health

Department:
Health
REPUBLIC OF SOUTH AFRICA

THE SOUTH AFRICAN ANTIRETROVIRAL TREATMENT GUIDELINES

2013

Date of Implementation 1 April 2013

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Acronym glossary

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Treatment
ARV	Antiretroviral
AZT	Zidovudine
CD4	Cluster of Differentiation 4
d4T	Stavudine
DNA PCR	DNA Polymerase Chain Reaction
EFV	Efavirenz
FBC	Full Blood Count
FTC	Emtricitabine
Hb	Haemoglobin
HepBSAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
IPT	Isoniazid Preventive Therapy
LPV/r	Lopinavir/ritonavir
MCH	Maternal and Child Health
MDR/XDR-TB	Multi-Drug Resistant / Extensively Drug Resistant Tuberculosis
NVP	Nevirapine
PHC	Primary Health Care
SRH	Sexual and Reproductive Health
TB	Tuberculosis
TDF	Tenofovir
WHO	World Health Organization

The South African Antiretroviral Treatment Guidelines 2013

1. Goals of the programme

a. Save lives and improve the quality of life of people living with HIV
b. Achieve best health outcomes in the most cost-efficient manner
c. Implement nurse-initiated treatment
d. Decentralise service delivery to PHC facilities
e. Integrate services for HIV, TB, MCH, SRH and wellness
f. Diagnose HIV earlier
g. Prevent HIV disease progression
h. Avert AIDS-related deaths
i. Retain patients on lifelong therapy
j. Prevent new infections among children, adolescents, and adults
k. Mitigate the impact of HIV and AIDS

2. Objectives

a. Ensure timely initiation of ARVs for treatment and prevention according to the Presidential mandates
b. Contribute to strengthening of the public and private health sectors' capacity to deliver high quality integrated health and wellness services
c. Implement cascade management and continuum of care
d. Minimize unnecessary drug toxicities
e. Improve clinical outcomes, promote adherence and improved retention of patients in care
f. Optimize the benefits of treatment as prevention by increasing coverage and annual HCT
g. Introduce fixed dose combination of highly effective ARV and improve adherence to treatment, care and support

3. Specific Objectives

1 To prioritise initiation of combination antiretroviral treatment for:
  1.1 Patients with CD4 counts <350 cells/mm^3 or with severe HIV disease (WHO 3 or 4) irrespective of CD4
  1.2 Patients co-infected with drug sensitive or resistant TB who should be initiated with ART irrespective of CD4 count
  1.3 Pregnant women with CD4 $\leq$ 350cells/mm^3 for lifelong ART and CD4 >350cells/mm^3 for prophylaxis
  1.4 Introduce fixed dose combination (FDC) ART for patients initiated with ART for the first time
  1.5 Introduce FDC ART for HIV positive pregnant women irrespective of CD4 count during pregnancy and during the breastfeeding period
  1.6 Phased introduction of FDC to patients with other co-morbidities (diabetes, hypertension and respiratory diseases, including TB)
  1.7 Phased introduction of FDC to patients who require switching due to drugs toxicity or switching from Stavudine (d4T) based regime
  1.8 Phased introduction of FDC to patients who are stable of ART and VL suppressed
2 To test all HIV exposed children under-five years and treat all those found to be infected with HIV.
3 To standardise first and second line therapy for children, adolescents, and adults in the public and private sector.

4 To move patients currently on Stavudine-containing regimens to Tenofovir-based FDCs, once creatinine clearance has been checked. Stavudine (d4T) to be used only under specific circumstances.
5 To strengthen capacity of nurses to initiate ARVs for treatment of pregnant women who are HIV positive for their own health and to prevent mother to child transmission.
6 To strengthen PHC facilities to initiate, manage, monitor and refer patients.

4. Adults and Adolescents

4.1 Standardised national eligibility criteria for starting ART regimens for adults and adolescents

Eligible to start Lifelong ART
▪ CD4 count ≤350 cells/mm3 irrespective of WHO clinical stage **OR** ▪ Irrespective of CD4 count ○ All types of TB (In patients with TB drug resistant or sensitive, including extra pulmonary TB) ▪ WHO stage 3 or 4 irrespective of CD4 count
Require fast track (i.e. ART initiation within 7 days of being eligible)
▪ HIV positive women who are pregnant or breast feeding **OR** ▪ Patients with low CD4 <200 **OR** ▪ Patients with Stage 4, irrespective of CD4 count **OR** ▪ Patients with TB/HIV co morbidity with CD4 count < 50 **(**Patients with Cryptococcus meningitis or TB meningitis (defer ART for 4-6 weeks)
Patients with CD4 above 350, Not yet eligible for ART
▪ Transfer to a wellness programme for regular follow-up and repeat CD4 testing 6-monthly. ▪ Advise on how to avoid HIV transmission to sexual partners and children ▪ Initiate INH prophylaxis if asymptomatic for TB ▪ Provide counselling on nutrition and contraception and do annual pap smear

4.2 Standardised national ART regimens for adults and adolescents

1st Line		
All new patients needing treatment, including pregnant women	TDF + FTC (or 3TC) +EFV FDC preferred	Replace EFV with NVP in patients with significant psychiatric co-morbidity or intolerance to EFV and where the neuro-psychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.
Adolescents	ABC + 3TC + EFV	At age 18 years an adolescent if eligible must be switched to the FDC
Contraindications to EFV	TDF + (FTC or 3TC) + NVP	Use NVP based regimen: In patients with significant psychiatric co morbidity or intolerance to EFV and where the neuro-psychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.
Contraindication to TDF	AZT+ 3TC +EFV or (NVP)	Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides
Contraindication to TDF and AZT	d4T + 3TC+ EFV (or NVP)	Renal disease and anaemia or the use of other nephrotoxic drugs, aminoglycosides
Contraindication to TDF, AZT and d4T	ABC + 3TC + EFV (or NVP)	Renal disease, anaemia, peripheral neuropathy, the use of other nephrotoxic drugs
Currently on d4T-based regimen	TDF + FTC(or 3TC) + EFV FDC preferred	Mandatory if patients experience toxicity and patients who are at high risk of toxicity (high BMI or pregnant). Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if well tolerated.
2nd Line		
Management of virological failure		If plasma HIV RNA >1000 copies. Check for adherence, compliance, tolerability and drug- drug interaction and assess psychological issues. Repeat VL test 2 months later. If plasma VL confirmed >1000copies change regime to second line therapy
Failing on a TDF-based 1st line regimen	AZT+3TC+ LPV/r	Patients with anaemia and renal failure switch to ABC
Failing on a d4T-based 1st line regimen	TDF+3TC (or FTC) and LPV/r	
Dyslipidaemia or intractable diarrhoea associated with LPV/r	Switch LPV/r to ATV/r	
Third line		
Failing any 2nd line regimen	Specialist referral	
Should be expert and genotype resistance testing based decision and supervised care Patients failing on second line therapy will be managed by an expert panel. The drugs for third line will be managed centrally. More discussion is required to deal with the modalities	Most likely regimen would be Raltegravir/Darunavir/ /Etravirine adjusted according to genotype Interpretation. Should be by expert and take into account prior exposure and predictable mutations	

4.3 Standardized National Monitoring for Adults and Adolescents with HIV

At initial Diagnosis of HIV	Purpose
Confirm HIV result with rapid antibody test	Ensure that national testing algorithm has been followed
Do CD4 count if HIV positive and WHO clinical staging	To assess eligibility for ART To assess eligibility for fast-tracking
Screen for pregnancy or ask if planning to conceive	To identify women who need ART for life or ARV prophylaxis for PMTCT (see section 6)
Screen for TB symptoms using the WHO questionnaire	To identify TB/HIV co-infected
Do the CD4 count on the same day	To identify eligibility for ART or ARVs for prophylaxis if pregnant
Do HB or FBC if requires AZT Creatinine if requires TDF For patients initiated on Nevirapine based regime do ALT	To detect anaemia or neutropenia, To detect renal insufficiency To exclude liver disease

On ART	Purpose
CD4 at 1 year on ART	To monitor immune response to ART
VL at month 6, 1 year on ART and then every 12 months	To identify treatment failures and problems with adherence
ALT only if on NVP and develops rash or symptoms of hepatitis	To identify NVP toxicity
FBC at month 3 and 6 if on AZT	To identify AZT toxicity
Creatinine at month 3 and 6, 1 year then every 12 months if on TDF	To identify TDF toxicity
Fasting cholesterol and triglycerides at month 3 if on LPV/r	To identify LPV/r toxicity

At Routine Follow-Up Visits for those not yet eligible for ART	Purpose
Repeat CD4 count at 6 months	To see if they have become eligible for ART
WHO clinical staging at every visit	To see if they have become eligible for ART
Screen for TB symptoms to identify TB suspects Offer IPT if no TB symptoms	To identify TB/HIV co-infection To prevent TB activation
Offer prevention for HIV positives	To prevent HIV transmission and re-infection To prevent STIs

4.4 Indications for urgent up-referral prior to initiation or when on therapy

- eGFR less than 60 ml/min
- Hb less than 8 g/dl
- BMI less than 18.5 kg/m2
- In a patient with TB or other opportunistic infection , poor response to TB or OI treatment

5. Infants and Children

5.1 Standardised national eligibility criteria for starting ART regimens for Infants and Children

Eligible to Start ART
▪ All children less than 5 years of age, irrespective of CD4 • Children 5 years to 15 years with WHO clinical stage 3 or 4 or CD4 ≤350 cells/µl
Require Fast-Track (i.e. start ART within 7 days of being eligible)
▪ Children less than 1 year of age ▪ WHO clinical Stage 4 ▪ MDR or XDR-TB ▪ CD4 Count < 200 cells/µl Or < 15%

5.2 Standardised national ART regimens for Infants and Children

First Line Regimen	
All infants and children under 3 years (or < 10kg)	ABC + 3TC + LPV/r
Children ≥ 3 years (and ≥ 10kg)∞	ABC + 3TC + EFV
Currently on d4T-based regimen	Change d4T to ABC if viral load is undetectable If viral load >1000 copies/ml manage as treatment failure If viral load between 50 – 1000 copies/ml – consult with expert for advice
Second Line Regimen	
Failed first line Protease Inhibitor (PI)-based regimen	
Failed first line PI-based regimen	**Recommended second line regimen**
ABC + 3TC + LPV/r	**Consult with expert for advice***
d4T + 3TC + LPV/r	
Unboosted PI-based regimen	
Failed First line NNRTI based regimen (discuss with expert before changing)	
Failed first line NNRTI-based regimen	**Recommended second line regimen**
ABC +3TC + EFV (or NVP)	AZT + 3TC + LPV/r
d4T +3TC + EFV (or NVP)	AZT + ABC + LPV/r
Third line regimens	
Failing any 2nd line regimen	Refer for specialist opinion – Regimen based on genotype resistance testing, expert opinion and supervised care Access to third line ART will be managed centrally by the National Department of Health

∞ Children ≥ 3 years and exposed to NVP for 6 weeks or longer (PMTCT) should be initiated on ABC + 3TC + LPV/r

*Recommended Second Line regimen under expert advice NB: Some paediatric second line ART agents are not licensed by the MCC and are not available for routine use at the time of publication of this guideline	
ABC + 3TC + LPV/r	No previous daily NVP for PMTCT AZT + 3TC+ EFV* + LPV/r * Use NVP if <3 years or <10kg Previous daily NVP for PMTCT Treat with third line regimen
d4T + 3TC + LPV/r	No previous daily NVP for PMTCT AZT + ABC + EFV* + LPV/r * Use NVP if <3 years or <10kg Previous daily NVP for PMTCT Treat with third line regimen
Previously on a regimen with unboosted PI (e.g. ritonavir alone), or with rifampicin while on LPV/r	Must be managed by an expert on basis of genotype resistance testing to confirm PI susceptibility.

5.3 Standardized national monitoring for Infants and Children with HIV

At initial Diagnosis of HIV	Purpose
Verify HIV status	Ensure that national testing algorithm has been followed
Document Weight, Height, Head Circumference (<2yrs) and Development	To monitor Growth and Development + identify eligibility for ART
Screen for TB symptoms	To identify TB/HIV co-infected
WHO Clinical Staging	To determine if patient is eligible for ART
Do the CD4 count	Children < 5 years – Baseline, DO NOT wait for CD4 count to start ART
	Children ≥ 5 years – To determine eligibility for ART and start cotrimoxazole prophylaxis as per national guidelines
Hb or FBC if available	To detect anaemia or neutropenia

At Routine Follow-Up Visits (patients not yet on ART)	Purpose
Document Weight, Height, Head Circumference (<2 years) and Development	To monitor Growth and Development and to see if patient has become eligible for ART
Check that a CD4 count has been done in the last 6 months	To determine if patient has become eligible for ART
WHO Clinical Staging	To determine if patient has become eligible for ART
Screen for TB symptoms	To identify TB/HIV co-infection

At Initiation of ART (Baseline)	Purpose
Hb or FBC	If less than 8g/dl start ART and refer for specialist opinion
CD4 count (if not performed in last 6 months)	Baseline assessment
HIV Viral Load (VL)	Baseline assessment
Cholesterol + Triglyceride if on PI-based regimen	Baseline assessment
Creatinine + urine dipstix if on TDF regimen	If abnormal refer for specialist opinion
ALT (if jaundiced or on TB treatment)	To assess for liver dysfunction

On ART	Purpose
Height, Weight, Head Circumference (<2yrs) and Development	To monitor Growth and Developmental stage
Clinical assessment	To monitor response to ART and exclude adverse effects
CD4 at 12 months into ART, and then every 12 months	To monitor response to ART, stop cotrimoxazole prophylaxis as per national guidelines
VL at 6 months and 12 months into ART, THEN 6 monthly in children <5 years AND 12 monthly in children 5 - 15 years	To monitor viral suppression response to ART To identify treatment failure and to identify problems with adherence
Hb or FBC at month 1, 2, 3 into ART and then annually if on AZT	To identify AZT-related anaemia
Cholesterol + Triglyceride at 12 months into ART and then every 12 months if on PI-based regimen	To monitor for PI-related metabolic side-effects
Clinical drug-related adverse events	To identify drug-related adverse events If develops jaundice or rash on EFV or NVP do Liver function test and refer to specialist

6. HIV-positive pregnant and breastfeeding Women and HIV-exposed Infants

6.1 Standardised national ART and ARV regimens for women who are HIV positive and pregnant, breastfeeding and their HIV-exposed Infants

Maternal Regimens		
Woman	**Regimen**	**Comment**
1st antenatal visit		
All women at first antenatal visit (any gestational age)	FDC initiated immediately	If there is a contraindication to the FDC: Start AZT immediately and review within a week. (Refer to PMTCT algorithm 1)
Currently on lifelong ART	Continue the ART regimen If the woman is on a compatible regimen (EFV, 3TC, TDF) change to FDC	Check a VL when pregnancy diagnosed
2nd antenatal visit (1 week later)		
Creatinine ≤ 85µmol/l Any CD4 cell count	Continue FDC	
Creatinine > 85µmol/l **Contraindication to TDF** (renal disease) CD4 ≤350cells/mm^3	AZT + 3TC + EFV	If haemoglobin <7g/dl AZT is contraindicated. Use d4T instead of AZT. (Refer to PMTCT Algorithm 3) Refer for investigation for cause of renal disease
Creatinine > 85µmol/l **Contraindication to TDF** (renal disease) CD4 >350cells/mm^3	AZT in pregnancy sdNVP + sd TDF + FTC and AZT 3hrly in labour	(Refer to PMTCT Algorithm 3)
Contraindication to EFV (active psychiatric illness) CD4 ≤350cells/mm^3	TDF + FTC + NVP	Substitute LPV/RTV for NVP in women with CD4 counts >250cells/mm^3
Contraindication to EFV (active psychiatric illness) CD4 >350cells/mm^3	AZT in pregnancy sdNVP + sd TDF + FTC and AZT 3hrly in labour	
Labour		
Unbooked and presents in labour and tests HIV positive	sdNVP + sd TDF + FTC and AZT 3hrly in labour Start FDC after delivery if woman will breastfeed	Assess maternal ART eligibility before discharge
Post Natal		
All woman breastfeeding and diagnosed as HIV positive during pregnancy	Continue FDC	If there is a contraindication to the FDC: Start AZT immediately and review within a week.
All woman breastfeeding and diagnosed as HIV positive during breast feeding	FDC initiated immediately	If there is a contraindication to the FDC: Start AZT immediately and review within a week. (See PMTCT algorithm 4)

Infant Regimens		
Infant	**Regimen**	**Comment**
Mother on lifelong ART or antenatal prophylaxis received (including TDF + 3TC/FTC + EFV or AZT)	NVP at birth and then daily for 6 weeks	If mother is breastfeeding and not virally suppressed e.g. late booking or established poor adherence, continue NVP for infant throughout breastfeeding until one week post cessation of breastfeeding
Mother did not get any ART before or during delivery and tests HIV positive post delivery	NVP as soon as possible and daily for 6 weeks	Assess ART eligibility as soon as possible for both mother and baby (as per infant testing algorithm)
Unknown maternal status because orphaned or abandoned	Give NVP immediately* Test infant with rapid HIV test. If positive continue NVP for 6 weeks. If negative discontinue NVP	Follow up at 6 weeks with HIV PCR
Mother on AZT regimen (due to any contraindication to the FDC regimen and had a CD4 >350cells/mm^3)	NVP at birth and then daily for 6 weeks	Test infant with 6 week HIV PCR test. If negative and breastfeeding continue NVP till one week after complete cessation of breastfeeding

***** If rapid HIV test can be done within 2 hours, then wait for HIV result before commencing NVP

ARV Adult Dosing Guide		
Drug	**Dosage**	**Comments**
TDF (Tenofovir)	300mg daily	Tenofovir is contraindicated if serum creatinine>85µmol/L during pregnancy (or creatinine clearance of <50ml/min in non-pregnant adults)
d4T (Stavudine)	30mg 12hrly po	All adult patients now receive 30mg regardless of weight
3TC (Lamivudine)	300mg daily	
FTC (Emtracitabine)	200mg daily	
NVP (Nevirapine)	200mg daily po X 2 weeks then 200mg 12 hourly po For PMTCT purposes single dose (sdNVP) is used as a 200mg tablet given once	Should be used with caution with TB treatment Avoid NVP if CD4 count >250cells/mm^3
EFV (Efavirenz)	600mg nocte	Avoid if active psychiatric illness
lopinavir 200mg /ritonavir 50mg	2 tabs 12 hourly (Lop400mg/Rit100mg)	Preferably taken with food. Boosting required with TB treatment refer to TB guidelines in 7.1 of these guidelines for dose
AZT (Zidovudine)	300mg 12 hourly po	Avoid if severe anaemia (Hb<8g/dl)

NVP Infant Dosing Guide			
	Birth Weight	**Dose**	**Quantity**
NVP syrup (10mg/ml)	<2.0kg	2mg/kg (first 2 weeks) then 4mg/kg (next 4 weeks)	0.2ml/kg 0.4ml/kg
	Birth to 6 weeks 2.0-2.5kg birth weight	10mg/d	1ml
	Birth to 6 weeks ≥ 2.5kg birth weight	15mg/d	1.5ml

7. Special Considerations

7.1 TB Patients

Suspect TB if 2 or more of the following symptoms are present:

1. Cough any duration
2. Sputum production which may occasionally be blood stained
3. Fever
4. Drenching night sweats
5. Unexplained weight loss
6. Loss of appetite, malaise, tiredness
7. Shortness of breath, chest pains
8. New palpable lymphadenopathy

The patient that presents with TB before commencing ART:

HIV positive TB patients qualify for lifelong ART regardless of CD4 cell count.

Complete 2 to a maximum of 8 weeks of TB therapy before commencing ART (**and as soon as possible if CD4 count is less than 50 cells cells/mm3**)

In general, ART should be initiated as soon as the patient is tolerating their TB therapy; this is usually within 2-4 weeks.

EFV-based regimens are generally preferred in patients with active TB; however, other regimens are also effective. Dose adjustment of PI may be required. Patients on Lopinavir/Ritonavir should have their dose doubled slowly over two weeks (to 800/200 mg twice a day).

Patient developed tuberculosis while on ART:

ART should be continued throughout TB treatment.

Patients on Lopinavir/Ritonavir should have their dose doubled slowly over two weeks (to 800/200 mg twice a day); all other regimens can be continued unmodified. Monitor and investigate appropriately for hepatotoxicity symptoms.

Continue these changes to Lopinavir/Ritonavir until two weeks after completion of TB treatment.

Antiretroviral Treatment for Adults with Concomitant TB	
TB develops while on ART	**TB diagnosed before starting ART**
Continue ARV therapy throughout TB treatment. **First-line regimen**. Patient can remain on the regimen they are taking.	**CD4 count >350/mm^3:** Delay ART for two months (until intensive phase of TB therapy is complete). **CD4 count 100 – 350/mm^3**

Second-line regimen: The lopinavir/ ritonavir dose should be doubled (from 2 tablets 12 hourly to 4 tablets 12 hourly) while the patient is on rifampicin-based TB treatment. Monitor ALT monthly. Reduce lopinavir/ ritonavir to standard dose 2 weeks after TB treatment is completed.	Introduce ART between 2-8 weeks **CD4 count of <100/mm^{3}or other serious HIV illness:** Introduce ART regimen as soon as the patient is stabilized on TB therapy (within 2 weeks after starting TB therapy). First line ART regimen: 1. Tenofovir 300mg daily 2. Lamivudine 300mg daily 3. Efavirenz 600mg at night

7.2 INH Prophylaxis

a. All people living with HIV should be screened for active TB and eligibility for ART.
b. Those who are eligible should be started on ART.
c. TB preventive therapy is an effective intervention for HIV infected individuals.
d. All people living with HIV, in whom active TB has been reasonably excluded, should be started on IPT (as soon as practically possible after initiation of ART in those who are eligible for ART).
e. In patients with no TB signs or symptoms, TB prophylaxis with Isoniazid Preventive Therapy (IPT) should be started, unless alcohol abuse, adherence or side-effects are a concern, 5mg/kg to a maximum dose of 300mg daily, with pyridoxine 25mg/day. **A TST (Mantoux) test is required.**
f. Pregnancy is not a contraindication to INH prophylaxis.
g. If no TST is done IPT should be continued for 6 months as per existing guidelines but all effort should be made to perform TST as soon as possible after starting IPT.

Summary Recommendations		
	Pre-ART(CD4>350)	**On ART**
TST not done*	IPT for 6 months	IPT for 6 months
TST negative	IPT for 6 months	IPT for 12 months
TST positive	IPT for at least 36 months	IPT for at least 36 months

8 PMTCT Treatment Algorithms

Figure 1 PMTCT Algorithm 1 New HIV Positive Diagnosis During Pregnancy

Algorithm 1 is for all women who are newly diagnosed as HIV positive anytime during pregnancy AND women who enter ANC with known HIV positive status and not yet on ART.

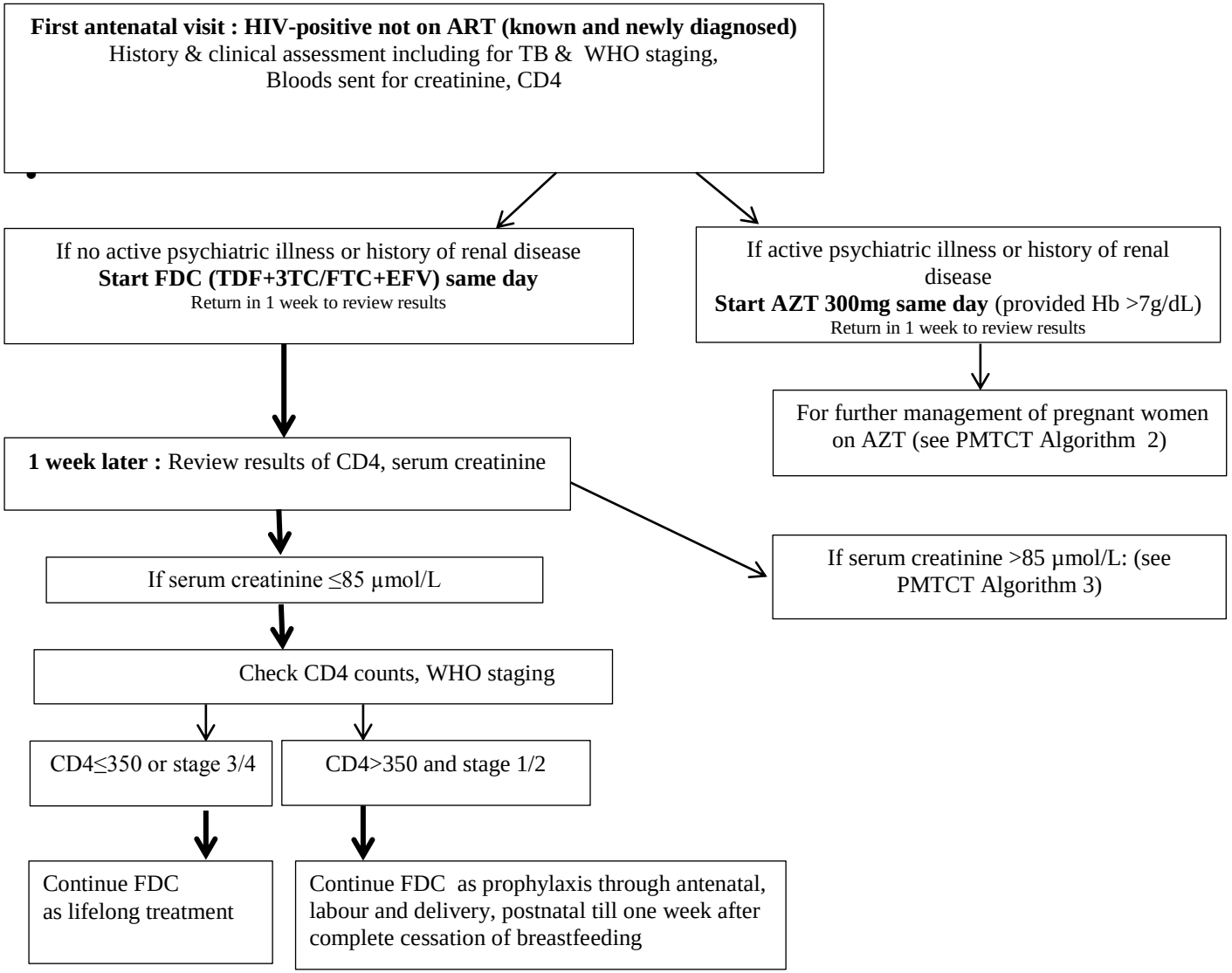


Figure 2 : PMTCT Algorithm 2 : Initiation of Antiretroviral Therapy During Pregnancy in Women with Active Psychiatric Illness

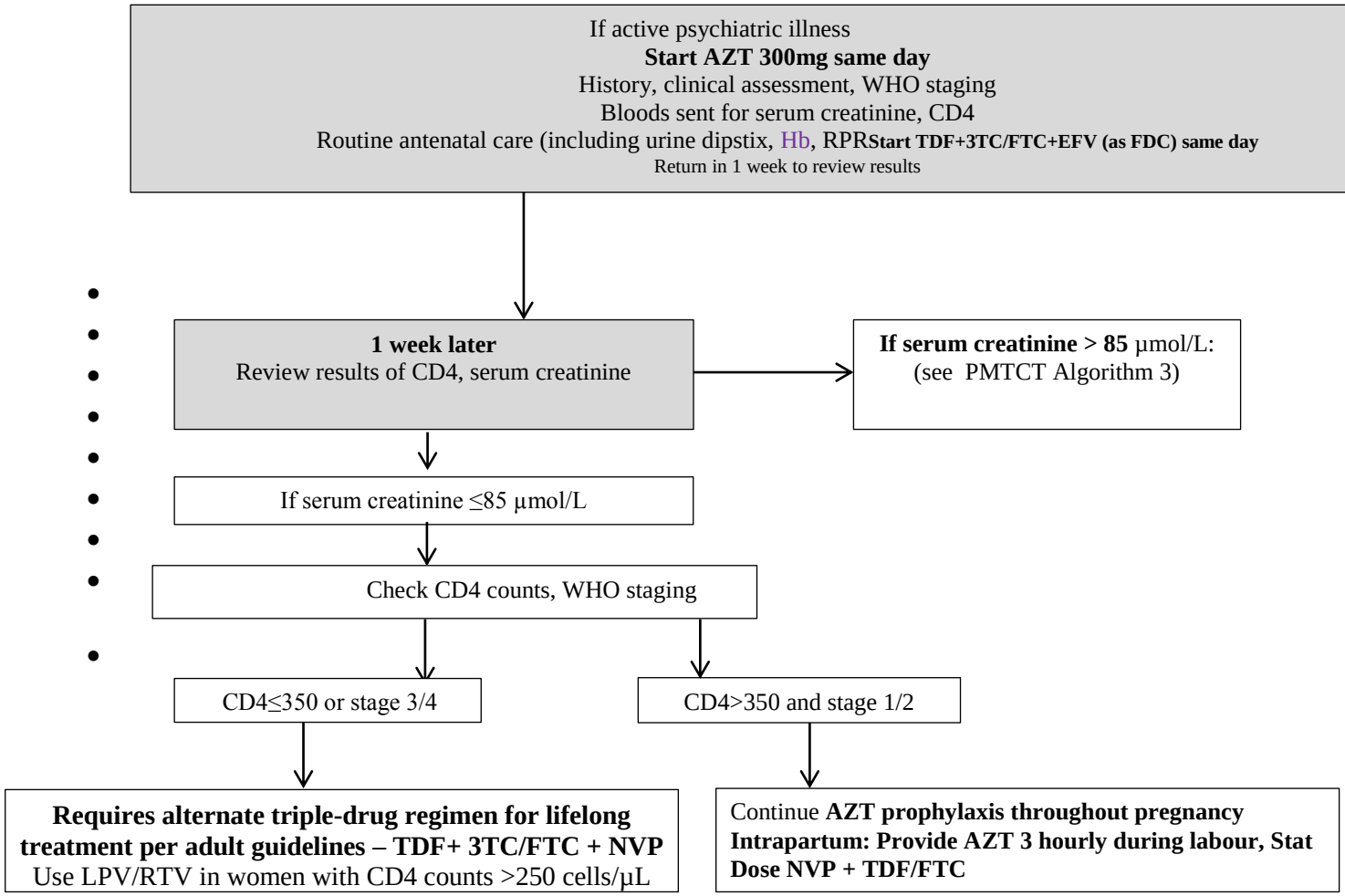


Figure 3 : PMTCT Algorithm 3: Initiation of Antiretroviral Therapy During Pregnancy in Women with Serum Creatinine >85 µmol/L

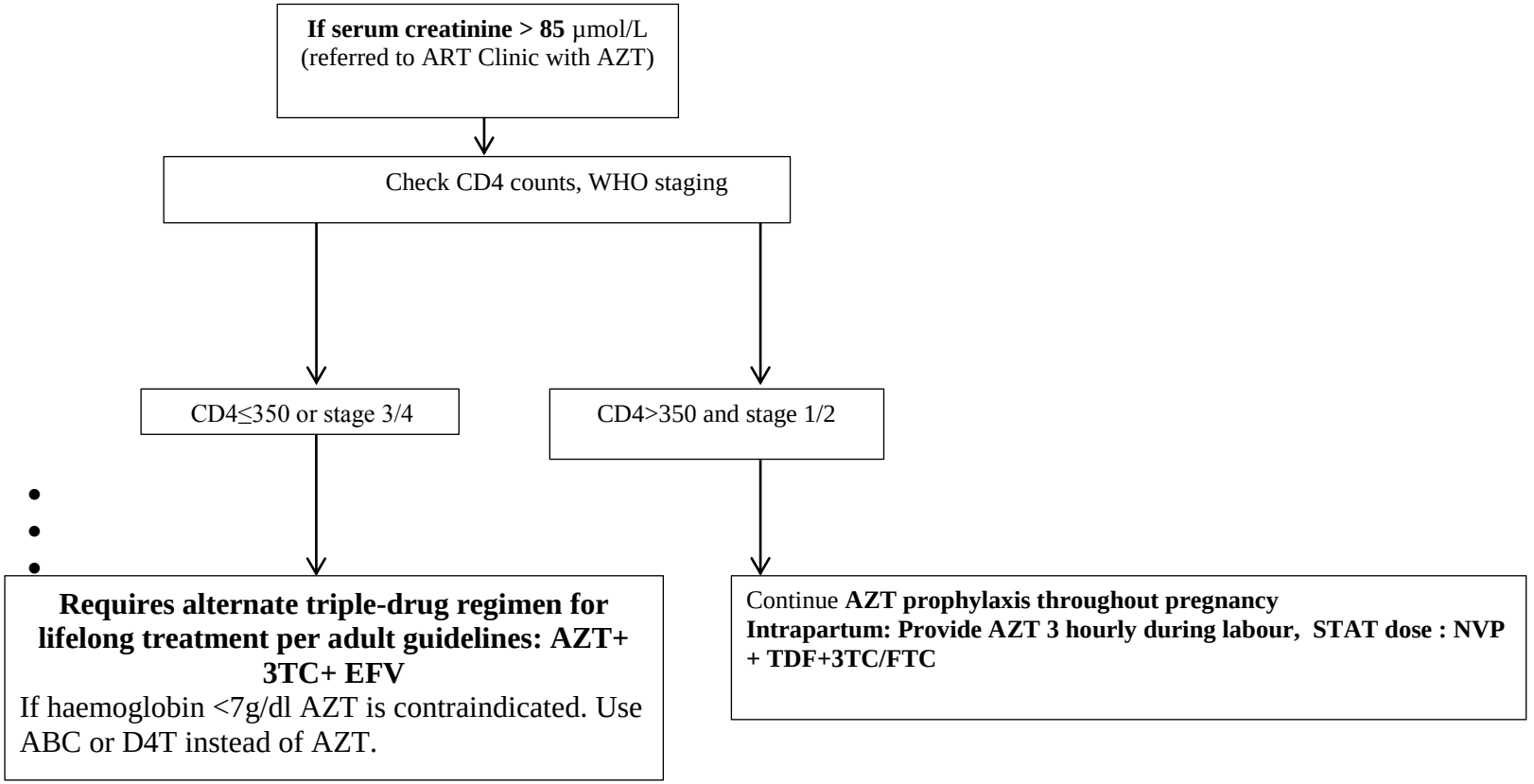
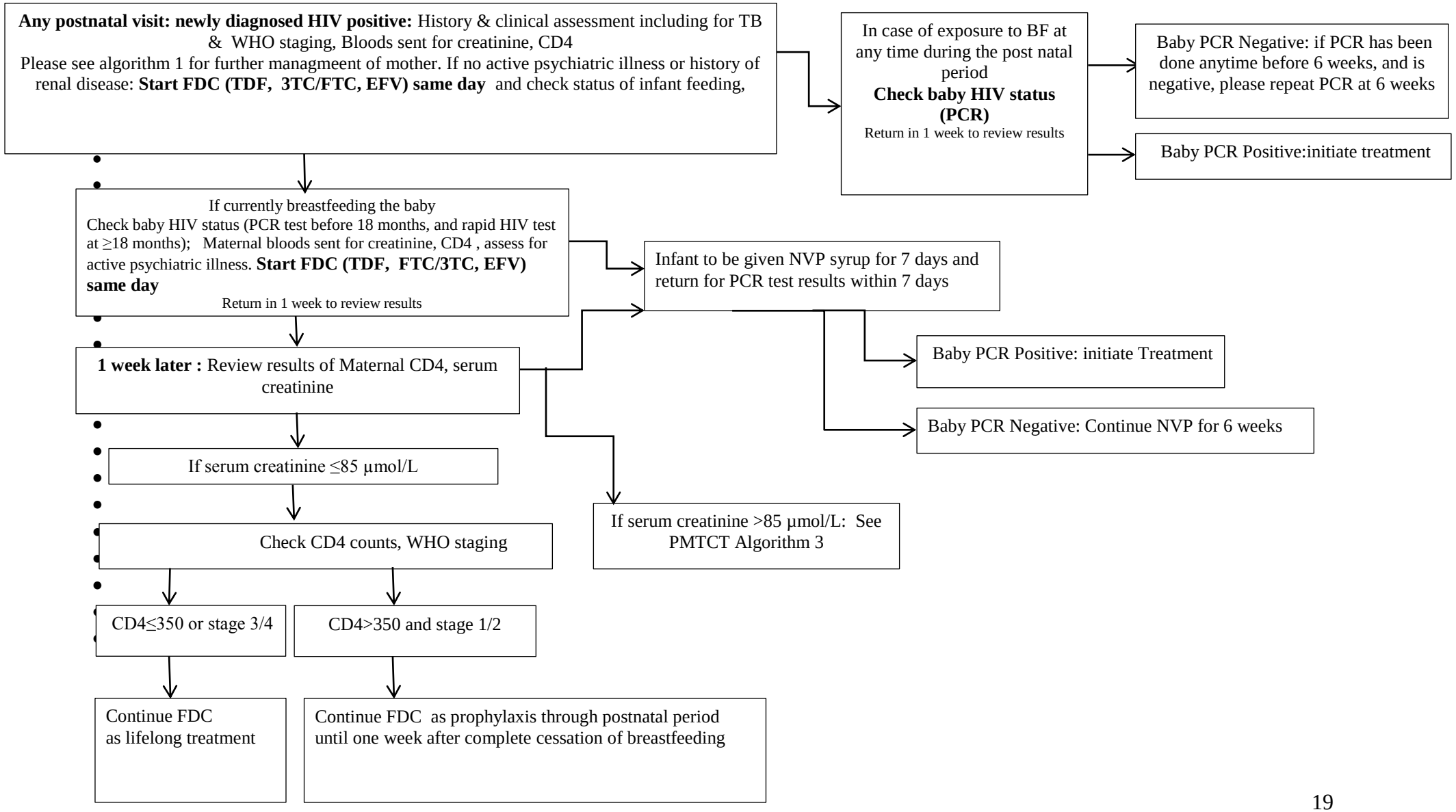


Figure 4 : PMTCT Algorithm 4 : For Women Newly Diagnosed HIV Positive During Postnatal Period



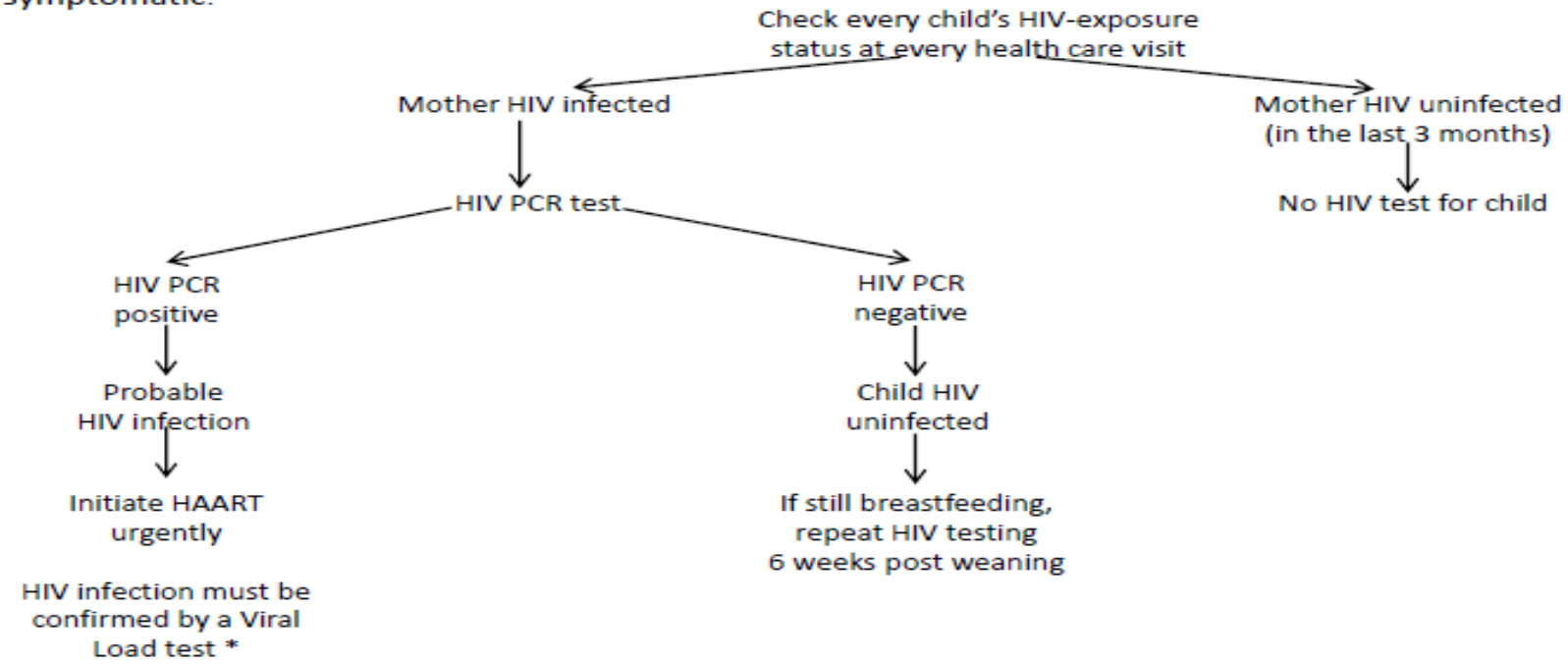
9 Testing Algorithm for Infants

Testing algorithm 1 for infants < 18 months of age

Diagnosis of HIV infection in infants and children

1. Children <18 months old

- All HIV-exposed infants require PCR testing at 6 weeks of age, 6 weeks post weaning and at any age if the child is symptomatic.



- A detectable Viral Load confirms HIV infection. HAART initiation should not be delayed by waiting for the Viral Load result.

If the HIV infection status of an infant initiated on HAART is in doubt, discuss further HIV testing required with your nearest HIV PCR laboratory

Testing algorithm 2 for infants ≥ 18 months of age

2. Children ≥18 months old

- All HIV-exposed children require a rapid test at 18 months of age, except HIV-infected children on HAART