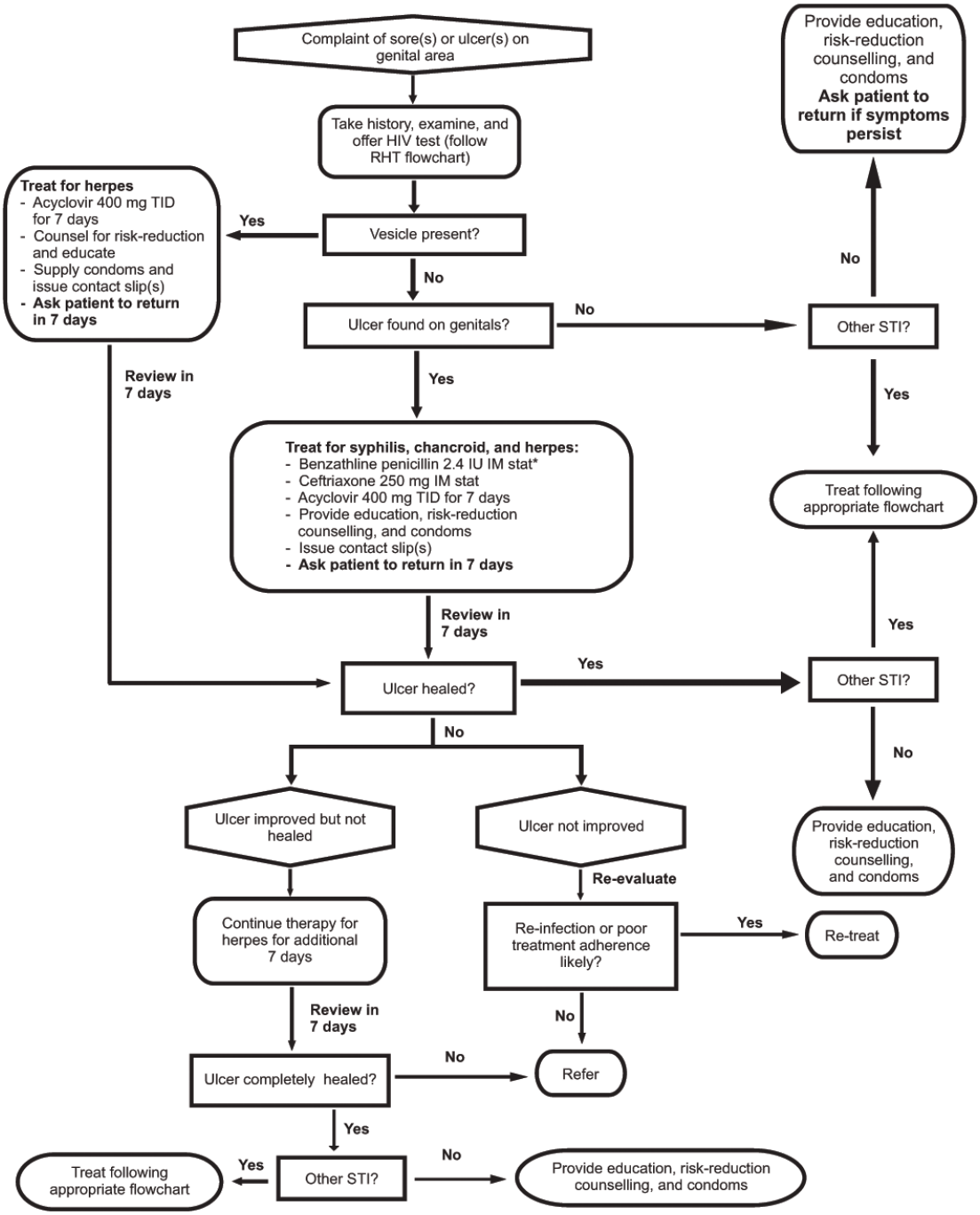
STI Treatment Algorithms: Management of RPR/VDRL Positive Cases



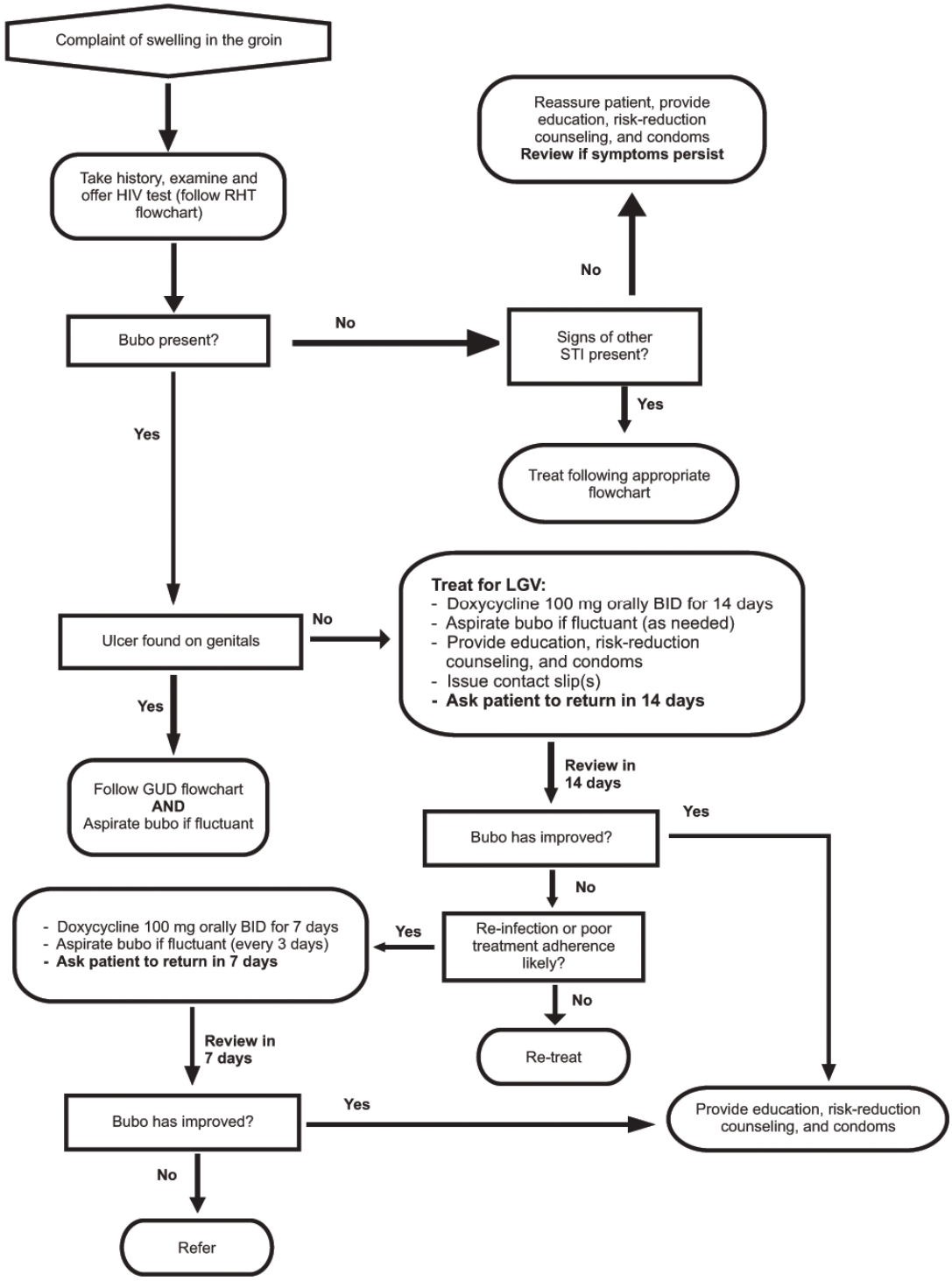
STI Treatment Algorithms:Urethral Discharge Flowchart



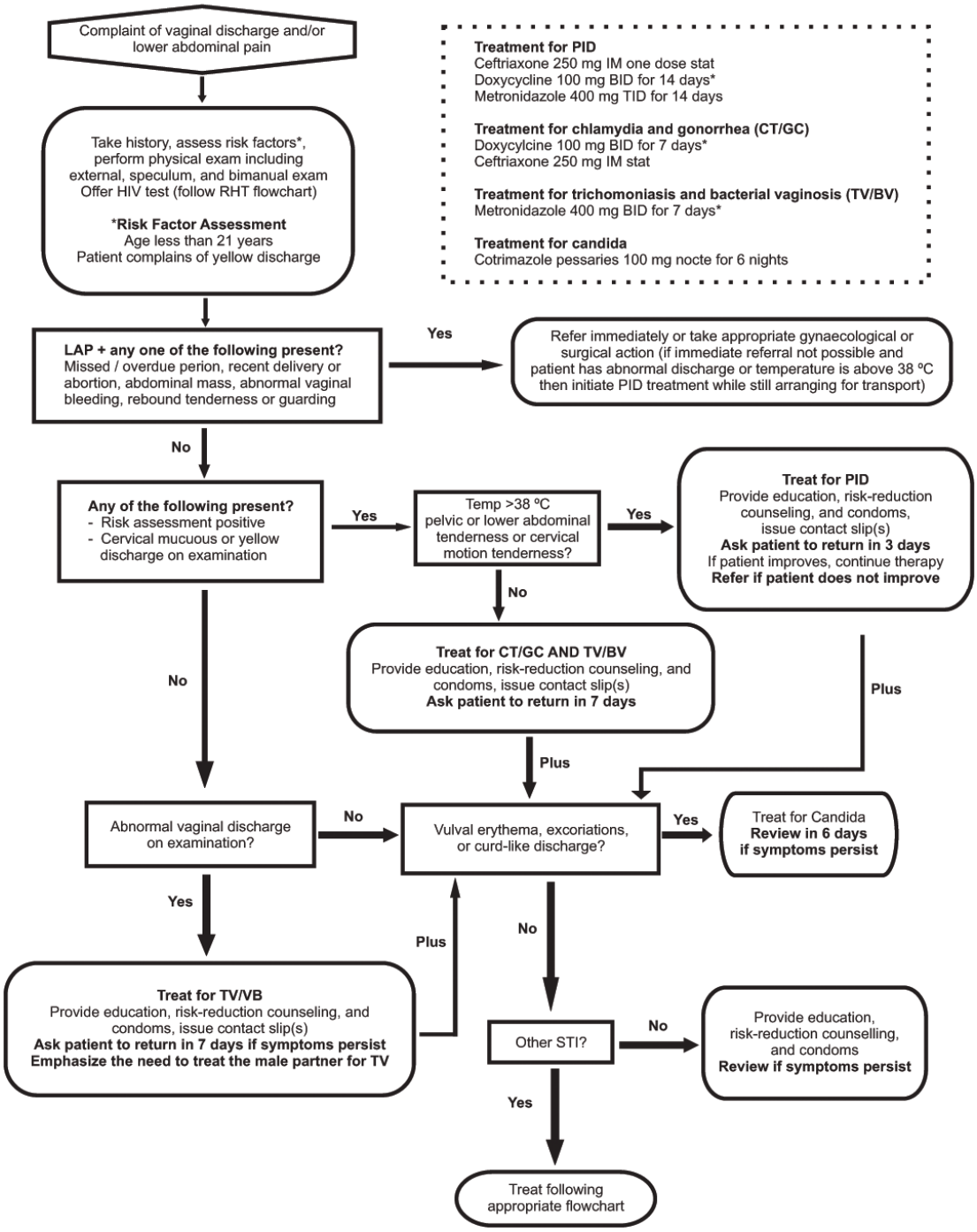
STI Treatment Algorithms:Genital Ulcer Disease Flowchart



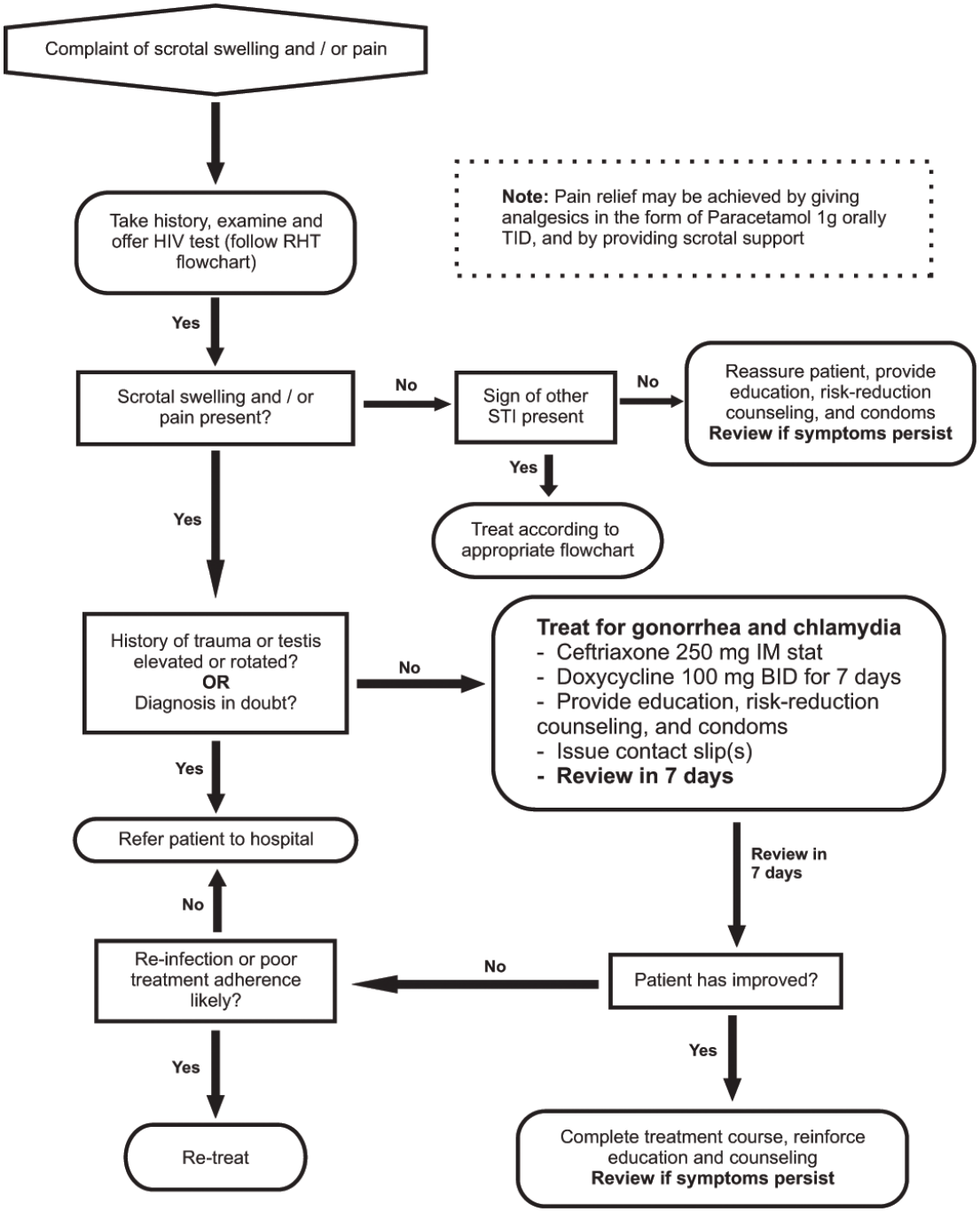
STI Treatment Algorithms:Inguinal Bubo Flowchart



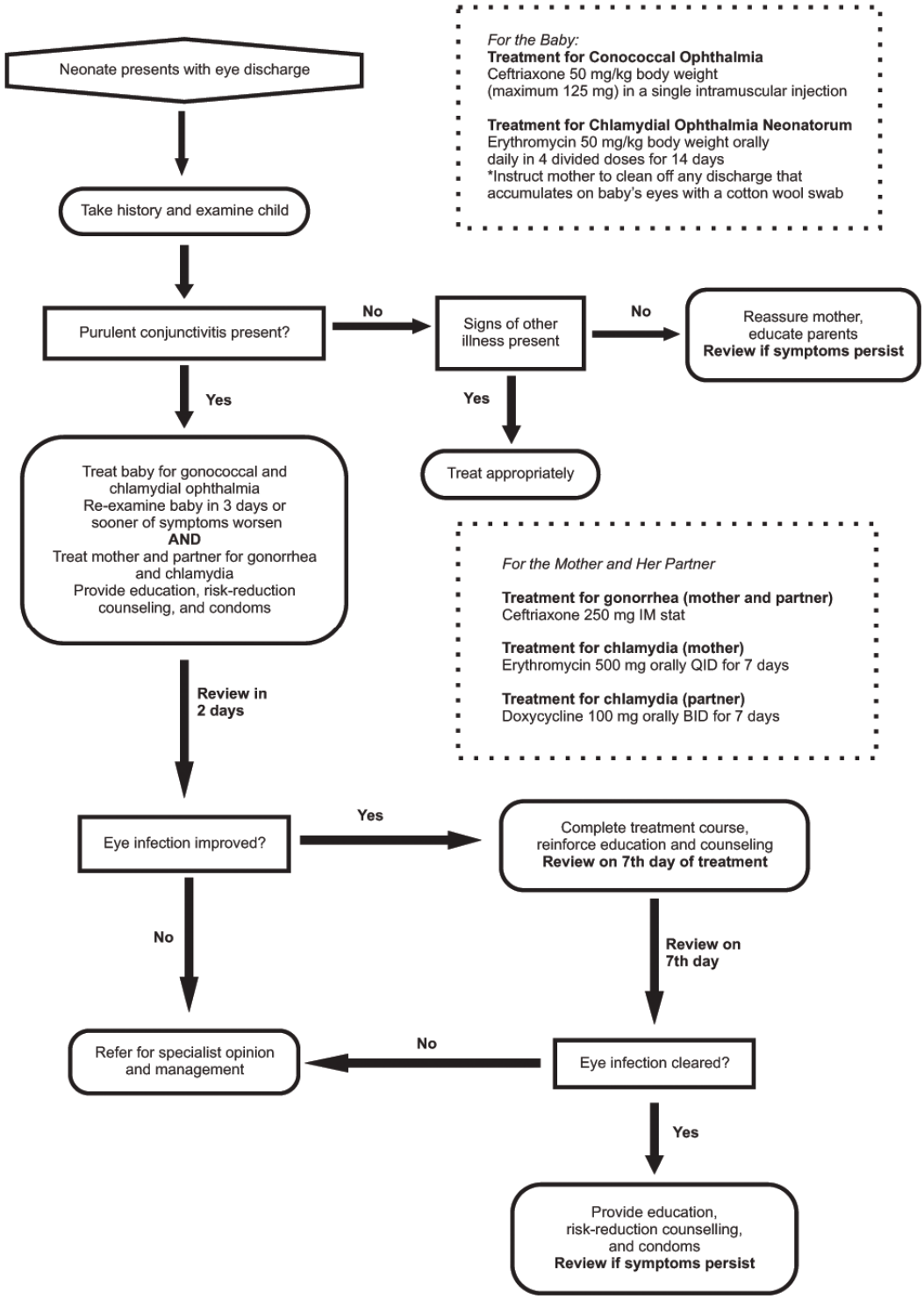
Vaginal Discharge and Lower Abdominal Pain - Cervical or Vaginal Infection



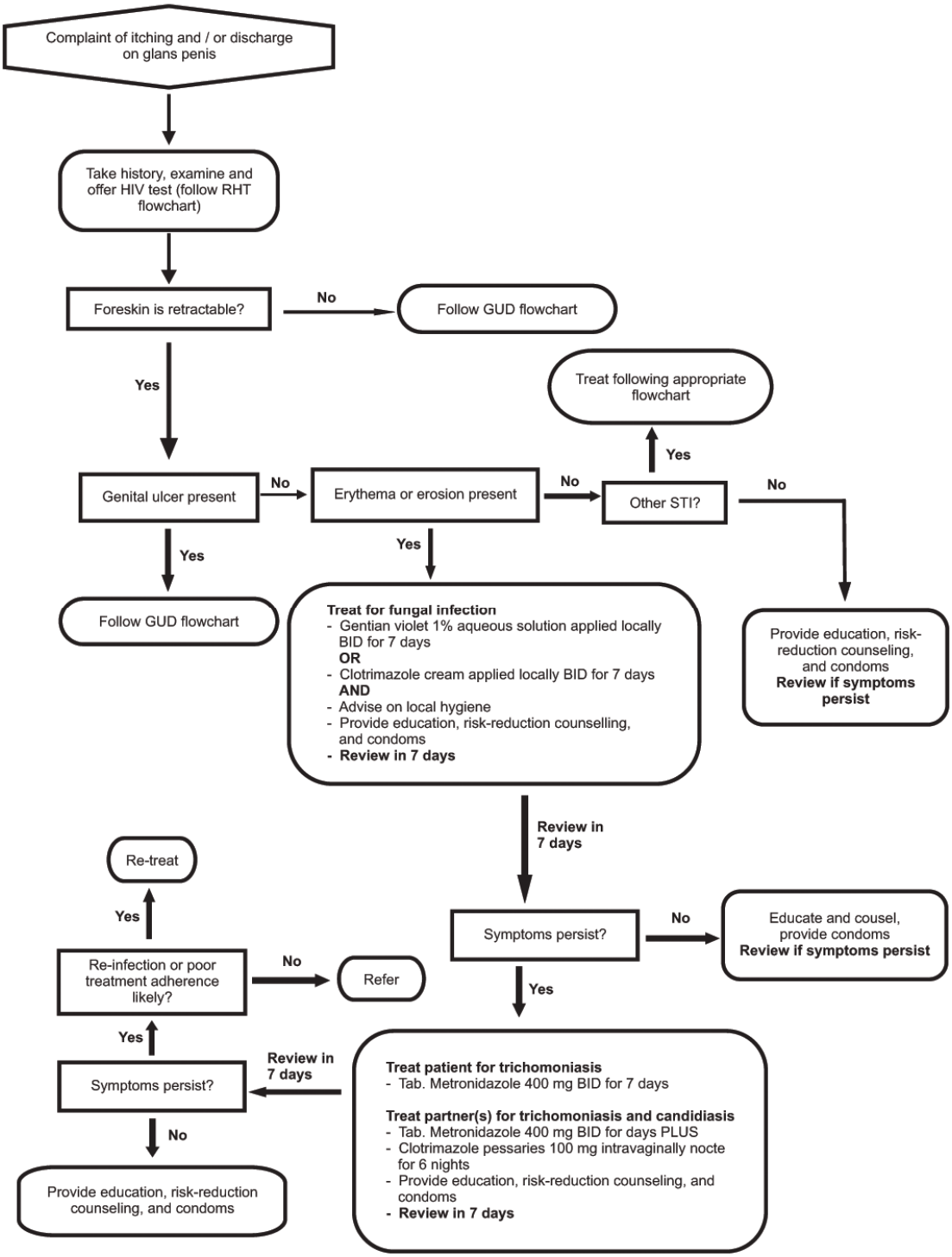
STI Treatment Algorithms:Acute Scrotal Swelling Flowchart



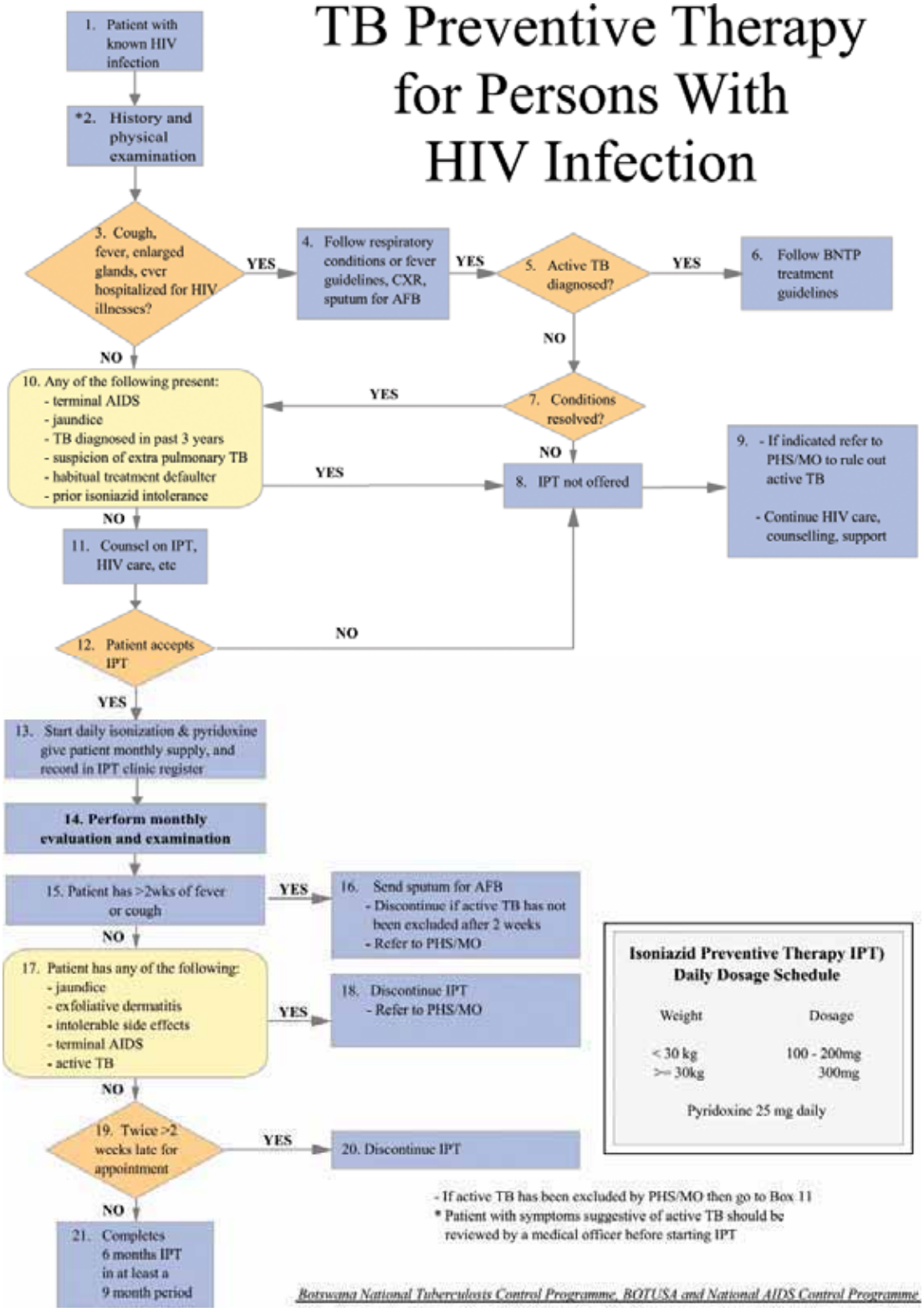
STI Treatment Algorithms:Ophthalmia Neonatorum Flowchart



STI Treatment Algorithms:Balanitis Flowchart



TB Preventive Therapy for Persons With HIV Infection



- WHO PEDIATRIC ARV DOSING GUIDES

The principles that were followed in developing the WHO simplified tables include the following:

- It is preferable to use one formulation or fixed combination of any given drug(s).
- Oral syringes or other standardized devices of various sizes should be made available to support accurate dosing of liquid formulations.
- Large volumes of liquid or syrup formulations should be avoided where possible
- In general, children should be switched to available solid formulations as soon as possible or as soon as they are tolerated.
- If liquid or syrup formulations are difficult to use for reasons of storage, volumes required, palatability or excipient nature solid dosage formulations are preferable
- If solid formulations of first-line and second-line drugs developed for children are not available, acceptable or suitable, solid formulations currently used for adults can be used.
- Many tablets, but not all, may be divided in half but generally not further for drug safety reasons. Scored tablets are more easily split. Some tablets cannot be split and WHO recommends that where possible tablet splitting is conducted in the dispensing pharmacy using appropriate tablet cutters.
- Some adult FDCs may result in underdosing of individual components in children, Underdosing of FDCs should be avoided, particularly with drugs where there are concerns about rapid emergence of resistance (e.g. NNRTI drugs). In order to deliver induction dosing of nevirapine (NVP) during the first two weeks of therapy, triple drug fixed-dose combinations should not be used but rather the individual components of the regimen should be prescribed
- Different dosing between a.m. and p.m. should be avoided where possible. However, in order to keep all regimens to no more than twice daily, there are instances where different quantities of solid dosage forms can be administered a.m. as opposed to p.m.
- The doses in the tables are presented in weight bands, accepting that some deviation from target dosing will occur.
- Children have to be weighed at each clinic visit, and dose changes are required as children grow and/or gain weight.
- When capsules are opened or tablets dissolved or crushed and added to food or liquid, it is important that the entire volume/amount of vehicle be taken to ensure administration of the full dose.

Weight-based doses were determined by using body surface area values calculated from median heights-for-weight from international growth charts using the formula:

BSA = square root[[weight (kg) X height (cm)] /3600]

From this work it is clear that formulations, particularly fixed dose combination formulations in solid forms for treating smaller children (under 10 – 14 kg) are urgently needed to allow scale up of treatment for younger infants and children. WHO will make available additional guidance on required formulations, dosing information, and required pharmacovigilance activities.

- DRUG FORMULATIONS AND DOSAGES

1. NRTIs

Lamivudine (3TC)	
Formulations	
Oral Solution:	10 mg/ml
Tablet:	150 mg
Age (weight), dose and dose frequency	
Target dose:	4 mg/kg/dose twice daily to a maximum of 150 mg 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 twice daily
Note: Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are now available (175)	
Other comments	
General: • Well tolerated • No food restrictions • Also active against hepatitis B Oral Solution: • Store solution at room temperature (i.e. 25 ºC; use within one month of opening) Tablets: • Store at 25 ºC (permitted range: 15 ºC to 30 ºC) • Can be crushed and contents mixed with a small amount of water or food and immediately taken. Pharmacokinetic data: Available for all ages	

Lamivudine: Recommended dosing based on weight bands				
Weight range (kg)		**Formulation**	**Dose (ml, tablets)**	
Bottom	**Top**	**Target dose** 4 mg/kg/dose twice a day to a maximum 150 mg/dose twice daily	**a.m.**	**p.m.**
5	5.9	10 mg/ml solution	3 ml	3 ml
6	6.9	10 mg/ml solution	3 ml	3 ml
7	7.9	10 mg/ml solution	4 ml	4 ml
8	8.9	10 mg/ml solution	4 ml	4 ml
9	9.9	10 mg/ml solution	4 ml	4 ml
10	10.9	10 mg/ml solution	5 ml	5 ml
11	11.9	10 mg/ml solution	5 ml	5 ml
12	13.9	10 mg/ml solution	6 ml	6 ml
		or 150 mg tablets	0.5	0.5
14	16.9	150 mg tablets	0.5	0.5
17	19.9	150 mg tablets	0.5	0.5
20	24.9	150 mg tablets	1	0.5
25	29.9	150 mg tablets	1	1
30	34.9	150 mg tablets	1	1

Stavudine (d4T)

Formulations

Oral Solution:	1 mg/ml
Tablet:	15 mg, 20 mg, 30 mg, 40 mg

Age (weight), dose and dose frequency

Target dose:	1 mg/kg/dose
Dose at <30 kg:	1 mg/kg/dose twice daily
Dose at >30 kg:	30 mg/dose twice daily
Dose at >60 kg:	currently 40 mg twice daily recommended; (using 30 mg dosing leads to delay or reduction of toxicity, although limited data on efficacy are available).

Other comments

General:

- Well tolerated
- **Do not use stavudine with zidovudine (AZT) due to an 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 ºC (permitted range: 15 ºC to 30 ºC)
- After constitution, needs refrigeration and storage in original container; discard any unused portion after 30 days
- Must be well shaken prior to each use

Capsules:

- Can be opened and mixed with small amount of food or water (stable in solution for 24 hours if kept refrigerated)

Pharmacokinetic data:

- Available for all ages

Stavudine: Recommended dosing based on weight bands					
Weight range (kg)		**Formulation**		**Dose (ml, tablets)**	
Bottom	**Top**	**Target dose** 1 mg/kg/dose twice daily up to 30 mg/dose twice daily		**a.m.**	**p.m.**
5	5.9	1 mg/ml syrup		6 ml	6 ml
6	6.9	or	20 mg capsules	0.5	0.5
			1 mg/ml syrup	7 ml	7 ml
7	7.9	or	20 mg capsules	0.5	0.5
			1 mg/ml syrup	8 ml	8 ml
8	8.9	or	20 mg capsules	0.5	0.5
			1 mg/ml syrup	9 ml	9 ml
9	9.9	or	20 mg capsules	0.5	0.5
			1 mg/ml syrup	10 ml	10 ml
10	10.9	15 mg capsules		1	1
11	11.9	15 mg capsules		1	1
12	13.9	15 mg capsules		1	1
14	16.9	20 mg capsules		1	1
17	19.9	20 mg capsules		1	1
20	24.9	20 mg capsules		1	1
25	29.9	30 mg capsules		1	1
30	34.9	30 mg capsules		1	1

Zidovudine (AZT [or ZDV])

Formulations

Syrup:	10 mg/ml
Capsules:	100 mg and 250 mg
Tablet:	300 mg

Age (weight), dose and dose frequency

Target dose for infants >6 weeks old:

Oral 180 – 240 mg/m^2 per dose given twice daily (total daily dose of 360 – 480 mg/m^2)

Maximum dose 300 mg/dose given twice daily

Adult dose 250 – 300 mg/dose given twice daily

MTCT Prevention Dose:

Target dose in infants:	*Oral:* 4 mg/kg every 12 hours starting within 12 hours after birth and continuing up to 1 – 6 weeks of age, depending on national recommendations
	Intravenous: 1.5 mg/kg infused over 30 minutes, every 6 hours until oral dosing is possible

Notes:
- For children with suspected nervous system involvement dose of 240 mg/m^2 per dose given twice daily may be more beneficial

Other comments

General:
- **Do not use stavudine with zidovudine (AZT) due to an antagonistic effect**
- No food restrictions
- Use with caution in children with anemia due to potential for bone marrow suppression

Syrup (oral solution):
- Preferred in children <8 kg since accurate dosing with capsules is not practical in smaller children
- Is stable at room temperature but needs storage in glass jars and is light-sensitive

Capsules
- May be opened and dispersed in water or on to a small amount of food and immediately ingested.
- Storage at 15 ºC to 25 ºC

Tablets
- Storage at 15 ºC to 25 ºC
- 300 mg 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 and immediately ingested

Pharmacokinetic data:
- Available for all ages

Zidovudine: Recommended dosing based on weight bands; Range of tablets, capsules and syrup available					
Weight range (kg)		**Target dose** 180 – 240 mg/m^2/dose twice daily		**Dose (ml or capsules or tablets)**	
Bottom	**Top**	**Formulation**		**a.m.**	**p.m.**
5	5.9	10 mg/ml syrup		6 ml	6 ml
6	6.9	10 mg/ml syrup		7 ml	7 ml
7	7.9	10 mg/ml syrup		8 ml	8 ml
8	8.9	10 mg/ml syrup		9 ml	9 ml
		or	100 mg capsules	1	1
9	9.9	10 mg/ml syrup		10 ml	10 ml
		or	100 mg capsules	1	1
10	10.9	10 mg/ml syrup		10 ml	10 ml
		or	100 mg capsules	1	1
11	11.9	10 mg/ml syrup		10 ml	10 ml
		or	100 mg capsules	1	1
12	13.9	10 mg/ml syrup		11 ml	11 ml
		or	100 mg capsules	1	1
14	16.9	100 mg capsules		2	1
		or	300 mg tablets	0.5	0.5
17	19.9	100 mg capsules		2	1
		or	300 mg tablets	0.5	0.5
20	24.9	100 mg capsules		2	2
		or	300 mg tablets	0.5	0.5
25	29.9	100 mg capsules		2	2
		or	300 mg tablets	1	0.5
30	34.9	100 mg capsules		3	3
		or	300 mg tablets	1	1

Zidovudine: Recommended dosing based on weight bands; 100mg capsules and syrup available

Weight range (kg)		Target dose 180 – 240 mg/m^2/dose twice daily		Dose (ml or capsules)	
Bottom	**Top**	**Formulation**		**a.m.**	**p.m.**
5	5.9	10 mg/ml syrup		6 ml	6 ml
6	6.9	10 mg/ml syrup		7 ml	7 ml
7	7.9	10 mg/ml syrup		8 ml	8 ml
8	8.9	10 mg/ml syrup		9 ml	9 ml
		or			
		100 mg capsules		1	1
9	9.9	10 mg/ml syrup		10 ml	10 ml
		or			
		100 mg capsules		1	1
10	10.9	10 mg/ml syrup		10 ml	10 ml
		or			
		100 mg capsules		1	1
11	11.9	10 mg/ml syrup		10 ml	10 ml
		or			
		100 mg capsules		1	1
12	13.9	100 mg capsules		1	1
14	16.9	100 mg capsules		2	1
17	19.9	100 mg capsules		2	1
20	24.9	100 mg capsules		2	2
25	29.9	100 mg capsules		2	2
30	34.9	100 mg capsules		3	3

Zidovudine: Recommended dosing based on weight bands; 300mg tablets and syrup available				
Weight range (kg)		**Target dose** 180 – 240 mg/m^2/dose twice daily	**Dose (ml or tablets)**	
Bottom	**Top**	**Formulation**	**a.m.**	**p.m.**
5	5.9	10 mg/ml syrup	6 ml	6 ml
6	6.9	10 mg/ml syrup	7 ml	7 ml
7	7.9	10 mg/ml syrup	8 ml	8 ml
8	8.9	10 mg/ml syrup	9 ml	9 ml
9	9.9	10 mg/ml syrup	10 ml	10 ml
10	10.9	10 mg/ml syrup	10 ml	10 ml
11	11.9	10 mg/ml syrup	10 ml	10 ml
12	13.9	10 mg/ml syrup	11 ml	11 ml
14	16.9	300 mg tablets	0.5	0.5
17	19.9	300 mg tablets	0.5	0.5
20	24.9	300 mg tablets	0.5	0.5
25	29.9	300 mg tablets	1	0.5
30	34.9	300 mg tablets	1	1

WHO encourages the use of fixed-dose combinations when formulations of assured quality and proven bioequivalence are available and offer operational advantages. Not all the FDCs in this table have been evaluated for prequalification by WHO.

AZT + 3TC: Recommended dosing based on weight bands					
Weight range (kg)		**Target dosing as for individual components**		**Dose**	
Bottom	**Top**	**Formulation**		**a.m.**	**p.m.**
14	16.9	300 / 150	tablet	0.5	0.5
17	19.9	300 / 150	tablet	0.5	0.5
20	24.9	300 / 150	tablet	1	0.5
25	29.9	300 / 150	tablet	1	0.5
30	34.9	300 / 150	tablet	1	1

Abacavir (ABC)

Formulations

Oral Solution: 20 mg/ml

Tablet: 300 mg

Age (weight), dose and dose frequency

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

Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are now available.

Other comments

General:

- **Parents must be well 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 a small amount of water or food and immediately ingested
- Storage at room temperature of 20 ºC to 25 ºC

Oral Solution:

- Storage at room temperature of 20 ºC to 25 ºC ; may be refrigerated

Pharmacokinetic data:

- Available for children over the age of 3 months (see comment above)

Abacavir: Recommended dosing based on weight bands				
Weight range (kg)		**Target dosing** <16 years or <37.5 kg 8 mg/kg/dose given twice daily Maximum dose >16 years or ≥37.5 kg 300 mg/dose given twice daily	**Dose (ml or tablets)**	
Bottom	**Top**	**Formulation**	**a.m.**	**p.m.**
5	5.9	20 mg/ml syrup	2 ml	2 ml
6	6.9	20 mg/ml syrup	3 ml	3 ml
7	7.9	20 mg/ml syrup	4 ml	4 ml
8	8.9	20 mg/ml syrup	4 ml	4 ml
9	9.9	20 mg/ml syrup	4 ml	4 ml
10	10.9	20 mg/ml syrup	5 ml	5 ml
11	11.9	20 mg/ml syrup	5 ml	5 ml
		or		
		300 mg tablet	0.5	0.5
12	13.9	20 mg/ml syrup	6 ml	6 ml
		or		
		300 mg tablet	0.5	0.5
14	16.9	300 mg tablet	0.5	0.5
17	19.9	300 mg tablet	0.5	0.5
20	24.9	300 mg tablet	1	0.5
25	29.9	300 mg tablet	1	1
30	34.9	300 mg tablet	1	1

Didanosine (ddI [dideoxyinosine])

Formulations

Oral Solution from pediatric powder/water:	10 mg/ml (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	125 mg, 200 mg, 250 mg, 400 mg (designed for once daily dosing preferred but still not widely available)

Age (weight), dose and dose frequency

Dose <3 months:	50 mg/m^2/dose twice daily
Dose at 3 months to <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/dose once daily

Once-daily dosing for chewable tablets is authorized in the United Kingdom for children over the age of 6 years.

Other comments

General:

- ddI is degraded rapidly unless given as an enteric formulation or combined with buffering agents or antacids
- In children this effect may be less marked and ddI may not have to be administered on an empty stomach

Oral Suspension:

- Is not easy to use and should be avoided if possible
- Should 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)
- ddI tablets should be chewed, crushed or dispersed in water or clear juice before they are taken
- They should not be swallowed whole

Enteric-coated beadlets in capsules:

- Can be opened and sprinkled on a small amount of food

Pharmacokinetic data:

- Available for all ages

Didanosine: Recommended dosing based on weight bands Once daily EC capsules			
Weight range (kg)		**Target dosing** Maximum dose >13 years or ≥60 kg 400 mg once daily	**Dose (capsules)**
Bottom	**Top**	**Formulation**	**a.m. or p.m.**
10	10.9	125 mg EC capsule	1
11	11.9	125 mg EC capsule	1
12	13.9	125 mg EC capsule	1
14	16.9	200 mg EC capsule	1
17	19.9	200 mg EC capsule	1
20	24.9	250 mg EC capsule	1
25	29.9	250 mg EC capsule	1
30	34.9	250 mg EC capsule	1

Didanosine: Recommended twice-daily dosing based on weight bands					
Weight range (kg)		**Target dosing** <3 months: 50 mg/m^2/dose twice daily 3 months to <13 years: 90 – 120 mg/m^2/dose twice daily ≥13 years or >60 kg 200 mg/dose twice daily or 400 mg once daily		**Dose (ml or tablets)**	
Bottom	**Top**	**Formulation**		**a.m.**	**p.m.**
5	5.9		10 mg/ml suspension	4 ml	4 ml
		or	25 mg chew tablet	2	2
6	6.9		10 mg/ml suspension	5 ml	5 ml
		or	25 mg chew tablet	2	2
7	7.9		10 mg/ml suspension	6 ml	6 ml
		or	25 mg chew tablet	2	2
8	8.9		10 mg/ml suspension	6 ml	6 ml
		or	25 mg chew tablet	2	2
9	9.9		10 mg/ml suspension	6 ml	6 ml
		or	25 mg chew tablet	2	2
10	10.9		10 mg/ml suspension	6 ml	6 ml
		or	25 mg chew tablet	3	2
11	11.9		10 mg/ml suspension	7 ml	7 ml
		or	25 mg chew tablet	3	3
12	13.9		10 mg/ml suspension	7 ml	7 ml
		or	25 mg chew tablet	3	3
14	16.9		10 mg/ml suspension	8 ml	8 ml
		or	25 mg chew tablet	4	3
17	19.9		10 mg/ml suspension	9 ml	9 ml
		or	25 mg chew tablet	4	4
20	24.9	or	25 mg chew tablet	5	5
25	29.9	or	25 mg chew tablet	5	5
30	34.9	or	25 mg chew tablet	5	5

Note: 25 mg chew tablets can be substituted with other strengths to the same mg amount but each a.m. and p.m. dose must always be made up of at least **two** tablets

2. NNRTIs

Efavirenz (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

Age (weight), dose and dose frequency

Target dosing: 19.5 mg/kg/day (syrup) or 15 mg/kg/day (capsule or tablet)
Weight greater than 40 kg, 600 mg once daily

Other comments

General:

- Storage at 25 ºC (permitted range: 15 ºC to 30 ºC)
- Insufficient data on dosing for children <3 years old
- EFV can be given with food but if taken with food, especially high fat meals, absorption can be increased by an average of 50%
- EFV is best given at bedtime in order to reduce CNS side-effects, especially during first two weeks

Capsules:

- May be opened and added to a small amount of food or liquid; they have a very peppery taste but can be mixed with sweet foods to disguise the taste

Pharmacokinetic data:

- Available for children over 3 years of age
- Insufficient data on dosing for children <3 years old

Efavirenz: Recommended once-daily dosing based on weight bands			
Weight range (kg)		**Target dosing** 15 mg/kg/day(capsule/tablet) Weight >40 kg: 600 mg once daily	**Dose (capsules, tablets) Once daily, 3 years and above**
Bottom	**Top**	**Formulation**	
10	10.9	200 mg capsule	1
11	11.9	200 mg capsule	1
12	13.9	200 mg capsule	1
14	16.9	mg capsule	200 mg + 50 mg
17	19.9	mg capsule	200 mg + 50 mg
20	24.9	mg capsule	200 mg + 100 mg
25	29.9	mg capsule	200 mg + 100 mg + 50 mg
30	34.9	200 mg capsule	2
35	39.9	200 mg capsule	2
>40		600 mg tablet	1

Nevirapine (NVP)

Formulations

Oral suspension: 10 mg/ml

Tablet: 200 mg

Age (weight), dose and dose frequency

Target dose for maintenance: 160 – 200 mg/m^2 to maximum dose of 200 mg taken twice daily.

Special considerations on dosing:

a) Induction dose: once daily for first 14 days; it is generally ½ the daily maintenance dose given once daily except where the maintenance dose is divided unequally between a.m. and p.m.

b) Maintenance dose: target is 160 – 200 mg/ m^2/dose 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 ½ tablet p.m. Due to the prolonged half-life of nevirapine the fluctuation in drug exposure associated with this dosing schedule is acceptable.

d) 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.

Dosing for MTCT prevention: 2 mg/kg/dose within 72 hours of birth once only

If the maternal dose of nevirapine was given less than 2 hours before delivery, then administer 2 mg/kg/dose to the infant immediately after birth and repeat within 24 – 72 hours of first dose

If the infant weight is not available, administer the 0.6 ml oral suspension

Other comments

General:

- 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
- Storage at 25 ºC (permitted range: 15 ºC to 30 ºC)

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.

Pharmacokinetic data:
- Available for all ages

Nevirapine: Recommended induction dosing based on weight bands				
Weight range (kg)		**Target dosing** Half of daily maintenance dosing (160 – 200 mg/m^2/dose to max 200 mg)		**Dose (ml or tablets)**
Bottom	**Top**	**Formulation**		**Once daily**
5	5.9	10 mg/ml syrup		6 ml
6	6.9	10 mg/ml syrup		7 ml
7	7.9	10 mg/ml syrup		8 ml
8	8.9	10 mg/ml syrup		9 ml
9	9.9	10 mg/ml syrup		9 ml
		or		
		200 mg tablets		0.5
10	10.9	10 mg/ml syrup		10 ml
		or		
		200 mg tablets		0.5
11	11.9	10 mg/ml syrup		10 ml
		or		
		200 mg tablets		0.5
12	13.9	10 mg/ml syrup		11 ml
		or		
		200 mg tablets		0.5
14	16.9	200 mg tablets		0.5
17	19.9	200 mg tablets		1
20	24.9	200 mg tablets		1
25	29.9	200 mg tablets		1
30	34.9	200 mg tablets		1

Nevirapine: Recommended <u>maintenance</u> dosing based on weight bands				
Weight range (kg)		**Target dosing** Half of daily maintenance dosing (160 – 200 mg/m^2/dose to max 200 mg)	**Dose (ml or tablets)**	
Bottom	**Top**	**Formulation**	**a.m.**	**p.m.**
5	5.9	10 mg/ml syrup	6 ml	6 ml
6	6.9	10 mg/ml syrup	7 ml	7 ml
7	7.9	10 mg/ml syrup	8 ml	8 ml
8	8.9	10 mg/ml syrup	9 ml	9 ml
9	9.9	10 mg/ml syrup	9 ml	9 ml
		or		
		200 mg tablets	0.5	0.5
10	10.9	10 mg/ml syrup	10 ml	10 ml
		or		
		200 mg tablets	0.5	0.5
11	11.9	10 mg/ml syrup	10 ml	10 ml
		or		
		200 mg tablets	0.5	0.5
12	13.9	10 mg/ml syrup	11 ml	11 ml
		or		
		200 mg tablets	0.5	0.5
14	16.9	200 mg tablets	1	0.5
17	19.9	200 mg tablets	1	0.5
20	24.9	200 mg tablets	1	0.5
25	29.9	200 mg tablets	1	1
30	34.9	200 mg tablets	1	1

Lopinavir/ritonavir (LPV/r) [coformulation]

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

Age (weight), dose and dose frequency

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 + 100 mg ritonavir taken twice daily

Other comments

General:

- Should be taken with food
- Preferably, oral solution and capsules should be refrigerated; however, can be stored at room temperature up to 25 ºC for two months; at >25 ºC drug degrades more rapidly
- There are many drug-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:

- Do not have food restrictions although bioavailability is increased when administered with food
- Cannot be split

Pharmacokinetic data:

- Available for 6 months of age or older

Lopinavir/ritonavir: Recommended dosing based on weight bands						
Weight range (kg)		**Target dosing** See table over for lopinavir and ritonavir target doses			**Dose (ml or tablets)**	
Bottom	**Top**	**Formulation**			**a.m.**	**p.m.**
5	5.9	80 mg lopinavir/20 mg ritonavir per		ml solution	1 ml	1 ml
6	6.9	80 mg lopinavir/20 mg ritonavir per		ml solution	1.5 ml	1.5 ml
7	7.9	or	80 mg lopinavir/20 mg ritonavir per	ml solution	1.5 ml	1.5 ml
			133 mg lopinavir/33mg ritonavir per	capsule	1	1
8	8.9	or	80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
			133 mg lopinavir/33mg ritonavir per	capsule	1	1
9	9.9	or	80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
			133 mg lopinavir/33mg ritonavir per	capsule	1	1
10	10.9	or	80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
			133 mg lopinavir/33mg ritonavir per	capsule	1	1
11	11.9	or	80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
			133 mg lopinavir/33mg ritonavir per	capsule	1	1
12	13.9	or	80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
		or	133 mg lopinavir/33mg ritonavir per	capsule	2	1
			200 mg lopinavir/50 mg ritonavir per	tablet	1	1
14	16.9	or	80 mg lopinavir/20 mg ritonavir per	ml solution	2 ml	2 ml
			133 mg lopinavir/33mg ritonavir per	capsule	2	1
		or	200 mg lopinavir/50 mg ritonavir per	tablet	1	1
17	19.9	or	80 mg lopinavir/20 mg ritonavir per	ml solution	2.5 ml	2.5 ml
			133 mg lopinavir/33mg ritonavir per	capsule	2	1
		or	200 mg lopinavir/50 mg ritonavir per	tablet	1	1
20	24.9	or	80 mg lopinavir/20 mg ritonavir per	ml solution	3 ml	3 ml
			133 mg lopinavir/33mg ritonavir per	capsule	2	2
		or	200 mg lopinavir/50 mg ritonavir per	tablet	1	1
25	29.9	or	80 mg lopinavir/20 mg ritonavir per	ml solution	3.5 ml	3.5 ml
			133 mg lopinavir/33mg ritonavir per	capsule	2	2
		or	200 mg lopinavir/50 mg ritonavir per	tablet	2	1

Weight Range (kg)		Target Dosing See table over for lopinavir and ritonavir target doses			Dose (ml or tablets)	
Bottom	**Top**	**Formulation**			**a.m.**	**p.m.**
30	34.9	or or	80 mg lopinavir/20 mg ritonavir per	ml solution	4 ml	4 ml
			133 mg lopinavir/33mg ritonavir per	capsule	3	3
			200 mg lopinavir/50 mg ritonavir per	tablet	2	2
35	39.9	or or	80 mg lopinavir/20 mg ritonavir per	ml solution	5 ml	5 ml
			133 mg lopinavir/33mg ritonavir per	capsule	3	3
			200 mg lopinavir/50 mg ritonavir per	tablet	2	2

- ADULT ARV DOSING GUIDES

From the United States DHHS January, 2008
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 Bio-availability	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 Bio-availability	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 Bio-availability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Emtricitabine (FTC) **EMTRIVA** Also available as : **ATRIPLA -** w/ EFV & TDF **TRUVADA** - w/ TDF	EMTRIVA- 200mg 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 **TRIZIVIR-** w/ 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 Bio-availability	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/high-caloric 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^3. 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 Bio-availability	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 ↑ 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

Sexual Maturity Rating (Tanner Staging) in Adolescents

Stage	Female				Male				
	Age Range (Years)	**Breast Growth**	**Pubic Hair Growth**	**Other Changes**	**Age Range (Years)**	**Testes Growth**	**Penis Growth**	**Pubic Hair Growth**	**Other Changes**
I	0 – 15	Pre-adolescent	None	Pre-adolescent	0 – 15	Pre-adolescent testes (≤2.5 cm)	Pre-adolescent	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 and 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 and 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

Failure Management Registry Form

NAME:					**DOB:** **M / F**
MASA#		**CM#**	**OMANG#**		Naïve at 1st Visit to IDCC? Yes / No **Received PMTCT Yes./No** **Date:**
Baseline CD4 **Date:**			**Initiation Regimen (1st line)**	date:	Side effects/Toxicities/Reason for switch
Baseline Viral Load **Date:**					
History	**Viral Load**	**CD4**	**2nd line Regimen**	date:	Side effects/Toxicities/Reason for switch
date:					
date:					
date:					
date:			**3rd line Regimen**	date:	Side effects/Toxicities/Reason for switch
date:					
date:					
date:					
date:			**4th line Regimen**	date:	Side effects/Toxicities/Reason for switch
date:					
date:					
date:					
RESISTANCE TESTING			**5th line Regimen**	Date:	Side effects/Toxicities/Reason for switch
Date:					
Reviewed by:					
Date:					
Reviewed by:					
Date:					
Reviewed by:					
Date:					
Reviewed by:					

ADHERENCE REVIEW

Adherence Partner identified: Yes / No	Dementia: Yes / No
Substance Abuse: Yes / No	Too ill: Yes / No
Drug/Drug Interactions: Yes / No	Concurrent Tb medications? Yes /No
Date of specialized education/counseling intervention:	
OTHER NOTES:	

Masa

Antiretroviral Therapy

Lenaneo la Melemo ya go Ritibatsa Mogare wa HIV/AIDS

BOTSWANA HARVARD AIDS INSTITUTE PARTNERSHIP FOR HIV RESEARCH AND EDUCATION

BIPAI Baylor International Pediatric AIDS Initiative

UNAIDS JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS

UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

World Health Organization

ACHAP

UNIVERSITY OF PENNSYLVANIA