Consolidated Guidelines for the

Prevention and Treatment of HIV and AIDS in Pakistan 2017

FOREWORD

National AIDS Control Program Pakistan in collaboration with its UN partners developed its first HIV treatment guidelines in 2005 which was subsequently revised in 2010 based on WHO new international recommendations. With constant research worldwide new evidence on more efficacious, durable and tolerable HIV treatment and care options have emerged based on which World Health Organisation recently revised its own recommendations in 2013. With these new recommendations WHO consolidated all aspects of HIV treatment and Care into one document for the ease of its readers and implementers.

To keep abreast with these new recommendations Pakistan also revised its National HIV treatment guidelines consolidating all aspects of HIV , prevention, treatment and care including PPTCT and Paediatric care into one document. Key areas covered include HIV diagnosis, antiretroviral therapy for adults, adolescents and children including special populations, prevention of Parent to Child Transmission, Post exposure Prophylaxis and prevention and management of common opportunistic infections including Tuberculosis and Hepatitis. To increase patient compliance we have included Fixed Dose Combination of ARVs both in first and second line regimens. We have also tried to add testing and treatment steps in tables and algorithms for ready reference of its users which can easily be printed into posters to be available in our treatment centres all over the country.

The target audience of these guidelines are health care professionals providing care and treatment to PLHIV including doctors, clinical officers, nurses, pharmacists, service providers, laboratory technologists and program management staff.

The development of this edition of the Guidelines has been done through extensive efforts put in by multiple agencies and stakeholders at all levels of HIV arena. The process was spearheaded by National Technical Working Group for HIV treatment and care that took up the task of hiring the consultant, conducting national consultations and getting feedback from experts and implementers and incorporating it into the document and then reviewing the final document word by word and page by page in a series of meetings.

We hope that this Guideline will increase the knowledge of its target audience on the new recommendations on HIV prevention, treatment and care and will help in rapid scale up of comprehensive and quality assured services to its clients in Pakistan.

Director General Health Services

Ministry of National Health Services Regulations and Coordination

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Contents

Abbreviations and Acronyms

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral (drug)
ATT	Anti tuberculous therapy
ATV	Atazanavir
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine (also known as ZDV)
BMI	Body mass index
CD4	T–lymphocyte cell bearing CD4 receptor
CDC	United States Centers for Disease Control and Prevention
CrAg	Cryptococcal Antigen
CSW	Commercial Sex Worker
CNS	Central nervous system
CPT	Co-trimoxazole preventive therapy
d4T	Stavudine
DALYs	Death- and disability-adjusted life-years
DBS	Dried blood spot
ddI	Didanosine
DNA	Deoxyribonucleic acid
DRV	Darunavir
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay

EPI	Expanded Programme on Immunization
ETV	Etravirine
EWI	Early Warning Indicators
FDC	Fixed Drug Combination
FPV	Fosamprenavir
FPV/r	Fosamprenavir/ritonavir
FTC	Emtricitabine
GNP+	Global Network of People Living with HIV
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance
HSV	Herpes Simplex Virus
HTC	HIV Testing and Counselling
INH	Isoniazid
INSTI	Integrase Strand Transfer Inhibitor
IPT	Isoniazid preventive therapy
IPV	Injectable Polio Vaccine
IRIS	Immune reconstitution inflammatory syndrome
KP	Key populations
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MDR	Multidrug-resistant TB, resistant to at least isoniazid and rifampicin
MTCT	Mother-to-child transmission (of HIV)
NFV	Nelfinavir
NNRTI	Non-nucleoside reverse-transcriptase inhibitor

NRTI	Nucleoside reverse-transcriptase inhibitor
NVD	Normal Vaginal Delivery
NVP	Nevirapine
OST	Opioid substitution therapy
OPV	Oral Polio Vaccine
PCR	Polymerase chain reaction
PI	Protease inhibitor
PICO	Population, Intervention, Comparison and Outcomes
PCP	Pneumocystis (jirovecii) pneumonia
PMTCT	Prevention of Mother-to-child transmission (of HIV)
PPTCT	Prevention of Parent to Child Transmission (or HIV)
PrEP	Pre-exposure prophylaxis of HIV
PWID	People Who Inject Drugs
RAL	Raltegravir
RBV	Ribavirin
RIF	Rifampicin
RNA	Ribonucleic acid
RTV	Ritonavir
sd-NVP	Single-dose nevirapine
TAM	Thymidine analogue mutation
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TPV	Tipranavir
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization

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Summary of Recommendations

HIV Testing and Counselling (HTC)	• HIV testing and counselling should be voluntary and adhere to the five C's. • In Pakistan community based HIV testing and counselling for key populations should be prioritized and scaled up with linkages to prevention, care and treatment services. HTC should include the partners of the key populations. • Provider-initiated testing and counselling is recommended for adults, adolescents and children who present with signs and symptoms or medical conditions that could indicate HIV infection including HIV-exposed children. • HTC should be offered in STI clinics, TB clinics, PWIDs, Blood transfusion services, medical and pediatric clinics catering to high risk and general population, and to patients suffering from Hepatitis B and C. It should also be offered in antenatal care settings in geographically prioritized areas. • HIV diagnosis should be confirmed based on WHO recommended 3 test strategy on rapid test kits
Antiretroviral therapy in Adults and Adolescents	**When to Start** • ART should be initiated in all individuals regardless of CD4 counts o Priority should be given to those with a CD4 of <500 cells/mm^3 **What to Start** • First-line ART should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI). • In adults and adolescents, following fixed-dose combination is recommended as the preferred option to initiate ART. o TDF + 3TC+ EFV In case of contraindications or non-availability one of the following options is recommended : o AZT+3TC+EFV o AZT+3TC+NVP o TDF+3TC+NVP
Antiretroviral therapy in pregnant and breastfeeding women	• ART should be initiated in all pregnant and breastfeeding women with HIV and then continued indefinitely thereafter, regardless of the CD4 count or the WHO clinical stage. • All HIV exposed infants should receive postpartum antiretroviral prophylaxis to reduce transmission of HIV. • Infant prophylaxis should be initiated at weight-appropriate doses as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. • A 6-week neonatal nevirapine regimen can be used for full-term infants when the mother has received a standard ART regimen during

	pregnancy with sustained viral suppression and there are no concerns related to maternal adherence. • Dual prophylaxis (AZT+NVP) is recommended in infants at higher risk of HIV acquisition, including those born to HIV-infected women who: a. Have not received antepartum or intrapartum ART, or b. Have received only intrapartum ART, or c. Have received antepartum ART but do not have viral suppression near delivery. • To establish HIV exposure in infants a. Less than 4 months age: expedited HIV testing (RDT) of mothers and/or infants is recommended as soon as possible, either during labor or after birth, with immediate initiation of dual infant prophylaxis if the initial expedited test of the mother is positive. If supplemental maternal testing is negative, ART prophylaxis can be discontinued. b. More than or 4 months of age: expedited HIV testing (RDT) of mothers is preferred to RDT testing of infants (waning maternal antibody level may give a false negative result). If an RDT is done in an infant, a negative result should be followed by retesting at 18 months or at cessation of breastfeeding. A positive test should be followed by a NAT for confirmation. A NAT should be done at outset in a sick infant or one in whom the mother is not available.
Antiretroviral therapy in children	d. ART should be started in all children diagnosed with HIV regardless of CD4 count a. For children younger than 5 years priority should be given to those who are younger than 2 years, or, clinical stage 3 or 4, or, CD4 count <750 cells/ mm^3 or CD4 percentage <25% b. For children 5 years or older priority should be given to those with WHO clinical stage 3 or 4, or, CD4 count of <350/mm^3 e. Children younger than 3 years or weighing less than 3.5kg should be started on a. ABC (or AZT) +3TC+LPV/r f. Children older than 3 years but younger than 10 years should be started on a. ABC (or AZT) +3TC+EFV (or LPV/r) g. Adolescents (10-19 years) or weighing over 35kg should be started on the same ART as adults
Treatment monitoring and diagnosis of treatment failure in all populations	• Viral load is recommended as the preferred monitoring approach to diagnose and confirm ART failure. • CD4 need not be repeated if >350/mm^3 and Viral loads are suppressed. • If viral load is not routinely available CD4 count and clinical monitoring should be used to diagnose treatment failure. • Second-line ART for adults and children should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-

	boosted protease inhibitor (PI) or integrase inhibitor. Reinforcement of adherence should be provided. • In the second line regimen, TDF should be switched to AZT and vice-versa, FTC should be continued as before or may be interchanged by 3TC. •
Co-infections: Management /Screening / Prevention	**Trimethoprim-sulfamethoxazole prophylaxis** • For **HIV exposed infants** trimethoprim-sulfamethoxazole prophylaxis (CPT) is universally indicated starting at 4-6 weeks after birth and maintained until cessation of risk of HIV and exclusion of HIV infection. • CPT is recommended for all infants, **children and adolescents living with HIV irrespective of clinical and immune conditions.** **Priority should be given to all children less than 5 years** regardless of clinical stage or CD4 count, or, children with clinical stage 3 or 4, or CD4 count ≤350 /mm^3. CPT can be discontinued in children who are 5 years or older who are clinically stable/virally suppressed on ART for more than 6 months, and with a CD4 count >350 /mm^3 **HIV/TB** • All PLHIV should be screened for TB with a clinical algorithm. If the evaluation shows no TB, patients should be offered IPT (300 mg/day for adults, 10 mg/kg/day for infant/child) for 6 months irrespective of the degree of immunosuppression. • TB patients with known positive HIV status should receive at least 6 months of rifampicin treatment regimen. **Others** • **Cryptococcal meningitis** should be treated with either amphotericin B or high dose fluconazole in the intensive phase, followed by lower dose fluconazole in the consolidation and maintenance phase. • **MAC** prophylaxis must be provided to all HIV infected individuals with a CD4 count of below 50 cell/mm^3. • **Syphilis** should be treated according to the stage o Early syphilis: Benzathine penicillin G 2.4 million units as a single dose. o Late syphilis or unknown stage of syphilis: Benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks. • Treatment of genital infections with ***Neisseria gonorrhoeae*** and ***Chlamydia*** *trachomatis* is ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose.

	Vaccination • Children with HIV should be vaccinated according to the EPI schedule, but BCG should be deferred till HIV infection has been ruled out. Live viral vaccines like oral poliovirus vaccine can be given regardless of CD4 count but measles and chickenpox should be deferred in a severely immunosuppressed child (CD4 count ≤200 cells/mm^3 or %CD4 < 25%). Additionally, children should be offered influenza vaccination annually. • Adults with HIV should be routinely vaccinated for HBV, pneumococcus, tetanus and HPV.
Routine health care of HIV infected individuals	• Elements of general medical care should be integrated into HIV care. • Nutritional support and assessment must be done for children with HIV at every visit. • Barriers to adherence should be assessed and addressed in each visit. Adherence should be monitoring using a combination of viral loads, pharmacy refill records, self-reporting and pill counting.
Prevention	• All patients with HIV should be counselled regarding combination prevention strategies. • Post exposure prophylaxis (PEP) should be offered to all occupational and non-occupational exposures within 72 hours of the exposure. The standard regimen of TDF+3TC (or FTC) +LPV/r is recommended for 28 days. • Pre-Exposure Prophylaxis is recommended for all individuals at risk of HIV and should contain TDF with or without 3TC
Program Monitoring and Early Warning Indicators	Early Warning Indicators (time pill pick-up, retention in care, pharmacy stock outs, dispensing practices, VL suppression at 12 months) should be reported by all programs to the provincial program managers.

Section 1: Introduction

Background and Context

The National AIDS Control Program with the support of WHO, developed country's first National Guidelines for HIV Treatment for Adults in 2006 which were revised in 2010. In 2007 NACP with the support of WHO developed Pakistan's National Guidelines on Management of HIV infection in Children. Similarly Pakistan's National PPTCT Guidelines were developed in 2006 and revised in 2011.

WHO in 2013 revised its ART recommendations based on new emerging evidence, which prompted the need to review the Pakistan's national ART guidelines and adapt the new international recommendations and best practices to the local context. The 2013 WHO ART Guidelines provided a consolidated document based on which Pakistan's ART guidelines for adults, children and pregnant women (PPTCT) have all been combined in one document.

The consolidated document provides guidance on using ARV drugs in the context of the continuum of HIV prevention, treatment and care. The guidance covers the use of ARV drugs for all age groups and populations and it promotes consistency of approaches.

Objectives

The objectives of the consolidated guidelines are to:

- Provide a standardized and simplified approach for the use of antiretroviral drugs in Pakistan, based on scientific evidence and adapted to local needs and resources.
- Identify the most potent, effective, and feasible first-line, second-line regimens as components of expanded national response for HIV prevention, treatment and care. Outline treatment strategies and recommendations for all age groups, pregnant women, special populations (PWID, HIV-TB co-infections or Hepatitis B co-infections)
- Introduce recommendations applicable to the majority of PLHIV, the optimal timing of ART initiation, preferred first-line and second-line ARV regimens and criteria for ART switching.
- Serve as a reference manual for health care professionals involved in the treatment and care of PLHIV in the public and private sector.

Target audience

These guidelines are intended for physicians, nurses, psychologists, and other healthcare providers involved in an integrated medical care approach.

Section 2: HIV Testing and Counselling (HTC)

HIV testing and counselling is considered the gateway to HIV prevention, treatment and care. Globally it is estimated that about half of the people living with HIV do not know their status. Moreover, those who are aware of their status, often test late which leads to treatment delays and poor health outcomes and ongoing transmission. The overall goal of the HTC program is to identify as many people living with HIV as early as possible after acquiring HIV infection, and links them appropriately and in a timely manner to prevention, treatment and care services.

For more details regarding HIV Testing and Counselling please refer to "Pakistan country strategy for HIV Testing & Counselling based on Situation & Response Analysis (updated 2013)". Below is a brief summary of the basic concepts of HTC.

2.1: HIV testing and counselling guiding principles

All forms of HIV testing and counselling should be voluntary and adhere to the five C's: consent, confidentiality, counselling, correct test results and connections to prevention, treatment and care, services. Mandatory or coerced testing is never appropriate, whether that coercion comes from a health care provider or from a partner or family member.

While details regarding the principles of counselling can be found in "Pakistan country strategy for HIV Testing & Counselling based on Situation & Response Analysis (updated 2013)", the following key principles apply to all instances of HIV testing and counselling.

2.1.1: Consent

Patients being offered HIV test should be informed that they have the right to decline or defer the test (opt-out approach). A verbal consent is sufficient and written consent is not required.

2.1.2: Confidentiality

HIV testing and counselling services are confidential. In other words, the HIV testing and counselling provided will not be disclosed to anyone else without the expressed consent of the person being tested. Disclosure to children should only be made after consent of the parents.

2.1.3: Counselling

While written consent is not required, counselling must still be performed regarding risk reduction behavior and linking to care. HIV testing and counselling services must be accompanied by appropriate and high quality pre-test information and post-test counseling. Clients must also be given an opportunity to ask questions and clarify any concerns.

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2.1.4: Correct test results

HIV testing and counselling providers should strive to provide high-quality testing services, and quality assurance mechanisms should be in place to ensure the provision of correct test results. Quality assurance may include both internal and external quality assurance mechanisms and should include support from the national reference laboratory as and when needed.

2.1.5: Connections to prevention, treatment and care services

Connections to prevention, treatment and care services should include the provision of effective referral to appropriate follow-up services as indicated, including long term prevention and treatment support.

2.2: Retesting prior to enrolment in care

Given the consequences of HIV diagnosis and treatment, it is a priority to retest all people who are diagnosed to be HIV positive prior to enrolment in HIV care in order to verify their sero-status. This will prevent the rare cases in which people may be misdiagnosed due to possible technical or clerical errors (including specimen mix-up through mislabeling and transcription errors) as well as random error (either by the provider or the test device). Retesting should be done on a new sample, ideally at the treatment center.

2.3: Who to test

All key populations and their partners in Pakistan should be offered periodic provider-initiated testing and counseling (PITC). In addition HIV testing and counselling should be considered in adults, adolescents or children who present with signs and symptoms or medical conditions that could indicate an HIV infection (including disseminated or unusual manifestations of TB), HIV-exposed children, children born to women living with HIV and symptomatic infants and children. Finally, HIV testing and counselling should be considered in patients presenting with sexually transmitted infections, or for antenatal care settings in geographically prioritized areas with high burden of known HIV.

Table 2.1: HIV testing and counselling in key populations

Who to test	When to test	Where to test
People with signs and symptoms of HIV infection	As soon as possible. Integrate in healthcare encounter	STI clinics; TB clinics; blood transfusion services; medical and pediatric clinics catering to high risk and general population; pediatric

		malnutrition units; hematology-oncology units; mobile units conducting rapid testing (IDUs), health care settings such as hospitals and clinics
Partners of people with HIV	As soon as possible after the index case is diagnosed. For a negative person in serodiscordant couples, offer retesting every 6-12 months	Clinical settings, including primary healthcare settings, ART, TB, STI clinics; VCT/HTC settings
Families with index cases	As soon as possible after the family member is diagnosed	ART clinics, maternal and child health and antenatal care settings, community outreach
Key populations: PWID, MSM, transgender people, sex workers and those with recurrent exposure to blood products (e.g. thalassemics or hemodialysis patients)	Every 6-12 months	STI clinics Medical facilities Outreach services for KPs and harm-reduction services
Pregnant women	When husband is a PWID. Husband is known HIV positive. In areas where there is evidence of high number of PLHIV in the general population	Antenatal care
Infants and children <18 months old	Early infant diagnosis at 4-6 weeks for all infants whose mothers are living with HIV or if there is an exposure and maternal status is unknown; determine the final infant HIV infection status after 18 months and/or when breastfeeding ends	Maternal and child health services Paediatrics clinics
Children with signs and symptoms of HIV infection	As soon as possible.	In health care settings

or who have a family member living with HIV	Integrate with healthcare encounter	
Adolescents from key populations	Youth-friendly services	STI clinics, outreach

2.3.1 HIV testing and counselling in infants and children

All HIV-exposed infants should be tested for HIV within 4 to 6 weeks of birth so that those already infected can start ART. Mortality is very high amongst untreated infants infected with HIV in the first year of life, making early HIV testing, prompt return of results and rapid initiation of treatment essential. Because of the presence of persisting maternal HIV antibodies in children up to 18 months of age, HIV infection in this age group can only be definitively confirmed using virological tests. Virological tests include detection of viral nucleic acid (HIV DNA, RNA or TNA-total nucleic acid on serum or dried blood spot) or p24 antigen. Final (or definitive) diagnosis at the end of the risk period for mother to child transmission (i.e. after breastfeeding ends) should be ensured. A positive HIV antibody test prior to 18 months age is not helpful in establishing infection; however, a negative HIV antibody test in a known HIV-exposed infant can be useful to exclude HIV infection if there is no ongoing exposure. HIV antibody tests can reliably assess exposure in infants less than 4 months, however, for infants 4-18 months, the best way to ascertain exposure is testing mothers, and where mothers are not available for testing, following a negative serology test result in child with retesting at 18 months, or with nucleic acid testing (NAT) regardless of serology result if the child is sick. (See Annex 5 for the algorithm on HIV diagnosis in children less than 18 months of age.)

In infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result. Immediate initiation of ART saves lives and should not be delayed while waiting for the results of the confirmatory test. Despite these recommendations, only about 30% of perinatally infected infants are ultimately linked to appropriate care in a timely manner. Test results from virological testing in infants should be returned to the clinic and child/mother/caregiver pair as soon as possible, but at the very latest within 4 weeks of specimen collection. Positive test results must especially be fast-tracked to the mother-baby pair as soon as possible to enable prompt initiation of ART. Innovative approaches such as using NAT technologies at point of care at or around birth (0-2 days) can be considered in the future to improve rapid detection and treatment initiation in HIV-exposed infants in Pakistan.

For children 18 months of age and older (who are not breastfeeding or who have stopped breastfeeding at least six weeks earlier), standard HIV serological tests (such as rapid diagnostic tests) can be used to reliably determine HIV infection status. PITC for all children who are malnourished or have other signs or symptoms of HIV infection is also recommended. Finally HIV-exposed infants who are well should undergo final HIV serological testing at around 9 months of age (or at the time of the last immunization visit). If the Infant tests positive they should have a virological test to

identify HIV infection and the need for ART. The table below summarizes the testing required and actions taken depending on the exposure or symptoms of the child.

Table 2.2: HIV testing in infants and children

Category	Test required	Purpose	Action
Well HIV-exposed infant at birth	Virological testing at 4–6 weeks of age or earliest thereafter	To diagnose HIV	If positive, start ART without delay without waiting for result of second confirmatory test
Well HIV-exposed infant when 9 months old	HIV serological (antibody) test at 9 months	To identify infants who have persisting HIV antibody or have converted to sero-negative	For HIV seropositive, virological test and continued follow up is needed. For HIV seronegative, assume uninfected, repeat testing required if still breastfeeding six weeks after cessation of breast feeding
Infant or child with signs and symptoms suggestive of HIV infection	HIV serological test	To confirm exposure	If positive, perform virological test if <18 months of age to confirm infection
Well or sick child seropositive between 9 months and 18 months	Virological testing	To diagnose HIV	If reactive start HIV care and ART
Infant or child who has completely discontinued breastfeeding	Repeat testing six weeks or more after breastfeeding cessation by serology followed by virological testing for HIV-antibody-positive child if <18 months of age	To exclude HIV infection after exposure ceases	Infected infants and children <5 years of age, need to start HIV care, including ART

2.4: Diagnostics for HIV

The use of a single HIV test to diagnose HIV infection is not sufficient and must be confirmed. WHO recommends standardized testing strategies to maximize the accuracy of test results while minimizing costs. In each of these strategies, 3 different assays are used to confirm the diagnosis, while any of the available assays may be used, care should be taken that only WHO approved kits are used in the correct order. Also, each of the assays should be checking antibodies against a different antigen to prevent shared false non-reactivity or false reactivity. Finally if one of the assays is a 4th generation test (i.e.

checks for the P24 antigen as well as antibodies against HIV) this should be the first test done.

Full details regarding HIV Testing and Counselling can be found in the "Pakistan country strategy for HIV Testing & Counselling based on Situation & Response Analysis (updated 2013)". A copy of the testing algorithm may be found in Appendix 1 and is available on following web address:

http://www.nacp.gov.pk/policies_and_guidelines/treatment_and_care/

2.4.1 Early Infant Diagnosis (EID)

HIV diagnostic tests available for children under 18 months age in Pakistan have included the HIV antibody test and the HIV RNA test through NAT in serum. The former cannot differentiate between true infection and passive presence of maternal antibodies in the infant. A positive serological test needs confirmation with a virological test. HIV virological testing can definitively diagnose HIV in most non-breastfed HIV-exposed infants by age 1 to 2 months and in virtually all infected infants by age 4 months. Testing at birth will detect infants who were infected in utero and not those who become infected from exposure during or immediately prior to delivery (ie in the intrapartum period). HIV RNA assays (specificity 100% at birth, 1, 3 and 6 months of age for results ≥5000 copies/ml), available heretofore, could potentially be affected by maternal antenatal treatment or infant combination ARV prophylaxis. HIV RNA levels <5000 copies/ml may not be reproducible and should be repeated before they are interpreted as documenting HIV infection in an infant. HIV DNA PCR remains positive in most individuals receiving ARV treatment with a specificity of 99.8% at birth and 100% at 1, 3 and 6 months. It is not available in Pakistan. On the 15th June 2016, the GeneXpert, was prequalified by the WHO for HIV-1 qualitative determinations. It can be run on either dried blood spot samples or on whole blood.

The WHO indicates that the gold standard for an EID assay would be an assay of either DNA or TNA (total nucleic acids). DNA or TNA assays are called gold standard as they allow detection of infection even when viral load is low, which can be sometimes the case in infant infected across the time of birth because DNA is maintained even if RNA is low.

National AIDS Control Program (NACP), Pakistan in collaboration with UNICEF, has initiated early infant diagnosis of HIV by qualitative PCR (HIV-1 TNA) on GeneXpert machine, through Dried Blood Spot (DBS) sample collection technique with transportation to the central National Reference Laboratory , in Islamabad

Implementation Considerations in Pakistan

Every effort should be made to improve NAT uptake at 4 to 6 weeks (HIV-1 RNA/DNA/TNA), strengthen retention along the testing-to-treatment cascade, ensure confirmation of NAT-positive results with a second sample and ensure that infants who test negative by NAT are retained in care until a final diagnosis is made. The aim is to scale up and make EID available at point-of-care (POC) in the coming years.

2.4.2 Testing in Adolescents

Adolescents needing access to HIV testing may have been perinatally infected or acquired it through sex or injecting drugs. HIV testing with linkage to prevention, treatment and care should be offered for adolescents from key populations in all settings.

Section 3: Antiretroviral therapy

3.1: Overview

Appropriate and timely ART has the potential to prolong survival in infected patients to normal. However before initiation of therapy a number of considerations need to be taken into account including the entry points of the patient into the system, preparing the patient for therapy, understanding when to start treatment, choosing the optimal treatment for the patient (with considerations for the nutritional status, any comorbidities, potentially interacting medications, possible contraindications or dose adjustment) and finally adequate monitoring for both response and side effects. This section will cover each of these aspects in detail.

3.2: Entry points

A critical point for identifying the persons in need of treatment is through access to HIV Testing and Counselling (HTC) services, which function as a gateway to treatment services. While there are currently a limited number of functional HTC centers, political leadership and commitment have shifted significantly in favor of establishing these centers and providing access to ART. Entry points must provide or facilitate the link to HIV testing and counseling.

Entry points include:

1. Clinical services
2. STI service centers/clinics
3. Drug treatment centers
4. Maternal & Child Services (MCH)
5. Hepatitis B or C services
6. Blood Transfusion Services
7. TB care centers/programs
8. Community Outreach Services:
    a. High risk/vulnerable populations (sex workers, injecting drug users, truck drivers)
    b. Men having sex with men (homosexuals, bisexuals, Hijras)
    c. Migrant workers (international and national)
    d. Blood donors
    e. NGOs working with high risk or marginalized populations
9. Referral Services and Linkages

a. Adult and pediatrics' inpatient or outpatient hospitals/health care facilities
b. Referral systems through other public or private organizations

10. HTC services

HTC services should include counseling regarding the options for ART treatment, and all clients testing positive for HIV at HTC centers need to be referred to a HIV treatment center for confirmatory testing and further management.

An integrated family approach needs to be promoted for access to HTC and ART, with special emphasis on addressing the vulnerability of women and children in accessing services. During HTC or HIV related care for men, it is part of the medical responsibility to repeatedly request the participation of the wife and children and to promote HTC and HIV care if needed for the family.

Recent assessment based on Test and Treat Cascade analysis conducted in Punjab found that a large number of clients were lost during referral between the Service Delivery Point (SDP) and the treatment center. This weak link was identified as a major gap in treatment scale up. It is therefore recommended that the SDP should ensure the linkage of the client with treatment center and subsequent visits to the treatment center.

3.3: Preparation before starting ART

While starting ART is not an emergency, ART should also not be delayed in order to ensure retention in care. However starting therapy early must also be balanced with assessing the patient's readiness to embark on lifelong treatment. Therefore before starting ART, it is important to have a discussion with the patients regarding their willingness and readiness to initiate ART, the ARV regimen, dosage and scheduling, the likely benefits and possible adverse effects and the required follow-up and monitoring visits. People starting treatment and their caregivers should understand that the first ART regimen offers the best opportunity for effective viral suppression and immune recovery, and that successful ART requires them to take the medications exactly as prescribed as well as at a fixed time. For children with HIV, this conversation should directly involve the caregiver and should include a discussion about disclosing their HIV status. The choice to accept or decline ART ultimately lies with the individual person or his/her caretaker, and if they choose to defer therapy, ART can be offered again at a later visit. However, if mental health, substance use or other problems are identified as barriers to adherence, appropriate support should be provided, and readiness to initiate ART should be reassessed at regular intervals (see section 5.2). ART must not be started on patients who are unwilling or unable to take the medication regardless of the indication.

It should be stressed however, that the above assessment should not be extremely prolonged. Newly registered patients should be started on ART within 7 days of registration unless there are concerns regarding compliance. In fact, ART should be offered on the first visit in patients who are ready to start and are in a stable social environment.

In order to improve compliance, patients should be counseled beforehand regarding potential adverse effects and that many of these are temporary and may be treated or substitutions made for problematic ARV drugs. In patients with advanced HIV disease, IRIS may develop (see section 3.10) and patient should be asked to return to the center if there is any acute deterioration in their condition. Finally a detailed medication history (including supplements, herbal, hakimi or homeopathic medication) should be obtained before starting treatment.

People receiving ART should be counseled that; while the ARV drugs reduce the risk of HIV transmission, they cannot be relied on entirely to prevent other people from acquiring infection. They should be given advice on safer sex (including condom use) and avoidance of other high-risk activities, such as sharing of injecting equipment, to prevent transmitting HIV to other people.

Finally, in patients who have a high chance of being poorly compliant, (based on the patient's current psycho-social situation), ART should only be started when provisions are made for improving compliance. These may include measures such as involvement of a family member or a "treatment buddy" and in the case of PWID detoxification. Also patients who have defaulted on therapy once should be evaluated very carefully before restarting ART as with each subsequent course the chance of drug resistance will increase.

There is never an emergency to start ART, and it is best to preserve future options by not giving ART to a patient who is consistently defaulting.

3.4: When to start

The body of evidence now points towards better outcomes with earlier initiation of ART. This is especially so, given the availability of safer drugs which are easier to use. Moreover treatment may lead to a reduction in the transmission of HIV in the population.

3.4.1: Adults and Adolescents (10-19 years)

ART should be offered to all patients regardless of the CD4 count, WHO clinical stage or co-morbidities/co-infections. However, ART should be started as a priority on any patient above 10 years age with a CD4 of less than 350 cells/mm^3 or advanced WHO clinical stage (3 or 4).

3.4.2 Children below ten years of age

ART should be initiated in all children below ten years of age infected with HIV, regardless of WHO clinical stage or CD4 cell count. As a priority, ART should be initiated:

- in all children diagnosed in first year of life,
- for children between 1-10 years of age living with HIV, all children younger than 2 years, or, younger than 5 year with WHO clinical stage 3 or 4 or CD4 count ≤750cells/mm^3 or CD4% <25%, or, children between 5-10 years of age with WHO clinical stage 3 or 4 or CD4 count ≤350 cells/mm^3.

3.4.3 Women who are pregnant or breastfeeding (including PPTCT)

ART during pregnancy and breastfeeding in women with HIV is primarily used for the mother's health and to prevent the exposed child from becoming infected. Additionally, it may also offer benefits for preventing the sexual transmission of HIV. In order to make implementation of PPTCT/PMTCT easier, increase ART coverage and accessibility as well as harmonize regimens, all women who are pregnant and not already on ARTshould be started on ART immediately regardless of their CD4 count or their clinical symptoms.

After delivery, mothers should exclusively breastfeed their infants for the first 6 months of life followed by introduction of appropriate complementary foods thereafter. Breastfeeding should continue for the first 12 months of life and should only stop once a nutritionally adequate and safe diet without breast-milk can be provided.

ART in mothers should continue indefinitely once breastfeeding has stopped regardless of the mother's CD4 count, WHO clinical criteria or co-morbid conditions. This will ensure that the mother is already on ART and virally suppressed at the time of her next pregnancy.

The table below summarizes the recommendations of when to start ARVs in all age groups

Table 3.1: Recommendation on when to start ART in all age groups

Population	Recommendation
Adults and adolescents (≥10 years and ≥35kg)	Initiate ART in all patients regardless of CD4, clinical status and co-morbidities Priority: WHO Clinical Stage 3-4 and/or CD4 of less than 350 cells/mm^3
Children less than 10 years or weighing <35kg	Initiate ART in all patients regardless of CD4, clinical status and co-morbidities Priority: Diagnosed in first year of life Age 1 to less than 10 years living with HIV: - Age less than 2 years - Age less than 5 years with WHO clinical Stage 3-4 and/or CD4 of ≤ 750 cells/mm^3 - Age 5 to less than 10 years with WHO clinical stage 3-4 and/or CD4 of ≤350cells/mm^3
Women who are pregnant or breastfeeding	Initiate ART in all regardless of WHO clinical stage and CD4 cell count

3.5: What to Start

Annexures 6 and 7 list the dosages of ARVs used in Pakistan. Annexures 8-10 list side-effects and renal and hepatic adjustments to ARV dosages.

3.5.1: First line ART in adults

Preferred regimen:

For most **new** patients the first-line ART consists of a backbone of two NRTIs (always including 3TC or FTC) with one INSTI. While various combinations are possible, the preferred regimen is:

TDF + 3TC + DTG

This regimen is preferred over other regimens for a variety of reasons. Primarily because this regimen is available in a FDC as a single tablet once a day which improves compliance. This regimen is also less frequently associated with severe adverse events and has a better virological and treatment response compared with other once- or twice-daily regimens. DTG also has fewer CNS related side effects compared to EFV and has a higher genetic barrier to resistance. Moreover, if failure on this regimen is detected early, susceptibility to AZT is maintained, which can then be used in the second-line regimen.

However this regimen is not currently recommended in pregnancy and in patients with TB co-infections.

Patients *already* on the previous preferred regimen of TDF+3TC+EFV should be continued on this regimen if they are stable on this.

Alternate regimens

In cases where the primary regimen cannot be used due to toxicity or side effects, an alternative regimen may be used. In the alternative regimen the following drugs may be switched

Substitutions for TDF:

TDF may not be used in patients with poor renal function as well as those in whom TDF may have been used in the past to treat Hepatitis B infection. In such patients AZT may be used in place of TDF. In rare circumstances ABC may be used (especially in the presence of kidney disease and anemia, however a backbone of ABC+3TC is associated with more treatment failure in patients where the viral loads are high. ABC may also be associated with increased cardiovascular mortality in patients with underlying ischemic heart disease as well as the ABC hypersensitivity reaction (in those with the HLA B57*01 allele).

Substitutions for DTG:

The safety of DTG in pregnancy is not well established however early studies do not show a risk of fetal abnormalities. Till further data is available, newly diagnosed patients who are pregnant should be started on TDF+3TC+EFV. However if a patient is stable on TDF+3TC+DTG and becomes pregnant, the regimen need not be changed.

Rifampin has interactions with DTG and leads to reduction in DTG levels. In patients co-infected with TB who have not been started on therapy, TDF+3TC+EFV should be used. Similarly if a patient is diagnosed to have TB while on DTG, the patient should be shifted EFV. However if EFV cannot be used (due to prior adverse effects or failure), the dose of DTG should be doubled by providing extra DTG along with the TDF+3TC+DTG FDC.

Therefore the alternate regimens and indications are as follows

Table 3.2: Alternative HIV regimens

Indication	Substitution	Comments
TDF induced nephrotoxicity	AZT	Avoid in anaemia
	ABC	Avoid if VL suspected to be high or IHD
DTG in pregnancy or TB	EFV	
	Double dose DTG	Use if EFV cannot be used

ART in Hemodialysis patients

HIV patients on hemodialysis (HD) pose a special challenge when selecting an ART regimen as both TDF and AZT cannot be used. Moreover, 3TC also requires renal adjustment. In these patients a regimen of ABC +3TC + EFV is recommended. Moreover, as the dose of 3TC in HD is 15 mg once daily (after an initial dose of 50 mg), the 3TC syrup should be used (i.e. 1.5 ml of the 10 mg/ml syrup).

3.5.2: First line ART in pregnant and breastfeeding women (PPTCT)

While there were initial concerns regarding EFV safety in pregnancy, recent studies have shown this drug to be safe in all trimesters. Moreover, despite earlier concerns, no nephrotoxicity or effects on bone density were found in breastfeeding infants whose mothers were on TDF. Therefore, in order to simplify and harmonize regimens across population groups and to avoid the severe hepatic side effects with NVP (which women with CD4 counts > 250/mm^3 are at a risk of), following standard FDC is recommended in pregnant and breastfeeding women:

TDF+3TC+EFV

Amongst the alternate regimens, the integrase inhibitors should be avoided given the current lack of safety data.

3.5.3 First line ART in adolescents

First line ART for adolescents should consist of two NRTIs plus an NNRTI or an INSTI. Identifying the most suitable regimen for adolescents is of critical importance in light of documented risk of poor adherence relative to adults in some settings which places them at high risk for treatment failure and the development of drug resistance. The WHO 2013

guidelines recommended that adolescents be started on an EFV-containing regimen combined with TDF and 3TC to reduce pill burden and promote harmonization with adult regimens and formulations. In 2016, new recommendations are based on careful consideration of risks (CNS toxicity of EFV with possibility of poor adherence) and benefits (use of tenofovir or abacavir maximizing response to AZT in second line ART, once daily dosing of FDCs), the values and preferences of adolescents living with HIV and the programmatic advantage of full harmonization with first line adult recommendations. A specific consideration for clinicians and other health-care providers relates to whether and how regimen changes can be introduced among clinically stable adolescents who started ART during childhood. As children get older, more options become available with advantages over current first-line regimens, such as FDCs, improved toxicity profile and dosing advantages. The choice between a full regimen change and single drug substitutions should be made in the context of adult regimen harmonization and the convenience of one daily medications in the best formulations available.

Alternative options include:

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

ABC (or AZT) + 3TC + EFV (or NVP)

3.5.4: First line ART in children

First line ART in children three to ten years

Children between 3 to 10 years of age should be started on:

ABC + 3TC + EFV

EFV is considered safe after age 3 years. Children who are on ABC+3TC+LPV/r as infants may be switched to ABC+3TC+EFV to help with dosing, palatability and preserving PIs for future regimens. This switch should only be done if the child is virologically suppressed. Also the viral load must be rechecked again 3 months after the switch. Though this change is optional and children may remain on LPV/r if stable without any issues related to drug administration, EFV would be a better choice for those initiating ART with other once-daily drugs.

First line ART in children less than 3 years

For infants and children younger than 3 years, the NRTI backbone for an ART regimen should be ABC (or AZT) + 3TC. In this age group, a regimen containing a PI (LPV/r) is superior to one with an NNRTI, both in children who may be exposed to NVP during the PPTCT period and for those without prior exposures. Patients on regimens with LPV/r (compared to one with NVP) have a reduced risk of discontinuing treatment and of virological failure or death. Moreover the genetic barrier to resistance of LPV/r is superior to that of NVP in that, resistance does not compromise future second-line PI use. The preferred regimen for children less than 3 years is therefore:

ABC (or AZT) +3TC+LPV/r

It should be noted that using LPV/r oral liquid should be avoided in premature babies (born 1 month or more before the expected date of delivery) until 14 days after their due date or in full-term babies younger than 14 days of age. With early infant diagnosis, challenges may arise in starting the preferred regimen. Therefore in such cases an alternate regimen of ABC (or AZT) + 3TC + NVP may be used. However NVP should be substituted with LPV/r at the earliest opportunity, preferably at two weeks when LPV/r syrup can be administered.

Where viral load monitoring is available, consideration can be given to substituting LPV/r with EFV at 3 years of age after viral suppression is sustained.

Children less than 3 years with TB co-infection (and if AZT is contraindicated)

It should be noted, that given the interaction of PIs with rifampicin, children less than 3 years of age who are co-infected with TB cannot be given LPV/r. In these cases where TB and HIV have been diagnosed together, a triple NRTI regimen of AZT+3TC+ABC should be used when starting ART. Similarly, if an infant is diagnosed to have TB while already on the preferred regimen, the child should be switched to AZT+3TC+ABC while ATT continues. Once the TB treatment has completed, the regimen should immediately be changed back to the preferred regimen. Also in circumstances where AZT cannot be used (e.g. in severe anemia), ABC + 3TC + RAL may be used as an alternative. However, this regimen should only be reserved for very special circumstances as while RAL is approved for use in infants and children from the age of 4 weeks, there is very limited evidence to regarding its use as a first-line drug in infants and young children and d4T can be used instead. Moreover, the available formulations may be difficult to administer. Finally as RAL is metabolized primarily by UGT1A1, caution should be used when co-administration RAL with rifampicin. Rifampicin may reduce plasma levels of RAL and the impact on efficacy of RAL due to this is unknown at this time

Table 3.3: ART regimens in children

Age	Preferred regimen	Alternative regimen(s)
Younger than 3 years or less than 3.5 kg	ABC+3TC+LPV/r	AZT+3TC+LPV/r (In case of ABC hypersensitivity) ABC+3TC+NVP (In case LPV/r formulation not tolerated. Caution: both ABC and NVP can cause skin rash) AZT + 3TC+ ABC (only while on anti-tuberculosis therapy)

Between 3 years and 10 years	ABC+3TC+EFV	AZT + 3TC + EFV (In case of ABC hypersensitivity) TDF + 3TC + EFV (In case of AZT toxicity) ABC+3TC+NVP (In case adult EFV formulation is difficult to administer mg/kg (Annex 7). Caution: both ABC and NVP can cause skin rash. ABC+3TC+LPV/r (Can continue regimen used below age 3 years if clinically stable on it and tolerating ART)
Older than 10 years or more than 35 kg	TDF+3TC+EFV	TDF+3TC+NVP AZT+3TC+NVP AZT+3TC+EFV

3.5.5: Infant Prophylaxis

~~ART should be initiated urgently in all pregnant and breast feeding women, even if they are identified late in pregnancy or postpartum, because the most effective way to prevent mother-to-child HIV transmission is to reduce maternal viral load.~~ WHO guidance on infant prophylaxis in the setting of maternal ART has not been modified since 2010. It is recommended that all breastfed infants should be given daily NVP for 6 weeks. When maternal ART has been started late in pregnancy, during labor or in the postpartum period, infants who are breastfeeding may not be adequately protected from HIV because it takes several weeks for maternal viral load to be suppressed. In such situations, programs were advised to consider increasing the duration of infant prophylaxis to 12 weeks rather than 6 weeks of NVP. Since that time, new data have become available, showing that combination/dual infant prophylaxis is more effective than single-drug prophylaxis for the prevention of intrapartum mother-to-child transmission in infants born to mothers who have not received antepartum ART. The goal of the new recommendation is to optimize infant prophylaxis and further reduce rates of peripartum and breast milk transmission, especially for infants whose mothers have not benefited from optimal care.

Defining high risk infants:

Factors such as prolonged rupture of membranes, preterm delivery and low birth weight are no longer associated with increased risk of transmission when mothers are receiving

ART. The critical determinants of transmission risk in the ART era are maternal viral load and duration of maternal ART.

The following circumstances are considered as high risk:

- New HIV infection in a pregnant or breastfeeding woman with a prior negative test during pregnancy (i.e. seroconversion during pregnancy)
- HIV exposure first identified during delivery or in the postpartum period in a breastfed infant
- If viral load testing is available, pregnant woman whose viral load exceeds 1,000 copies/ml within 4 weeks prior to delivery
- If viral load testing is not available, pregnant women on ART for less than 4 weeks.

Revised Recommendations:

- Infants born to HIV-positive mothers with high transmission risk, should receive dual prophylaxis with AZT (twice daily) and NVP (once daily) for a minimum of first 6 weeks of life, whether they are breastfed or formula fed.
- Breastfed infants born to HIV-positive mothers with high transmission risk, including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis) using either AZT (twice daily) and NVP (once daily) or NVP alone.
- Breastfed infants born to HIV-positive mothers with standard transmission risk should receive 6 weeks of infant prophylaxis with daily NVP.
- Formula fed infants at ~~high or~~ standard risk of acquiring HIV from their mothers, should receive 4-6 weeks of infant prophylaxis with daily NVP or twice daily AZT.

The table below summarizes various scenarios related to the mother's ART and how prophylaxis to the infant should be delivered. Annexure 5 also depicts PPTCT as an algorithm.

Table 3.4: Infant Prophylaxis and maternal ART based on infant risk

Scenario	Maternal ARV prophylaxis	Infant ARV prophylaxis	Infant CPT
Mother diagnosed with HIV during pregnancy and plans to breast feed[a,b]	Initiate maternal ART. Consider C-section if mother not virally suppressed at term and facilities available. If not then proceed with NVD	**Standard Risk* and Breastfed** If <u>mother's VL is undetectable</u> at 36 weeks of pregnancy start once daily monotherapy NVP (6 weeks).	Start CPT when infant is 4-6 weeks old. Rule out HIV by performing HIV TNA PCR at 6 weeks, and, after cessation of breastfeeding by repeating HIV-TNA PCR test. •If negative at 6 weeks stop CPT. •If positive, send second HIV-RNA or TNA test and start ART without delay (continue CPT).
		High Risk* and Breastfed[o] If <u>mother's VL is over 1000 copies</u> at 36 weeks of pregnancy, or, she has been on ARV for less than 4 weeks prior to delivery, start dual	

		prophylaxis with AZT (twice daily) and NVP (once daily and continue for first 12 weeks of life. Rule out HIV by performing HIV-RNA or TNA PCR at 6 weeks • **In case HIV-TNA is unavailable at 6 weeks, or test result is negative, continue dual therapy for first 12 weeks of life** regardless of duration of breastfeeding (monitor drug AE) • In case of positive HIV-TNA PCR at 6 weeks, send second HIV-RNA or TNA test and start ART without delay	
Mother diagnosed with HIV during pregnancy and plans replacement feeding[a,b]	Initiate maternal ART. Consider C-section if mother not virally suppressed at term and facilities available. If not then proceed with NVD	**Standard Risk* and Replacement Feed** If <u>mother's VL is undetectable</u> at 36 weeks of pregnancy start once daily monotherapy NVP (6 weeks) **High Risk* and Replacement Feed** If <u>mother's VL is over 1,000 copies</u> at 36 weeks of pregnancy, or, she has been on ARV for less than 4 weeks prior to delivery, start dual prophylaxis with twice daily AZT and once daily NVP for first 6 weeks of life. Rule out HIV by performing HIV-RNA or TNA PCR at 6 weeks • **In case HIV-TNA is unavailable at 6 weeks, or test result is negative,** stop AZT + NVP at 6 weeks • In case of positive HIV-TNA PCR at 6 weeks, send second HIV-RNA or TNA test and start ART without delay	Start CPT when infant is 4-6 weeks old Rule out HIV by performing HIV-RNA or TNA PCR at 6 weeks • If negative at 6 weeks, stop CPT • If positive send second HIV-RNA or TNA test. start ART without delay and continue CPT.
High risk Mother diagnosed with HIV during	Initiate maternal ART. Consider C-section if mother not virally	**High Risk* and Breastfed[o]** Start dual prophylaxis with twice daily AZT and once daily NVP for first 12 weeks of life.	Start CPT when infant is 4-6 weeks old Rule out HIV by performing HIV-RNA or TNA PCR at 6

labour or immediately postpartum (within 72 hours) and plans to breastfeed	suppressed at term and facilities available. If not then proceed with NVD	Rule out HIV by performing HIV-RNA or TNA PCR at 6 weeks**:** • **In case HIV-TNA is unavailable at 6 weeks, or, test result is negative, continue dual therapy for first 12 weeks of life** regardless of duration of breastfeeding (monitor drug AE) • If positive, send second HIV-RNA or TNA sample and start ART without delay	weeks, and, after cessation of breastfeeding. • If negative stop • If positive send second HIV-RNA or TNA sample and start ART without delay (continue CPT)
Mother diagnosed with HIV during labour or immediately postpartum (within 72 hours) and plans replacement feeding	Refer mother for HIV care and evaluation for treatment	**High Risk* and Replacement Feed** Start dual prophylaxis with twice daily AZT and once daily NVP for first 6 weeks of life. Rule out HIV by performing HIV-RNA or TNA PCR at 6 weeks or as soon as possible thereafter • **In case HIV-TNA is unavailable at 6 weeks, or test result is negative, continue dual therapy for first 6 weeks of life** • If positive, send second HIV-RNA or TNA sample and start ART without delay	Start CPT when infant is 4-6 weeks old. Rule out HIV by performing HIV-RNA or TNA PCR at 6 weeks or as soon as possible thereafter •If negative at 6 weeks, stop CPT •If positive send second sample of HIV-RNA or TNA and start ART without delay (continue CPT)
Infant identified as HIV exposed 'beyond' immediate postpartum period (after 72 hours of birth) (through infant or maternal HIV antibody testing)	Initiate maternal ART	**High Risk* +Breastfed^{o}** Start dual prophylaxis with twice daily AZT and once daily NVP for 12 weeks Rule out HIV by performing HIV-RNA or TNA PCR at 6	Start CPT when infant is 4-6 weeks old. Rule out HIV by performing HIV-RNA or TNA PCR at 6 weeks, and after cessation of breastfeeding •If negative at 6 weeks, stop CPT

and is breastfeeding		weeks or as soon as possible thereafter •In case HIV-TNA is unavailable at 6 weeks, or test result is negative, continue dual therapy for 12 weeks and arrange for HIV RNA/TNA testing soon as possible •If positive, send second sample of HIV-RNA or TNA and start triple ART without delay	•If positive send second sample of HIV-RNA or TNA and start ART without delay (continue CPT)
Infant identified as HIV exposed 'beyond' immediate postpartum period (after 72 hours of birth) (through infant or maternal HIV antibody testing) and is not breastfeeding	Refer mother for HIV care and evaluation for treatment	**High Risk* and Replacement feed** No prophylaxis. Rule out HIV by performing HIV-RNA or TNA PCR at the earliest thereafter or at 6 weeks • If positive send second sample of HIV-RNA or TNA and start ART without delay	Start CPT when infant is 4-6 weeks old. Rule out HIV by performing HIV-RNA or TNA PCR at 6 weeks or soon as possible thereafter •If negative at 6 weeks, stop CPT •If positive send second sample of HIV-RNA or TNA and start ART without delay (continue CPT)
Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue)	Determine an alternative ART regimen or solution; counsel regarding continuing ART without interruption	**Increase in Standard Risk during breastfeeding[o]** Continue infant NVP until 6 weeks after maternal ART is restarted Rule out HIV by performing HIV-RNA or TNA PCR at 6 weeks and after cessation of breast feeding • If negative, continue NVP until 1 week after breastfeeding has ended • If positive, second sample of HIV-RNA or TNA and start ART without delay	Start CPT when infant is 4-6 weeks old and continue till 1 week after breastfeeding ends. Rule out HIV by performing HIV-RNA or TNA PCR after cessation of breastfeeding • If negative stop NVP • If positive, second sample of HIV-RNA or TNA and start ART without delay

*High risk of maternal to child transmission during antepartum and/or peripartum period

[o]High risk of maternal to child transmission during breastfeeding (postpartum period)

3.6: Monitoring ART

3.6.1: Before initiation of ART

On their first visit to ART center, all patients should undergo an HIV test (HIV serology) for confirmation (see section 2.2). Following this, all patients should have a CD4 count done at baseline and then serially every 6 months regardless of baseline CD4 counts .

Patients should also be screened once for hepatitis B (by HBsAg), HCV (anti HCV) and for syphilis (by RPR). Additionally, in PWID and thalassemics, annual screening for HCV and HBV should continue. Screening for TB should be performed at each visit using the set of screening questions. A PPD and chest x ray may also be done at the time of the initial diagnosis (see section 4.2). Finally, as part of integrated delivery of care, assessment for presence of certain co-morbidities should be carried out. These include a clinical exam at each visit and a random blood sugar at the time of diagnosis (see section on 5.1.1).

3.6.2: At the time of initiation of ART

Once a decision to start ART has been made, certain baseline tests need to be sent in order to assess the safety of the regimen chosen, as well as to monitor future side-effects. These include:

a) pregnancy test (in child bearing women),
b) blood pressure measurement,
c) hemoglobin before starting AZT,
d) Kidney function tests including urine R/E, creatinine and estimated GFR (eGFR) before starting TDF
e) Alanine aminotransferase (ALT/SGPT) before starting NVP.

3.6.3: After initiation of ART

To assess response to the ART, VL should be conducted 3 months after the ART is started and then every 6 months thereafter. In certain instances, there may be a need for additional VL testing. For example VL should be checked at the time of diagnosis of pregnancy in patients who have become pregnant while on ART and again at 36 weeks of gestation. Similarly, VL should be checked earlier if therapy is changed (for reasons other than virological failure), e.g. in children being transitioned from a PI-based regimen to an NNRTI based regimen (see section 3.5.3). CD4 counts should be checked with the VL till the patient is documented to be virally suppressed. Once viral suppression has been achieved, routine CD4 counts are not required and patients need not be checked. Indications to continue monitoring CD4 counts despite virologic suppression include a CD4 below 350 cell/mm (in order to decide on holding prophylaxis) or clinical failure despite undetectable viral load (like in cases of HIV-2)

Moreover, patients on certain ART drugs should be tested periodically (every 3 to 6 months) to detect side effects. These include checking hemoglobin if on AZT, urine dipstick or Detailed Report (urine DR) and creatinine and eGFR if on TDF creatinine and Alanine aminotransferase (ALT/SGPT) if on NVP.

The table below summarizes the routine testing required in patients with HIV.

Table 3.5: Routine testing in PLHIV in relation to ART

Who	How often	Test / Evaluation
Baseline		
All patients	Once	HIV serology, HBsAg, HCV Ab, RPR, random blood sugar , CXR, CBC, Creatinine, ALT, /urine dipstick
Before starting ART		
All patients	At every visit	Clinical examination, screening for TB
	Every 6 months	CD4 count
PWID	Every year	HCV and HepBs Ag (if previously negative and unvaccinated)
MSM and SW	Every year	RPR and clinical screening for STIs
At the time of initiation		
In all patients	Once	Pregnancy test, clinical examination
If starting AZT	Once	Hemoglobin
If starting TDF	Once	Urine dipstick DR, creatinine/eGFR*
If starting NVP	Once	ALT
After initiation		
All patients	3 months after initiation and then every 6 months	VL, clinical examination, reinforcement of adherence
IF CD4 less than 350 cells/mm3 at the time of starting ART	Every 6 months	CD4 counts (till CD4 over 350 for 2 consecutive tests)
Suspected failure	Immediately	VL, CD4 counts and HIV resistance testing (if available)
If on AZT	Every 3 months	Hemoglobin
If on TDF	Every 3 months for the first year then 6 monthly Bone mineralization annually	Urine dipstick DR, creatinine/eGFR* Xray wrist/DXA scan

If on NVP	Every 3 months	ALT
If pregnant	At the time of establishment of pregnancy and at 36 weeks of gestation	VL
PWID	Every year	HCV and HepBsAg (if previously negative and unvaccinated)
Thalassemia/Disorders requiring regular blood product transfusions	Every year	HCV and HepBsAg (if previously negative and unvaccinated) Ferritin level to assess appropriateness of chelation

* eGFR can be calculated for adults as follows: $\frac{(age-140) \times weight}{72 \times creatinine}$ (multiply by 0.85 if female)

* eGFR can be calculated for children as follows: (0.41 × Height in cm) / Creatinine in mg/dL

3.7: Response and failure to ART

Monitoring individuals receiving ART is important to ensure successful treatment, identify adherence problems and determine whether ART regimens should be switched in case of treatment failure. Detecting failure earlier is essential, if this is due to poor compliance; interventions may be put in place quickly to improve compliance before the virus becomes resistant. Similarly, if resistant mutations do develop, switching therapy early will preserve future options. This is especially true for resistance in TDF-based regimens, where if stopped early, AZT susceptibility is maintained. Response may be assessed using virological criteria (VL measurement), immunologic criteria (CD4 counts) or clinical criteria (clinical signs and symptoms). Of these, the preferred means of assessing response and failure is using VL.

3.7.1: Clinical failure

Using clinical signs and symptoms is an inexpensive means of assessing if a patient has responded or is failing ART. However, this is extremely insensitive and non-specific and patients may often present very late or may appear to be failing but the change in condition is part of their clinical course (such as IRIS; see section3.10). Patients should therefore not be monitored solely on the basis of clinical response (or failure), though the following definitions may trigger earlier assessment for failure. Second-line ART should never be started based on clinical failure alone. Clinical failure is defined as:

a) Adults and adolescents

New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 conditions) after 6 months of effective treatment

b) Children

New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 conditions with exception of TB) after 6 months of effective treatment

3.7.2: Immunologic failure

Immunologic monitoring of patients using CD4 counts is a more accurate means of assessing failure as compared to clinical monitoring. However, using immunologic monitoring alone does pose certain difficulties. Firstly, CD4 counts tend to rise and fall more slowly compared to VL which leads to delays in detection of ART failure as well as difficulty in assessing if improving compliance has made an effect. Moreover, CD4 counts have lower sensitivity and positive predictive values for detecting failure compared to VL in both adults and children. This means that many cases of immunological failure may in fact have adequate virological suppression and are therefore at risk of being misclassified as having treatment failure and switched unnecessarily to second-line therapy. However, just as in clinical monitoring, immunologic monitoring may be used as a trigger to detect early virological failure. CD4 counts should therefore be checked twice yearly in all patients on ART. Finally in all cases of suspected immunologic failure, a concomitant infection must be ruled out, as this may decrease the CD4 counts. Immunologic failure is defined as

a) Adults and adolescents

CD4 count falls to the baseline (or below) OR a persistent CD4 levels below 100 cells/mm^3

b) Children younger than 5 years

Persistent CD4 levels below 200 cells/mm^3 OR CD4 <10%

c) Children older than 5 years

Persistent CD4 levels below 100 cells/mm3

3.7.3: Virological failure

Virological monitoring is the method of choice to assess response to ART. When compared with immunological and clinical monitoring, VL monitoring provides an early and more accurate indication of treatment failure and the need to switch to second-line drugs. This in turn reduces the accumulation of drug-resistance mutations and improves clinical outcomes. VL measurement can also serve as a proxy for the risk of transmission at the population level. VL should therefore be checked 3 months after starting or changing ART and every 6 months thereafter. A baseline VL, at the time of starting therapy is not required.

After 24 weeks of ART, any VL over 1000 copies/ml may indicate failure. In such cases, adherence must be reassessed and stressed (see section 5.2) and the VL rechecked 3 months later. If the VL remains over 1000 copies/ml, the patient should be labeled as virological failure and second-line ART initiated. In this case, resistance test is required or not ??. WHO recommend resistance after failure on second line ART.

It should also be noted, that "blips" or minor fluctuations in VL do occur on therapy and these are not associated with failure, development of resistance or with increased risk of transmission. A blip is defined as a VL of up to (but not more than) 1000 copies/ml in a previously suppressed patient followed by subsequent VLs of less than 50 copies/ml. Therefore, care must be taken to label a patient as virological failure only after 2 *consecutive* readings are over 1000 copies/ml (after correcting for adherence)

The definition for virological failure is therefore

Plasma VL above 1000 copies/ml (based on two consecutive viral load measurements within a 3 - month interval, with adherence support) after at least six months of using ARV drugs.

3.7.4: Drug Resistance testing and genotyping

Drug resistance in HIV is associated with various mutations, and therefore presence or absence of these mutations can help predict response. These mutations are detected using a process called genotyping. Currently the technology to perform genotyping is limited but may be expanded soon. If genotyping is available, this should be performed in all cases of treatment failure, especially those failing second-line therapy.

It should be noted that on stopping a failing regimen, the resistant (mutant) virus levels in the blood will decline over the next 2 weeks, to be replaced with the sensitive (or wild-type) virus. Therefore genotyping must be done *while the patient is still on the failing regimen.* Similarly, if a genotype is done after failing a second-line regimen, the viruses resistant to the first regimen may not be detected, though will re-emerge if the first-line therapy is restarted. Therefore it is important to interpret genotype results carefully and to seek expert advice before switching therapy based on this.

3.8: Drug toxicity

3.8.1: Tenofovir (TDF)

The main toxicity related to TDF is nephrotoxicity, characterized by proximal tubular cell dysfunction and may be associated with acute kidney injury or chronic kidney disease. Patients at risk of developing nephrotoxicity include older patients and those who already have underlying renal disease, are underweight (BMI <18.5 or body weight <50 kg), have untreated diabetes mellitus or hypertension or are using other nephrotoxic drugs or a boosted PI. As these patients are at risk of toxicity, a baseline creatinine should be performed before starting TDF. TDF should not started if the eGFR is <50 ml/min, or in patients with long-term diabetes, uncontrolled hypertension and renal failure.

TDF causes proximal tubular dysfunction (type 2 renal tubular acidosis) which leads to decreased reabsorption of glucose in the proximal tubules. Therefore the presence of glucose in a urine dipstick in patients, who do not have diabetes, is a cheap and fast

method of detecting TDF toxicity. In addition, patients on TDF should have blood pressure monitoring every visit to assess for hypertension.

TDF can also cause decrease in bone mineral density in children however the optimal method of evaluating the bone density is not available. X-Ray wrist/ DXA scanning may serve as a surrogate measure of bone mineralization. At this point it is unclear how reduced bone mineral density might impact future growth patterns or the risk of bone fracture. However, children on TDF should undergo regular growth monitoring on each visit.

Finally, while not a toxicity of TDF, it should be noted that *discontinuation* of TDF in a patient with HIV/HBV co-infection can lead to a flare of HBV..

3.8.2: Zidovudine (AZT)

AZT is associated with a risk of hematological toxicity and leads to macrocytic anemia. Risk factors for development of anemia include baseline anemia, neutropenia or a CD4 count of ≤200 cells/mm^3. Patients should therefore have hemoglobin checked before starting AZT, especially in adults and children with a low body weight, low CD4 counts and advanced HIV disease. In patients with severe anemia at baseline (hemoglobin <7.0 g/dl) AZT should be avoided as first-line therapy.

As with most NRTIs, AZT can also cause mitochondrial toxicity, manifested by lactic acidosis or severe hepatomegaly with steatosis. This is especially seen in patients who are overweight (BMI >25 or body weight >75 kg) or those who have had a prolonged exposure to nucleoside analogues. No laboratory monitoring is required for this, though this should be suspected in any patient on AZT presenting with abdominal pain or shortness of breath.

3.8.3: Nevirapine (NVP)

NVP can cause severe hepatoxocitiy, especially in patients with underlying hepatic disease, HBV and HCV co-infection or with concomitant use of hepatotoxic drugs. It is also seen more commonly when the CD4 count is high with rates higher in women with a CD4 ≥ 250 cells/mm^3 and men with a CD4 ≥ 400 cells/mm^3. The laboratory measurement of liver enzymes has very low predictive value to reflect development of liver toxicity in patients on NVP-containing regimens. However, monitoring hepatic enzymes is recommended, especially for women with HIV who have CD4 cell counts ≥250 cells/mm^3 and individuals with HIV who are co-infected wi th HBV or HCV. If possible NVP should be avoided in women with CD4 counts over 250 cells/mm^3.

NVP can also cause skin rash and in some cases Steven Johnson Syndrome. Though no clear risk factors have been identified for its development; however the presence of a rash should be clinically sought for in all patients on NVP at each visit to the clinic.

3.8.4: Efavirenz (EFV)

The main type of toxicity of EFV is related to the central nervous system, which typically resolves after a few weeks, and can be minimized by not taking the medication after a fatty meal. However, in some cases, they can persist for months or not resolve at all. Risk

factors for central nervous system side effects are pre-existing depression or other mental disorders and daytime sleepiness. Despite concerns about the potential risk of teratogenicity associated with using EFV during pregnancy, a recent meta-analysis (add reference) found no overall increase in the incidence of birth defects for first-trimester EFV exposure compared with other ARV drugs.

3.8.5: Abacavir (ABC)

The main concern with ABC is the Hypersensitivity reaction (HSR). This HSR is associated with the presence of the HLA-B*-5701 allele usually occurs in first 10-14 days and rarely after first 6 weeks. Patients with HSR will present with fever, GI symptoms, malaise, arthalgias/myalgias, respiratory problems (flu-like symptoms). However rash may be mild or altogether absent. Symptoms will usually resolve in the 3 to 5 days of holding ABC, however will worsen if the drug is not stopped. Importantly, if the patient is re-challenged with ABC after holding it for a HSR, a more severe and potentially fatal HSR may occur. There is also some suggestion that ABC is associated with an increased risk of cardiovascular events in patients with underlying ischemic heart disease.

3.8.6: Lopinavir/ritonavir (LPV/r)

LPV/r mainly causes gastrointestinal side effects especially diarrhea and nausea/vomiting. However as with the PIs, LPV/r is associated with metabolic side-effects, especially hypertriglyceridemia and the fat redistribution syndrome.

3.8.7: Raltegravir and Dolutegravir (RAL and DTG)

DTG may cause generally mild or moderate nausea, headache and diarrhea that do not limit treatment. Serious adverse effects include abnormal liver function, particularly in patients with HBV or HCV coinfection, and potentially serious hypersensitivity reactions (428). DTG is reported to affect renal function, with a 10% serum creatinine increase due to inhibition of renal transport protein and consequently an estimated reduction in creatinine clearance, but without any eGFR modification.

RAL has a favourable profile, with the most commonly reported adverse reactions – diarrhea, nausea and headache – reported as being mild to moderate and not limiting treatment. Severe adverse reactions – rash, hypersensitivity reactions, severe acute renal failure associated with rhabdomyolysis and depression – have been reported only rarely. RAL has also been linked to instances of Stevens-Johnson syndrome, which can be accompanied by hepatic involvement.

3.8.8: Management of ARV related toxicities.

Annexure 9 summarizes the side-effects and suggested management of commonly used ARVs in Pakistan.

The table below lists the lists the ARV related side-effects in a symptom directed fashion

Table 3.6: Common ARV side-effects and their management

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Adverse events	Major first-line ARVs	Recommendations
Hypersensitivity (Rash; Fever; Nausea, vomiting, diarrhea, abdominal pain; Malaise, general illness; Shortness of breath, cough, sore throat) Lactic acidosis Hepatic toxicity	ABC	Screen for other infectious viral causes. Early and regular follow up with warning clinical signs card to patient. Antihistamines can be given. If suspected, stop ABC. Replace with AZT or TDF.
Acute pancreatitis	d4T	Discontinue ART. Give supportive treatment with laboratory monitoring. Resume ART with an NRTI with low pancreatic toxicity risk, such as AZT or TDF.
Drug eruptions (mild to severe, including Stevens-Johnson syndrome or toxic epidermal necrolysis)	NVP EFV (less commonly)	In mild cases, symptomatic care. Rash due to EFV often stops spontaneously after 3–5 days without the need to change ART. If moderate rash, non-progressing and without mucosal involvement or systemic signs, consider a single NNRTI substitution (i.e. from NVP to EFV). In moderate and severe cases, discontinue ART and give supportive treatment. After resolution, resume ART with a PI-based regimen.
Dyslipidaemia	All NRTIs (particularly d4T) EFV	Consider replacing the suspected ARV
Anemia and neutropenia	AZT	If severe (Hb<7.0 g/dl and/or ANC <750 cells/mm^3), replace with an ARV with minimal or no bone marrow toxicity (e.g. d4T or TDF)
Hepatitis	All ARVs (particularly NVP)	If ALT is at more than five times the basal level, discontinue ART and monitor. After resolution, restart ART, replacing the causative drug (e.g. EFV replaces NVP).

Lactic acidosis	All NRTIs (particularly d4T)	Discontinue ART and give supportive treatment. After resolution, resume ART with TDF.
Lipoatrophy and lipodystrophy	All NRTIs (particularly d4T)	Early replacement of the suspected ARV drug (e.g. d4T for TDF or AZT)
Neuropsychiatric changes	EFV	Usually self-limited, without the need to discontinue ART. If intolerable to the patient, replace EFV with NVP or PI. Single substitution recommended without cessation of ART.
Renal toxicity (renal tubular dysfunction)	TDF	Consider substitution with AZT or ABC
Peripheral neuropathy	d4T	Replacement of d4T with AZT or TDF. Symptomatic treatment (amitriptyline, vitamin B6).

3.9: Drug interactions

A number of drugs may interact with ARVs and therefore it is essential that a list of medications that a patient is on, is obtained before ART is started and while therapy continues. Major drug interactions can be viewed at the following websites: www.who.int/hiv/pub/guidelines/arv2013/annexes and http://www.hiv-druginteractions.org/

A key contraindicated drug combination is rifampicin and PIs. When people co-infected with TB and HIV are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r can be used for the duration of TB treatment, by doubling the standard dose of LPV/r. For children, using a triple NRTI regimen (such as AZT + 3TC + ABC) should be considered. (see sections 3.5.4 and 4.2.4 for more details)

Ribavirin and peg-interferon alpha-2a are often used for treating HCV. Administration of these agents with AZT has been associated with an increased risk of anemia and hepatic decompensation. People co-infected with HCV and HIV and receiving AZT may need to be switched to TDF.

The newer HCV drugs may also interact with ART, especially the PI and the NNRTIs. Amongst the Directly Acting Antivirals (DAA) drugs for HCV, only sofosbuvir is considered to have the least interactions and can be used with ART. The second DAA, daclatasvir can be used with ARVs, however NNRTIs will reduce daclatasvir levels and therefore dose adjustment is required. While Velpatasvir is also recommended with sofosbuvir for genotype 3 HCV, this should not be used in patients on NNRTIs. It should also be noted that the older HCV treatment regimen comprising of ribavirin and

pegylated interferon alpha-2a has been associated with an increased risk of anaemia and hepatic decompensation when used with AZT

Itraconazole and ketoconazole are often used to treat fungal infections. Studies have shown that NVP may decrease the concentrations of these antifungal agents to sub-therapeutic levels. Alternative antifungal agents (such as fluconazole) could be used to ensure adequate treatment of fungal infections among people with HIV. However, it should be noted that fluconazole does not have any coverage for molds. In cases where itraconazole is being used to treat a mold infection, Amphotericin B should be used.

WHO recommends methadone and buprenorphine for treating opioid dependence. Co-administering EFV decreases methadone concentrations. This could subsequently cause withdrawal symptoms and increase the risk of relapse to opioid use. People receiving methadone and EFV should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose.

ARV drugs have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. Limited data suggest potential drug interactions between many ARV drugs (especially some NNRTIs and boosted PIs) and estrogen-based hormonal contraceptives. These interactions may alter the safety and effectiveness of both the hormonal contraceptive and the ARV drug. If women receiving ART decide to initiate or continue using hormonal contraceptives, consistently using condoms and other contraceptive methods is recommended both to prevent HIV transmission and to compensate for any possible reduction in the effectiveness of the hormonal contraception.

Concomitant use of boosted PIs and NNRTI with some antihistamine agents (such as astemizole and terfenadine) has been associated with severe and life-threatening reactions, such as cardiac arrhythmia. Alternative antihistamine agents include loratidine and cetirizine.

WHO recommends using statins for people with a 10-year cardiovascular risk exceeding 30%. Boosted PIs may lead to increased concentrations of lovastatin and simvastatin. Increased concentrations may increase the risk of developing serious adverse events such as myopathy (including rhabdomyolysis). Alternative dyslipidaemia agents should be used to prevent severe toxicity among people with HIV.

While co-administration of levothyroxine and ARVs has not been studied, ritonavir and efavirenz may lead to increased metabolism. Therefore, while levothyroxine can be used safetly with these drugs, TSH levels should be monitored closely when initially starting therapy. On the other hand Carbimazole and Propylthiouracil do not have any interactions with the available ARV agents.

The table summarizes the key interactions with the main ARVs used in Pakistan

Table 3.7: Key interactions with ARVs

ARV drug	Concomitant drug	Suggested management
AZT	Ribavirin and peg-interferon alfa-2a	First-line: substitute AZT with TDF Second-line: substitute AZT with d4T

Boosted PI (ATV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the PI dose Substitute with three NRTIs (for children)
	Lovastatin and simvastatin	Use an alternative dyslipidaemia agent (for example pravastatin)
	Estrogen-based hormonal contraception	Use alternative or additional contraceptive methods
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	TDF	Monitor renal function
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate
	Estrogen-based hormonal contraception	Use alternative or additional contraceptive methods
	Astemizole and terfenadine	Use an alternative anti-histamine agent
NVP	Rifampicin	Substitute NVP with EFV
	Itraconazole and ketoconazole	Use an alternative antifungal agent (for example fluconazole or Amphotericin B)
DTG	Carbamazepine, phenobarbital and phenytoin	Use alternative anticonvulsant agent
	Polyvalent cation products containing Mg, Al, Fe, Ca and Zn	Use DTG at least 2 hours before or at least 6 hours after supplements containing polyvalent cations

3.10: IRIS

IRIS is a spectrum of clinical signs and symptoms thought to be associated with immune recovery brought about by a response to ART. It is a widely recognized phenomenon that occurs among 10–30% of the people initiating ART, usually within the first 4–8 weeks after initiating therapy. It may present in two different ways: paradoxical IRIS, when an opportunistic infection or tumor diagnosed before ART initially responds to treatment but then deteriorates after ART starts; or unmasking IRIS, in which initiating ART triggers disease that is not clinically apparent before ART. It should be considered only when the presentation can not be explained by a new infection, expected course of a known infection or drug toxicity.

The clinical spectrum is diverse, and IRIS has been reported for many different infections, tumors and non-infectious conditions. The most serious and life-threatening forms of paradoxical IRIS are for TB, cryptococcosis, Kaposi's sarcoma and herpes zoster. BCG vaccine–associated IRIS (localized and systemic) may occur in infants infected with HIV. A low CD4+ cell count (<50 cells/mm^3) at ART initiation, disseminated opportunistic infections or tumors and a shorter duration of therapy for opportunistic infections before ART starts are the main risk factors. IRIS is generally self-limiting, and interruption of ART is rarely indicated, but people may need to be reassured in the face of protracted symptoms to prevent discontinuation of or poor adherence to ART.

The most important steps to reduce the development of IRIS include: earlier HIV diagnosis and initiation of ART before a decline to below 200 CD4 cells/mm^3; improved screening for opportunistic infections before ART, especially TB and Cryptococcus; and optimal management of opportunistic infections before initiating ART. Timing of ART in people with opportunistic infections requires balancing a greater risk of IRIS after early initiation against continuing high mortality if ART is delayed (see sections 3.4.1, 4.2.4 and 4.3).

3.11: Second and Third line ART

3.11.1:Adults/adolescence

In patients who are failing their first-line therapy, the NRTI backbone should be modified, so that TDF (or ABC) is switched to AZT. Alternatively, if AZT was used in the initial regimen this should be changed to TDF. In both circumstances, 3TC or FTC should be continued as it is. On the other hand, the third drug should be switched to a boosted PI (such as LPV/r or ATV/r), regardless if this was an NNRTI (EFV or NVP) or an integrase inhibitor (RAL or DTG).

Rarely, it may not be possible to start AZT (e.g. due to profound anemia), and in such cases a two drug combination of RAL + LPV/r may be used as a second alternative, provided that RAL was not part of the initial failing regimen.

For HIV and HBV co-infected patients, both TDF and 3TC should be continued in the second-line regimen for their anti-HBV activity as well as to reduce the risk of hepatic flares. However, a third NRTI should be added to the regimen (e.g. changing TDF+3TC+EFV to AZT+TDF+3TC+LPV/r).

For people with active TB disease receiving rifampicin, all boosted PIs in standard doses are contraindicated because of drug interactions and significant reductions in PI plasma concentrations. In this situation, LPV/r must be used with an adjusted dose of LPV/r 800 mg/200 mg twice daily. However, this is associated with high levels of toxicity and requires close clinical and laboratory monitoring. Alternately, if rifabutin is used in place of rifampicin, all boosted PIs can be concomitantly administered in their standard doses.

3.11.2: Children

Recommending potent and effective second-line regimens for infants and children is especially difficult because of the current lack of experience in resource-limited settings and the limited formulations available. The second-line regimen used in children therefore depends on which initial regimen the child was on a priori.

Children less than 3 years of age

After failure of a first-line LPV/r-based regimen, children on the preferred regimen of ABC+3TC+LPV/r should be switched to AZT+3TC+RAL. However, if the child was on the alternate regimen of ABC+3TC+NVP this should be changed to AZT+3TC+LPV/r .

Children older than 3 years of age

The second line therapy in children older than 3 years will depend on if they were changed over from the preferred infant regimen or not. If they are still on ABC+3TC+LPV/r should be switched to AZT+3TC+EFV. However if they had been switched over to ABC+3TC+EFV, the regimen should be changed to AZT+3TC+LPV/r

Table 3.8: Second line regimens across age groups.

	Target population		**First-line ART regimen**	**Second-line ART regimen**
Adults and adolescents (≥10 years)	No additional comorbidities/co-infections		If AZT was used in first-line ART	TDF + 3TC + LPV/r
			If TDF or ABC was used in first line ART	AZT + 3TC + LPV/r
	Pregnant women		Same regimens recommended as above	
	HIV and TB co-infection		Rifabutin available	Standard PI-containing regimens as above
			Rifabutin not available	Same NRTI backbones plus double-dose LPV/r (LPV/r 800 mg /200 mg BID)
	HIV and HBV co-infection		If AZT was used in first-line ART	TDF + 3TC+LPV/r
			If ABC was used in first line ART	AZT + 3TC+LPV/r
			If TDF was used in first line ART	AZT + TDF + 3TC+LPV/r
Children	Younger than 3 years	ABC used in backbone	ABC + 3TC + LPV/r	AZT + 3TC + RAL
			ABC + 3TC + NVP	AZT + 3TC + LPV/r
		AZT used in backbone	AZT + 3TC + LPV/r	ABC + 3TC + RAL
			AZT + 3TC + NVP	ABC + 3TC + LPV/r
	Older than 3 years	ABC used in backbone	ABC + 3TC + LPV/r	AZT + 3TC + EFV
			ABC + 3TC + EFV	AZT + 3TC + LPV/r
		AZT used in backbone	AZT + 3TC + LPV/r	TDF + 3TC + EFV
			AZT + 3TC + EFV	TDF + 3TC + LPV/r

3.11.3: Third Line Drugs

There are a very limited number of third line drugs currently available in the country. These include Abacavir and Raltegravir. However, choosing third line regimens is complicated and a robust regimen must be selected by taking in account previous ART regimens the patient has been on and predicting the logical resistance mutations which may have subsequently developed. This is essential as there may be cross resistance between Abacavir with AZT and TDF (depending on the mutation) and while raltegravir is a potent antiretroviral drug, it has a low barrier of resistance (i.e. resistance can develop rapidly). DRV/r is a newer generation PI which may be active in cases where

there is resistance to LPV/r and if possible should be part of the salvage regimen in a patient failing second line therapy.

Therefore whenever possible, the regimen must be guided with the help of a genotype (if available, see section 3.7.4), sent while on the failing regimen (or not more than 2 weeks after holding it). Finally third line drugs must also always be selected in consultation with an expert with experience in managing treatment experienced individuals.

Table 3.9: Suggested 3rd line options based on prior regimens

Population	First line regimen	Second line regimen	Third line regimen
Adult and adolescent	2 NRTI +EFV	2 NRTI +LPV/r	DTG (or RAL) +DRV/r ± 1-2 NRTIs
Pregnant or Breast Feeding women	2 NRTI +EFV	2 NRTI +LPV/r	DTG (or RAL) +DRV/r ± 1-2 NRTIs
Children (0-10 years)	2 NRTI +LPV/r	If less than 3 years: 2 NRTI + RAL	DTG (or RAL) +DRV/r + 1-2 NRTIs
		If more than 3 years: 2 NRTI + RAL or EFV	
	2 NRTI +EFV	2 NRTI +LPV/r	

Section 4: Co-infections and opportunistic : Management/Screening/Prevention

4.1: PCP and trimethoprim-sulfamethoxazole prophylaxis

Pneumocystis jiroveci pneumonia (PCP) (formerly *Pneumocystis carinii* pneumonia) is an often fatal, fungal infection of the lungs, predominately seen in patients with a CD4 count below 200 cells/mm^3. Moreover, children less than 12 months of age have the highest risk of PCP, with peak age of 3-6 months. Patient presenting with PCP will complain of dry cough, tachypnea, dyspnea and cyanosis/hypoxia while chest-x-ray may demonstrate any number of findings (including a normal x-ray). Treatment is with co-trimoxazole (with steroids in patients with severe hypoxia). In patients with severe co-trimoxazole allergy, primaquine with clindamycin may be used.

4.1.1: CPT indications

Co-trimoxazole preventive therapy (CPT) not only prevents PCP but also lowers the incidence of toxoplasma and bacterial infections. In adults, CPT should be provided to all symptomatic patients with a WHO clinical stage of 3 or 4. Additionally, all patients with a CD4 cell count ≤350/mm^3, should be started on CPT regardless of symptoms. Co-trimoxazole is safe in pregnancy and should be used even if the patient is pregnant.

Given the high rates and mortality in children under 1 year, CPT is recommended for all HIV-exposed infants starting at 4–6 weeks of age (or at first encounter with the health care system) and continued until HIV infection can be excluded. CPT is also recommended for HIV exposed breastfeeding children of any age, and should be continued until HIV infection can be excluded by HIV antibody testing (beyond 18 months of age) or virological testing (before 18 months of age) at least six weeks after complete cessation of breastfeeding.

Similarly, all children with an established HIV infection, who are younger than one year of age, should receive CPT regardless of symptoms or CD4 percentage. In these children, CPT should be continued till 5 years of age, after which they should be re-assessed based on adult criteria. In children diagnosed to have HIV between the ages of 1 year and 5 years CPT should be started if they are either symptomatic (WHO clinical stages 2, 3 or 4) or any clinical stage and a CD4 <25%. In children older than 5 years, CPT should be started based on adult recommendations.

4.1.2: Discontinuation of CPT

As mentioned above, CPT which was started in infants exposed to HIV at age 4-6 weeks can be stopped as soon as HIV has been ruled out. CPT started in children under 1 year of age with proven HIV should receive co-trimoxazole till at least 5 years of age, after which the decision to continue will depend on their immune status. Similarly once CPT is started in a child between the ages of 1 year and 5 years, it should be continued till at least 5 years of age, after which the decision to continue will depend on their immune

status. CPT started in adults, adolescents and children over 5 years of age may be stopped once the CD4 is ≥350 cells/mm^3 after 6 months of ART.

The table below summarizes the indications and criteria for discontinuation in various age groups.

Table 4.1: Indications and criteria for discontinuation of CPT

Age	Criteria for initiation	Criteria for discontinuation	Monitoring approach
HIV exposed infants	In all, starting at 4–6 weeks after birth	Until the risk of HIV transmission ends or HIV infection is excluded	Clinical at-least 3-monthly Intervals with CBC
<1 year	In all	Until 5 years of age and then re-assess	Clinical at-least 3-monthly Intervals with CBC
1–5 years	WHO clinical stages 2, 3 and 4 regardless of CD4 % OR Any WHO stage and CD4 <25%	Until 5 years of age and then re-assess	Clinical at 3-monthly Intervals with CBC
≥5 years, including adults	Any WHO stage and CD4 count <350 cells/mm^3 OR WHO 3 or 4 irrespective of CD4 level	when CD4 ≥350 cells/mm^3 after 6 months of ART	Clinical at 3-monthly Intervals with CBC

4.1.3: CPT in co-trimoxazole allergic patients

Children with a history of severe adverse reaction (grade 4 reactions such as exfoliative dermatitis, Stevens-Johnson syndrome or erythema multiforme, moist desquamation) to co-trimoxazole or other sulfa drugs and children with known glucose-6-phosphate dehydrogenase deficiency should not be prescribed CPT. Of note, routine testing for glucose-6-phosphate dehydrogenase deficiency is not recommended. Dapsone 2 mg/kg once daily, if available, is an alternative. Unfortunately, some children cannot tolerate either co-trimoxazole or dapsone and no alternative recommendation can be made in these circumstances.

Adults in whom co-trimoxazole cannot be continued or initiated due to adverse effect, dapsone 100 mg per day, if available, can be used as an alternative. However it should be pointed out that dapsone is less effective than co-trimoxazole in preventing PCP and also lacks the broad antimicrobial activity of co-trimoxazole.

Finally for mild to moderate allergic reactions, desensitization may be done using escalating doses of co-trimoxazole. Such patients should be referred to a tertiary care center where this facility is available.

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4.1.4: CPT doses

For adults, the dose of co-trimoxazole is 800/160mg once daily (2 tablets of the single strength formulation or one tablet of the double strength formulation). The dose of 400/80 mg may be used in some circumstances (moderate anemia).

See annexure 8 for dosing in children across different weight bands.

4.2: TB

Among people living with HIV, TB is the most frequent life-threatening opportunistic infection and a leading cause of death. ART should therefore be provided to all people with HIV with active TB disease. Details of ART in TB co-infected patients are outlined in section 3.4.1. Patients co-infected with HIV and TB should receive the standard anti-tuberculous regimens. Care should be taken that at least six months of a rifampicin containing regimen is used and therefore the use of the INH-ethambutol combination in the continuation phase is discouraged. Moreover, the optimal dosing frequency is daily during the intensive and continuation phases. Finally Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having HIV-associated TB or multidrug-resistant TB.

For children with HIV and TB, correct dosages of ATT should be used (INH 10mg/kg, Rifampicin 15mg/kg, Pyrazinamide 35-40mg/kg). If the child is WHO stage 1-2 and CD4 count is above need for ART then ATT should be completed before considering ART. If child has WHO stage 3 with a high CD4 count, ART can be started 2 months after ATT and child kept under close monitoring. If clinical WHO stage 4 or stage 3 with low CD4 count, then ATT should be initiated promptly and ARV within 2-8 weeks. If the child is already stable on an ART regimen and develops TB while on therapy, the regimen should be adjusted as suggested in annexure 7.

HIV care settings should also implement the WHO Three I's strategy:

- Intensified TB case-finding
- Isoniazid preventive therapy (IPT)
- Infection control at all clinical encounters.

4.2.1: Intensified TB case-finding

All adults and adolescents living with HIV should be screened at each encounter for TB using a clinical algorithm. The algorithm in annexure 9 uses the absence of clinical symptoms of; current cough, fever, weight loss or night sweats to identify adults and adolescents living with HIV who are *unlikely* to have active TB disease. Patients who do

not have any of these symptoms have a very low probability of having active TB and will therefore qualify to receive IPT. However, these symptoms are non-specific for active TB and therefore patients who have any one of the four symptoms should be evaluated for TB and other diseases and should not be given IPT unless active TB has been ruled out. Similarly, children living with HIV can be screened at each visit using the following set of questions: poor weight gain fever or current cough or contact history with a TB case. Poor weight gain is defined as reported weight loss, or very low weight (weight-for-age less than –3 z-score), or underweight (weight-for-age less than –2 z-score), or confirmed weight loss (>5%) since the last visit, or growth curve flattening.

For diagnosing TB, Xpert MTB/RIF should be used rather than conventional microscopy, culture and drug susceptibility testing (DST) as the initial diagnostic test in adults and children suspected of having multidrug-resistant TB (MDR-TB) or HIV-associated TB. Xpert MTB/RIF should also be used in preference to conventional microscopy and culture for cerebrospinal fluid specimens from patients suspected of having TB meningitis. Finally Xpert MTB/RIF may be used as a replacement test for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB, however care must be taken in interpreting negative results in certain cases (such as pleural fluid samples) where the Xpert MTB/RIF has a very poor sensitivity in detecting TB.

4.2.2: Isoniazid preventive therapy (IPT)

IPT reduces the risk of developing active TB in patients with HIV and the effect of IPT is highest in patients who are Tuberculin Skin Test (TST) positive. In patients who are TST negative, IPT provides a slight reduction in the chance of developing active TB, though this is small and not statistically significant. Therefore it is preferred to provide IPT to all patients who screen negative for active TB by clinical history (see section 4.2.1) and are TST positive. However, if a TST cannot be performed, then IPT can be provided regardless of the TST status.

Children living with HIV:

- Who do not have poor weight gain, fever, current cough, and are unlikely to have active tuberculosis, should be offered IPT.
- Who are over 12 months of age, and are unlikely to have active TB, should receive 6 months of INH preventive therapy (10 mg/kg) as part of a comprehensive package of HIV.
- Who are over 12 months of age, and have successfully completed a course of Tuberculosis treatment should receive INH for an additional 6 months.
- Who have a history of contact with a TB case should receive 6 months IPT.
- Who have poor weight gain, fever and cough, may have active tuberculosis and should be evaluated for TB and other diseases.

IPT for 6 months should be given to patients with HIV irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

The dose of IPT in adults should be 300 mg per day while for children 10 mg/kg/day co-administered with B6 (see annexure 7 for dosing across different weight bands).

4.2.3: Infection control at all clinical encounters

People living with HIV are at high risk of acquiring TB in health care facilities and congregate settings. Each health care facility should have a TB infection control plan for the facility that includes administrative, environmental and personal protection measures to reduce the transmission of TB in health care and congregate settings and surveillance of TB disease among workers. These measures include:

Administrative (facility-level infection control committee and protocols)

- A triage system to identify people suspected of having TB.
- Separate people with suspected or confirmed TB.
- Cough etiquette and respiratory hygiene.
- Rapid diagnosis with Xpert MTB/RIF (with prompt treatment of active TB).

Health care workers

- Surveillance and information dissemination
- Package of care for HIV-positive workers (ART and isoniazid preventive therapy)
- Protective equipment (particulate respirator masks that meet or exceed N95 standards)
- Relocation for health care workers living with HIV to a lower-risk area

Environmental

- Ventilation (mechanical or natural)
- Upper-room ultraviolet germicidal irradiation

Personal

- Spend as much time as possible outside
- Cough etiquette
- Sleep alone while smear-positive
- Avoid congregate settings and public transport while smear-positive

4.2.4: Principles of treatment of TB in HIV patients

While the treatment of TB in HIV follows the same principles as in a non-HIV infected person, it should be noted that patients with TB/HIV co-infections should receive at least six months of a rifampicin-containing treatment regimen. Also intermittent dosing is not recommended in HIV patients with TB.

Unique to HIV/TB co-infected patients are the drug-drug interactions and the optimal time to start ARVs. Briefly, care must be taken when rifampicin and LPV/r are given

together and in such cases the dose of LPV/r must be doubled. Moreover, NVP is not recommended with rifampicin and in such cases this should be changed to EFV in adults and children above 3 years or a triple NRTI regimen in children less than 3 years. Children less than 3 years who are already on a NVP-based regimen and cannot be shifted to triple NRTI can receive an increased NVP dosage (a 30% increase can be considered). (see section 3.5.4 for more details regarding ART in infants with TB). RAL may also be used as an alternative which may be used in place of NVP though efficacy is not known at this time due to potential reduction in levels by rifampin..

MDR TB and HIV co-infection poses a unique challenge, as mortality is higher if treatment for HIV is not initiated promptly. However, drug-drug interactions are not thought to be of concern as rifampin is not used in the MDR regimen and while the exact metabolic pathways of some second-line drugs (e.g. ethionamide, cycloserine, para-amino salicylate) is not clearly understood, it is believed most of these drugs will not have significant drug-drug interactions.

Due to the risk for IRIS (see section 3.10), if TB and HIV are diagnosed simultaneously then ATT should be started first followed by ARVs within 8 weeks. However, in CNS TB, ARV should not be started till at least 8 weeks of ATT has completed. On the other hand in patients with a CD4 count of <50 cell/mm^3 or those with MDR TB, ARV should be started within the first 2 weeks of starting ATT.

Table 4.2: Timing of starting ART in patients with TB/HIV co-infection

Criteria	CD4 Count	TB Treatment	Antiretroviral therapy
Non-MDR Pulmonary TB	>50 cell/mm^3	Start Immediately	Start between 2 to 8 weeks of starting ATT
Non MDR Extra pulmonary TB (**except CNS TB**)	>50 cell/mm^3	Start Immediately	
Non-MDR Pulmonary TB	<50 cell/mm^3	Start Immediately	Start within 2 weeks of starting ATT
Non MDR Extra pulmonary TB (**except CNS TB**)	<50 cell/mm^3	Start Immediately	
MDR pulmonary or extra pulmonary TB (**except CNS TB**)	Any	Start Immediately	
CNS TB (regardless of MDR status)	Any	Start Immediately	Start after 8 weeks of starting ATT

4.3: Cryptococcus

Cryptococcal meningitis is one of the most important opportunistic infections and a major contributor to mortality before and after ART is initiated. Cryptococcus meningitis presents as chronic meningitis with symptoms which may be very subtle such as personality changes and confusion. Often the typical signs and symptoms of acute meningitis like high fevers and neck stiffness are absent. Therefore, a high index of suspicion must be kept in any patient with central nervous system complaints, especially if the CD4 count is below 100 cells/mm^3. Prompt lumbar puncture with measurement of

CSF opening pressure and rapid CSF CrAg assay (either LA or LFA) is the preferred diagnostic approach. While an India ink test in the CSF may be done, this is less sensitive than a CrAg.

For therapy, a two-week induction phase with amphotericin B combined with fluconazole or an eight-week induction with high dose fluconazole should be followed by 8-weeks consolidation therapy with fluconazole. Once therapy has ended, secondary prophylaxis/maintenance therapy should be given with lower dose fluconazole. Secondary prophylaxis /maintenance therapy in adults, adolescents and children above two years of age can be discontinued when patients are stable and adherent to ART and anti-fungal therapy for at least one year with evidence of immune reconstitution. On the other hand, in children aged less than two years with successfully treated cryptococcal disease, anti-fungal maintenance treatment should NOT be discontinued. Primary prophylaxis or routine checking of CrAg is not recommended.

ART initiation is not recommended in patients with cryptococcal meningitis due to the high risk of IRIS with central nervous system disease, which may be life-threatening. In patients with a recent diagnosis of cryptococcal meningitis, ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy and after four weeks of treatment.

The table below summarizes the regimens for cryptococcal meningitis with the recommended doses and durations

Table 4.3: Summary recommendations of treatment of cryptococcal meningitis

	Amphotericin B availability	**Pre-hydration, electrolyte replacement, toxicity monitoring and management**	**Induction phase options**	**Consolidation phase options (8 weeks)**	**Maintenance/ secondary prophylaxis options**
Adults	Available	Available	Amphotericin 0.7-1 mg/kg/day (2 weeks) + fluconazole 800 mg/day (2 weeks)	Fluconazole 400-800 mg/day	Fluconazole 200 mg once daily
	Available	Not available for full 2 week induction period	Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 800 mg/day (2 weeks)	Fluconazole 800 mg/day	
	Not available	Not available	Fluconazole 1200 mg/day (8 weeks)	Fluconazole 800 mg/day	
	Available	Available	Amphotericin 1-1.5 mg/kg/day once	Fluconazole 10-12 mg/kg/ day	Fluconazole 6 mg/kg/day up to 200

			daily alone or in combination with + fluconazole 12 mg/kg/day on day 1 and then 10-12mg/kg/day IV	(max 800 mg/day) once daily IV or by mouth for a minimum of 8 weeks	mg/day once daily by mouth
	Available	Not available for full 2 week induction period	Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 12 mg/kg/day up to 800 mg/day (2 weeks)	Fluconazole 10-12 mg/kg/day (max 800 mg/day) once daily IV or by mouth for a minimum of 8 weeks	
	Not available	Not available	Fluconazole 12 mg/kg/day on day 1 and then 6-12mg/kg IV or by mouth (up to 1200 mg/day)	Fluconazole 12 mg/kg/day up to 800 mg/day	

[a] Duration of therapy for non-CNS disease depends on site, severity of infection and clinical response.

Once a patient has completed the consolidation therapy, secondary prophylaxis with fluconazole (200 mg/day) must be continued on all patients. Duration for adults is for at least one year AND with two readings of a CD4 count greater or equal to 100 cells/mm^3 (done 6 months apart) AND an undetectable VL. However if VL is not available then fluconazole should only be stopped after at least 1 year of therapy AND two readings of a CD4 count greater or equal to 200 cells/mm^3 (done 6 months apart). In children, secondary prophylaxis can be discontinued if ALL of the following criteria are fulfilled: age ≥6 years, asymptomatic on ≥12 months of secondary prophylaxis, CD4≥100 cells/mm^3 with undetectable viral load on ART at least 3 months. In all patients secondary prophylaxis must restarted if the CD4 drops below 100 cells/mm^3.

4.4: Mycobacterium Avium Complex

Mycobacterium avium complex (MAC) refers to infections caused by either *M. avium* or *M. intracellular.* Both strains cause identical infections and are diagnosed, managed and prevented similarly. The major risk factor for development of MAC in PLHIV is a CD4 cell count of <50 cells/mm^3. Incidence also varies geographically, and while rates in Pakistan are not known, these tend to be higher in the US and lower in Africa. Symptoms of disseminated MAC are nonspecific and include low grade fever, night sweats, abdominal pain, diarrhea, and weight loss. Diagnosis of MAC is problematic, given the lack of ability in most facilities to perform AFB blood cultures. Bone marrow cultures for AFB may be positive and CT scan may show lymphadenopathy (though may also be normal). Therefore in patients with a CD4 count of less than 50 cells/mm^3 and non-specific systemic complaints, empiric treatment of MAC with clarithromycin and ethambutol

may be considered if alternative causes have been ruled out. On the other hand, MAC prophylaxis should be avoided in a patient suspected of MAC in order to prevent development of resistance.

MAC prophylaxis is indicated in PLHIV with a CD4 count of <50 cells/mm^3. The preferred prophylactic regimen is Azithromycin 1500 mg once weekly. Prophylaxis should continue for three months after the CD4 is over 100 cells/mm^3.

MAC prophylaxis is indicated in children with severe immune-suppression (age <1 year with CD4 <750 cells/mm^3, age 1 to <2 years with CD4 <500cells/ mm^3, age 2 to <6 years with CD4 <75cells/ mm^3, age ≥6years with CD4 <50cells/mm^3). The preferred regimen is azithromycin 20mg/kg once weekly or clarithromycin 7.5mg/kg given twice daily. MAC prophylaxis cannot be discontinued in children <2 years. It can be discontinued after ≥6 months of ART in age 2 to <6 years with CD4 >200 cells/mm^3 for >3 consecutive months, and, in age ≥ 6years with CD4 >100cells/mm^3 for > 3 consecutive months.

4.5: Hepatitis B and C

Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV, including those on ART. A comprehensive approach includes prevention, hepatitis B and hepatitis C screening (see section 3.6), hepatitis B vaccination (see section 4.7) and treatment and care for people with HIV co-infected with hepatitis B and/or hepatitis C. Earlier guidelines recommended ART for all people co-infected with HIV and HBV regardless of CD4 count in those with evidence of severe chronic liver disease. Severe chronic liver disease includes cirrhosis and end stage liver disease, categorized into compensated and uncompensated. Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, spontaneous bacterial peritonitis, variceal hemorrhage and hepatic encephalopathy), sepsis or liver insufficiency. These guidelines of treatment have now been superseded by the new recommendation that all HIV infected individuals should receive ART irrespective of comorbidities. Nevertheless in settings where prioritization is required, people co-infected with HIV and HBV and evidence of severe chronic liver disease should be considered a priority for ART. WHO recommends that adults, adolescents and children with chronic hepatitis B and clinical evidence of cirrhosis (or cirrhosis based on non-invasive APRI test score more than 2 in adults) should be treated regardless of ALT, HBeAg status and HBV DNA levels. WHO guidelines for prevention, care and treatment of people with chronic hepatitis B provide recommendations on who should receive HBV treatment and recommend the use of NRTIs or entecavir for this treatment. The recommended NRTIs for HIV-HBV coinfection are TDF and 3TC or FTC. However of these, only TDF is recommended in WHO HBV guideline for HBV monoinfection. Lack of TDF in treatment regimen will lead to HBV flares due to ART-related IRIS. Discontinuation of 3TC has been associated with HBV reactivation, ALT flares, and in rare cases hepatic decompensation. If ARV drugs need to be changed due to toxicity or resistance, then TDF+3TC should be continued in addition to other drugs.

HCV-related liver disease progresses more rapidly in HIV-infected people. Treatment is therefore a priority. However, the decision to treat HIV-HCV is more complex than HCV alone because response rates are lower, the risk of potential toxicities is higher and treatment is complicated by a high pill burden, overlapping toxicities, and interactions between drugs used for treating HCV and HIV. In general, clinical stabilization of HIV disease with ART is advisable prior to starting treatment for HCV, especially in people with advanced immune suppression (CD4≤200 cells/mm^3). HCV treatment using older regimens (pegylated interferon and ribavirin) generally yielded low rates of success among HIV/HCV co-infected patients, but outcomes for HCV therapy using the newer, all oral direct-acting antivirals (DAAs) in HIV-HCV co-infected patients are comparable to those with HCV mono-infection. See appendix 16 and 17 for details regarding treatment regimens for HCV and section 3.9 regarding interactions of the newer DAA and ARVs.

Additional guidance can be sought from the following resources:.

(http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guidelines/en)

(http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en)

(www.who.int/hiv/pub/guidelines/hepatitis/en/index.html)

4.6 Sexually transmitted infections

HIV, other sexually transmitted infections and non-sexually transmitted infections of the reproductive tract frequently coexist. Most of these infections are asymptomatic, especially among women. However, even asymptomatic sexually transmitted infections can cause complications, get transmitted to sexual partners and enhance HIV transmission risk. On the other hand HIV infection alters the natural history of sexually transmitted infections.

The objectives of diagnosing and managing STIs include identifying the infection and providing appropriate treatment and preventing transmission. Screening, diagnosis and treatment of STIs should be offered routinely as part of comprehensive HIV care among adults and adolescents.

Diagnosis and treatment of the commonly encountered STIs are as follows

4.6.1: Syphilis

Clinical manifestations

Syphilis is transmitted through either sexual contact with the infectious lesions of the mucous membranes, via blood transfusion, or transplacentally to the fetus. The disease is classically divided into 2 stages, early syphilis (which includes primary syphilis, secondary syphilis and early latent syphilis and late syphilis (which include late latent syphilis and tertiary syphilis). Primary syphilis presents as a solitary, painless chancre at the site of inoculation in the vagina, penis or anus though may also be extra-genital. The primary lesion begins after a mean incubation period of 21 days and initially

appears as a raised papule which ulcerates and heals spontaneously within 3 to 10 weeks. Depending on the location, this is often missed by patients. However if untreated, the disease progresses to the secondary stage, four to eight weeks after the appearance of the primary lesion. The typical rash in secondary syphilis involves the skin (including palms and soles) and mucosal membranes, but is very variable and can be easily missed as well. In warm and moist areas of the body, such as the anus and labia, large white or grey raised lesions (condylomata lata) may develop as a result of the spread of the treponemes from the primary lesion and may be mistaken for warts. Following secondary syphilis, latent syphilis develops which is characterized by positive syphilis serology with no clinical symptoms or signs. Latent syphilis is often divided in two phases: early latent syphilis (within 2 years of the infection) and late latent syphilis (beyond 2 years of the infection). Differentiating between the two is important as treatment duration in both varies. Of note, while sexual transmission typically occurs only during primary, secondary and early latent infection, Mother-to-child transmission has been documented to occur up to several years after initial infection. In about 25% of untreated patients, clinical sequelae of tertiary syphilis may develop. These include neurological disease , cardiovascular disease (cardiosyphilis) and gummatous lesions (gumma). Neurosyphilis can occur at any stage of syphilis infection, though manifestation vary depending on the time of presentation. Early neurological manifestations include acute changes in mental status, meningitis, stroke, cranial nerve dysfunction and auditory or ophthalmic and ocular abnormalities. Late neurosyphilis occurs 10–30 years or more after infection and is characterized by tabes dorsalis and general paresis. The most common manifestation of congenital syphilis is second or third trimester fetal loss or premature labor. Infants born to mothers with positive syphilis serology should be examined for signs and symptoms of early congenital syphilis, including bullous rash, rhinitis, laryngitis, lymphadenopathy, hepatosplenomegaly, osteochrondritis, periostitis, meningitis and chorioretinitis. The signs of late congenital syphilis infection in children over the age of 2 years includes inflammatory manifestations affecting the eyes, ears and joints, as well as skeletal malformations. However many infants with syphilis infection will not have any manifestations.

Diagnosis

Diagnosis is done by the two types of serological tests for syphilis: non-treponemal and treponemal. However to confirm the diagnosis, both a non-treponemal and a treponemal test must be positive. The most widely available non-treponemal tests are the Venereal Diseases Research Laboratory (VDRL) and the rapid plasma reagin (RPR) tests. These non-treponemal are not highly specific for syphilis and can give false-positive results in a variety of conditions such as acute febrile viral infections and some chronic autoimmune diseases. Also non-treponemal tests may be negative for up to four weeks after the lesion of primary syphilis and can be negative in late latent syphilis. However, a negative non-treponemal test at three months after onset of the primary chancre virtually excludes the diagnosis of syphilis. Finally non-treponemal tests may be qualitative or quantitative. Quantitative non-treponemal test titres are used to monitor response to treatment with a four-fold reduction (e.g. from 1 : 16 to 1 :

4) after 3 to 6 months signifying effective treatment. Titres that differ by only one dilution (e.g. 1 : 8 versus 1 : 4 or 1 : 2 versus 1 : 1) are not considered significant.

Treatment

In adults and adolescents with early syphilis, benzathine penicillin G 2.4 million units as a single dose is recommended. When penicillin cannot be used (e.g. due to penicillin allergy) or is not available the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 14 days or ceftriaxone 1 g intramuscularly once daily for 10–14 days. However, in pregnant women, with early syphilis, only benzathine penicillin G 2.4 million units as a one-time dose once intramuscularly should be used. In case of penicillin allergy, desensitization is recommended. When desensitization is also not available, erythromycin 500 mg orally four times daily for 14 days or ceftriaxone 1 g intramuscularly once daily for 10–14 days or azithromycin 2 g once orally can be used with extreme caution. Please note that erythromycin and azithromycin do not cross the placenta and ceftriaxone may have cross allergy in a penicillin allergic patient.

In adults and adolescents with late syphilis or unknown stage of syphilis, benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks is recommended. Care must be taken that the interval between consecutive doses of benzathine penicillin should not exceed 14 days. When penicillin cannot be used (e.g. due to penicillin allergy) doxycycline 100 mg twice daily orally for 30 days may be used. Similar to early syphilis, in pregnant women with late syphilis or unknown stage of syphilis, only benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks should be given. When desensitization is also not available, erythromycin 500 mg orally four times daily for 30 days can be used with extreme caution.

In infants with confirmed congenital syphilis or infants who are clinically normal, but whose mothers had untreated syphilis, inadequately treated syphilis (including treatment within 30 days of delivery) or syphilis that was treated with non-penicillin regimens the following regimens may be used: Aqueous benzyl penicillin 100 000–150 000 U/kg/day intravenously for 10–15 days or Procaine penicillin 50 000 U/kg/day single dose intramuscularly for 10–15 days. However in infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection, only close monitoring is required.

4.6.2: Gonorrhea

Clinical manifestations

Uncomplicated gonococcal infection due to *Neisseria gonorrhoeae* usually presents as urethritis in men. Symptoms include urethral discharge and dysuria while on examination; a urethral discharge is noted, ranging from scanty and mucoid to copious and purulent. On the other hand gonorrhoea in women is often asymptomatic with only less than half complaining of non-specific symptoms such as abnormal vaginal discharge, dysuria, lower abdominal discomfort and dyspareunia. Examination may reveal vaginal discharge and cervical friability due to mucopurulent cervicitis. Other sites of infection such as rectal and oral are usually asymptomatic though occasionally

patients may complain of local symptoms. Untreated infections will usually resolve spontaneously but in women may lead to serious complications such as pelvic inflammatory disease, including endometritis, salpingitis and tubo-ovarian abscess, which can eventually predispose to ectopic pregnancy and infertility. Similarly untreated urethral infection in men can on occasion lead to epididymitis, urethral stricture and infertility. Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal conjunctivitis manifesting as purulent ocular discharge and swollen eyelids. Untreated conjunctivitis may lead to scarring and blindness.

Diagnosis

N. gonorrhoeae can be diagnosed by either culture or nucleic acid amplification tests (NAATs) though in some instances Gram stain may be sufficient. NAATs are highly sensitive and specific diagnostic tests that can be conducted on a wide range of samples, including urine (in men), vulvovaginal, cervical and urethral swabs, making these the test of choice for *N. gonorrhoeae*. However availability of NAATs is limited and use is restricted due to costs. Another drawback of NAATs is their inability to provide information on antimicrobial susceptibility. Therefore ideally, cultures should be done in parallel with NAATs to allow for susceptibility testing (depending on cost and availability of both).

Urethral and endocervical culture for *N. gonorrhoeae* is specificand cheaper with reasonable sensitivity. However, good specimen collection, timely inoculation into adequate and appropriate culture media, proper transportation and appropriate incubation are required. Gram-stained smears can provide a presumptive diagnosis of gonorrhoea, especially among symptomatic men with urethritis and is the least expensive and most readily available alternative. However, only 50–70% of asymptomatic infections in men are positive on Gram stain. Also gram stain diagnosis for cervical and rectal infection is less reliable and pharyngeal samples should not be analyzed.

Given the cost constraints and limited availability of these tests, a clinical diagnosis can also be made, based on the presence of symptoms such as vaginal and urethral discharge. However this will miss the asymptomatic patients and in case of treatment failure a culture/NAAT and alternative diagnosis must be sought.

Treatment

Given the emerging drug resistance in gonorrhea, dual therapy is recommended for all patients. Moreover, using two drugs allows for simultaneous treatment of chlamydia (which often causes co-infections). The recommended regimens for urethritis and oropharyngeal disease in adults and adolescents are

- ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose.
- cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose.

However, the IM ceftriaxone is preferred over the oral cefixime as this is more effective.

If failure occurs, reassess the patient to check if this is true failure or a reinfection (i.e. new worsening after complete resolution of symptoms). If reinfection is suspected, re-treat with one of the above regimens and reinforce safe sexual practices and provide partner treatment. On the other hand if treatment failure has occurred, but a recommended regimen was not used, retreat with one of the recommended regimens. Finally, if treatment failure occurred with one of the recommended regimens one of the following can be used:

- ceftriaxone 500 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
- cefixime 800 mg orally as a single dose PLUS azithromycin 2 g orally as a single dose
- gentamicin 240 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose.

In neonates with gonococcal conjunctivitis, one of the following treatment options can be used:

- ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose
- kanamycin 25 mg /kg (maximum 75 mg) IM as a single dose

For ocular prophylaxis, one of the following options for topical application to both eyes immediately after birth is recommended:

- tetracycline hydrochloride 1% eye ointment
- erythromycin 0.5% eye ointment
- povidone iodine 2.5% solution (water-based)
- silver nitrate 1% solution
- chloramphenicol 1% eye ointment

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4.6.3: Chlamydia

Clinical Manifestations

Chlamydial infection, caused by Chlamydia trachomatis, is the most common bacterial sexually transmitted infection worldwide. The three biovars of C. trachomatis, (each consisting of several serovars or genotypes), cause genital infections, lymphogranuloma venereum (LGV: a genital ulcer disease affecting the lymphoid tissues and trachoma (eye infection). For the purpose of these guidelines, only genital infections will be addressed.

Genital infections due to C. trachomatis do not produce symptoms in 70% of women and 50% of men. When symptomatic, women may complain of abnormal vaginal discharge, dysuria, and post-coital and inter-menstrual bleeding. Examination commonly reveals a friable cervix and discharge. Men usually present with urethral discharge and dysuria, sometimes accompanied by testicular pain. Similar to

gonorrhea, if left untreated, most genital infections will resolve spontaneously with no sequelae though on occasion they may result in complications, mainly in young women. The infection may ascend to the upper reproductive tract and cause PID, ectopic pregnancy, salpingitis and tubal factor infertility in women. In men it may lead to epididymitis in men. Extra-genital infections (oro-pharyngeal and rectal) are also common though usually asymptomatic except for occasional local symptoms.

Chlamydial infection in pregnancy is associated with preterm birth and low birth weight. Infants of mothers with chlamydia can be infected at delivery, resulting in neonatal conjunctivitis and/or nasopharyngeal infection. Symptoms of ophthalmia include ocular discharge and swollen eyelids. In newborns, nasopharyngeal infection can lead to pneumonitis.

Diagnosis

Nucleic Acid Amplification Tests (NAAT) is the recommended method to diagnose chlamydia due to its superior sensitivity and specificity and ability to use on a wide range of samples, including urine and vulvovaginal, cervical and urethral swabs. However currently the availability and cost of NAATs limit their use. Therefore often a clinical diagnosis may need to be made. However, when treating chlamydia empirically, coverage for gonorrhea should always be included.

Treatment

As the presentation of chlamydia and gonorrhea are similar, treatment for chlamydia alone must not be provided based on clinical symptoms alone. Instead, empiric treatment must include treatment for gonorrhea (which covers both organisms). However, if a definitive diagnosis of chlamydia has been made by NAAT and co-infection with gonorrhea has been ruled out then the following regimens may be used:

- Azithromycin 1 g orally as a single oral dose
- Doxycycline 100 mg twice daily for 7 days

In pregnant women, azithromycin should be used. In neonates with chlamydial conjunctivitis, the using oral azithromycin 20mg/kg/d once daily for 3 days, doses daily for 14 days. For ocular prophylaxis after exposure one of the following options for topical application to both eyes immediately after birth can be used:

- tetracycline hydrochloride 1% eye ointment
- erythromycin 0.5% ointment
- povidone iodine 2.5% solution (water based)
- silver nitrate 1% solution
- chloramphenicol 1% eye ointment

4.6.4: HPV

Cervical cancer is a preventable disease and is curable if diagnosed and treated early. Women living with HIV have a higher risk of pre-cancer and invasive cervical cancer. The risk and persistence of human papillomavirus infection (HPV) increases with decreasing

CD4 count and increasing HIV viral load. Invasive cervical cancer is a WHO HIV clinical stage 4 condition. Women living with HIV should be followed closely for evidence of pre-cancerous changes in the cervix, regardless of ART status or CD4 count and viral load. Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions that will prevent serious morbidity and mortality. Thus, all women with HIV should be screened for cervical cancer regardless of age. Immediate management for pre-cancerous and cancerous lesions should be provided. To date, concerns about safety or reduced efficacy among females who may be infected with HIV should not defer the initiation of large-scale HPV immunization. HIV testing should not be a prerequisite before routine HPV immunization.

4.7: Vaccinations

People living with HIV should be assessed for eligibility for vaccination at all stages of care. HIV-exposed infants and children and young adults with HIV should receive all vaccines under routine vaccination according to the EPI schedule. The BCG vaccine (live attenuated) is not recommended in HIV infected children or HIV exposed infants in whom infection has not been ruled out.

4.7.1: Vaccination in children

BCG

BCG is not recommended even in settings where tuberculosis is highly endemic. Normally given at birth, BCG vaccination should be deferred in HIV-exposed infants until confirmed to be HIV-negative. BCG vaccination of HIV-infected infants is of uncertain efficacy and is associated with significant safety concerns in untreated infants and in those on ART.

OPV

WHO recommends OPV (both routine and supplementary) should be given to symptomatic HIV-exposed and HIV-infected children especially in endemic Pakistan. OPV is normally given at birth, 6, 10 and 14 weeks (routine) and additionally 3-4 times every year during house-to-house Supplementary Immunization Activities (SIAs). IPV vaccination (non-EPI and optional, single dose in first year of life) is also recommended where available and affordable.

Pentavalent (DPT-Hib-HepB)

Normally given at 6, 10 and 14 weeks, these should be given on schedule irrespective of infection or exposure status. Partially or completely unvaccinated HIV children should receive 3 (catch-up) vaccines at least 4-6 weeks apart especially if younger than 7 years old. If partially or completely unvaccinated and older than 7 years, they should receive Hepatitis B series alone.

Measles containing vaccines (MCV)

Severely immunosuppressed (CD4 count≤200/mm3 or CD4% ≤10%) HIV-infected infants, children, adolescents, and young adults should not receive live measles virus

containing vaccines. However, those without evidence of severe immunosuppression should receive Measles (EPI) or MMR (non-EPI) vaccines. The zero dose should be administered at 9 months of age. The first, second and third doses may be given as per schedule (15 months, 5 years, 10-12 years) or as soon as 28 days after the zero dose. In the event of an outbreak in the community, vaccination with monovalent measles vaccine (or MMR) is recommended for infants as young as 6 months when exposure to natural measles is considered likely. If HIV-positive children and adolescents who are not WHO stage 3 or 4 are exposed to measles, IVIG is mandatory if there is no history of optimal vaccination in the past. For infants of unknown status born to HIV positive women and children in WHO stage 3 or 4, post exposure immune globulin prophylaxis should be administered.

Pneumococcal conjugate vaccine (EPI)

Recently introduced in EPI schedule, and given simultaneously with the Pentavalent vaccine and OPV during 6, 10 and 14 week visits, this ten-valent vaccine is highly recommended for all HIV-infected children. A 13-valent (non-EPI) vaccine is also available and can be used as a replacement if affordable.

Non EPI vaccines

Injectable Poliovirus Vaccine (IPV) is available in Pakistan as a combination vaccine (infanrix-hexa/quinvaxem, DaPT-Hib-HepB-IPV) and a single vaccine (Imovax). This is a killed vaccine. Simultaneous administration with OPV or sequential (2-3 doses of IPV followed by OPV) regimens are associated with higher efficacy. WHO recommends at least one IPV dose during infancy in addition to multiple oral polio vaccine for Pakistani children.

Hepatitis A is available as single-use vaccine, for patients 2 years and above, 2 doses 6-18 months apart. In view of shortage of pediatric hepatitis A vaccine, 0.5ml of the 1ml adult vaccine can be given to children.

Varicella: Varicella vaccine can be given as per schedule in 2 doses at 1 and 5 years age or 3 months apart after age 1 year. It is however contra-indicated in HIV-infected children with severe immune suppression (CD4 ≤10% and/or absolute counts ≤200 cells/μL). Efficacy of MMRV combination vaccine has not been studied in this population.

Rotavirus: Two doses of the pentavalent rotavirus vaccine are administered orally at 10 and 14 weeks of age in all infants. It is generally not given if age has exceeded 16 weeks. Rotavirus vaccine can be given simultaneously with other childhood immunizations (e.g., pentavalent, OPV etc). If immunization with rotavirus vaccine is being considered for an HIV-infected infant, severe immunosuppression (CD4% ≥10% and/or absolute counts ≥200 cells/μL) should be considered a contraindication to vaccine receipt. Rotavirus vaccine can be used for siblings living in the home of an HIV-infected patient.

Influenza vaccine: Influenza immunization is indicated for all HIV-infected children aged 6 months or older, as well as their close contacts. The inactivated intramuscular vaccine should be the only vaccine used for HIV-infected children. It should be administered before winter and repeated annually because of the vaccine's low immunogenicity and

changes in the type of influenza causing infection from year to year. For healthy close contacts of HIV-infected patients, the live-attenuated, cold-adapted vaccine can be used for contacts aged 5-49 years or the inactivated vaccine for those aged at least 6 months.

Meningococcal conjugate/Hajj vaccine: Despite the type of vaccine or the number of serogroups involved, these vaccines are safe for asymptomatic or symptomatic HIV patients. The type of vaccine used will dictate the age of receipt and the type of vaccine used.

HPV: Quadrivalent HPV vaccine is recommended for HIV-infected people between 9-26 years age. Vaccination before sexual debut is recommended as protective efficacy is highest in persons without prior HPV infection. The quadrivalent vaccine, Gardasil, contains the genital wart-causing HPV strains 6 and 11 and the cancer-associated strains 16 and 18. The bivalent vaccine, Cervarix, contains only the cancer-associated strains 16 and 18. Both vaccines are currently FDA approved for females aged 9-26 for the prevention of cervical and anal intraepithelial neoplasia and cancer and males aged 9-26 for prevention of anal intraepithelial neoplasia and HPV infection.

4.7.2: Vaccination in adults

Amongst adults, immune status of HBV should be sought by checking a HepBsAb and if HepBsAg is negative patients should be vaccinated for HBV with the standard (0, 1, 6 months) schedule. Adults and adolescents should also receive the tetanus vaccine every 10 years. Given the poor immunogenicity with the un-conjugated pneumococcal vaccine, all HIV infected adults should receive both the conjugated pneumococcal vaccine (PCV-13) and the unconjugated vaccine (PPSV-23). Individuals who have not received any pneumococcal vaccine should first receive the PCV-13, followed by the PPSV-23 eight weeks later and a second booster of the PPSV-23 five years later. For those patients who may have only received the PPSV-23 vaccine in the past, a single dose of the PCV-13 should be given one year or more after of the PPSV-23 vaccine. If the patient is eligible for a booster of the PPSV-23, this needs to be given after 8 weeks of the PCV-13 and at least 5 years after the original PPSV-23 vaccine. Adolescent girls should also receive 3 doses of the HPV vaccine, regardless of their sexual activity or prior history of HPV.

Section 5: Routine health care of HIV infected individuals

5.1: Key elements in general care

People living with HIV are at increased risk of developing a range of non-communicable diseases (NCDs), including cardiovascular disease, diabetes, chronic lung disease and some types of cancer. With effective ART, people living with HIV are now living longer and experiencing NCDs associated with ageing. Chronic HIV care provides the opportunity for screening, monitoring and managing NCDs, especially through primary care. WHO has defined a package of essential NCDs (WHO PEN) interventions along with recommendations on screening for and treating NCDs.

Routine health care and monitoring of HIV-infected children can be undertaken by general pediatricians, working in close coordination with infectious disease specialists as well as other members of the HIV care and support team (counselors, outreach workers). Components of such care include regular growth monitoring and nutritional assessment, neuro-developmental assessments, provision of safe feeding advice and nutritional support as needed, provision of age appropriate immunizations (see section 4.7.1), prophylaxis for prevention of opportunistic infections (see sections 4.1, 4.2 and 4.4), laboratory monitoring as indicated (see section 3.6), assessment of adherence to therapy (see section 5.2.4), management of common childhood infections such as acute respiratory infections, and diarrhea, as well as compassionate counseling and support, including referral to outreach services for families needing social support or food assistance.

5.1.1: Screening and care of non-communicable diseases in adults

Primary prevention of heart attacks and strokes should be carried out by asking about tobacco use in each visit and recommending tobacco cessation if the patient is using tobacco. Patients should also be encouraged to engage in regular physical activity 30 minutes a day, reduce intake of salt <5 g per day and increase fruits and vegetables. For patients with a high 10 years cardiovascular risk (>30%), referral should be made to a general physician to start aspirin, statins and antihypertensives.

Patients should be screened for hypertension on each visit by monitoring the blood pressure. Patients with a single reading of ≥160/100 mmHg or for people with persistent blood pressure ≥140/90 mmHg and 10 year cardiovascular risk >20% unable to lower blood pressure through life style measures should be referred to a general physician to start pharmacologic therapy.

Those patients with HIV who have already had an acute myocardial infarction or a stroke should have an aspirin added to their regimen. Additionally, monitoring and counseling tobacco cessation, healthy diet and regular physical activity should continue. These patients should be referred for starting an angiotensin-converting enzyme inhibitor, beta-blocker (AMI only) and statins.

Finally, all HIV patients with diabetes should be referred to a general physician for counseling for routine foot-care, eye exam and screening for nephropathy.

5.1.2: Screening and care of non-communicable diseases in children

5.1.2.1: Thalassemia Major

Beta thalassemias are a group of hemoglobinopathies characterized by a chronic anemia, inability of the body to compensate for low hemoglobin (signs of increased cardiac effort, tachycardia, sweating, poor feeding, and poor growth) and symptoms of ineffective hematopoiesis (splenomegaly and bone changes). The mainstay of treatment in Pakistan, in view of non-feasibility of bone marrow transplantation is chronic transfusion therapy. In the absence of strict monitoring of pre-transfusion blood screening, these patients are at high risk of acquiring HIV, HCV and HBV in addition to a host of other blood borne viral, bacterial and protozoal infections.

Almost half of pediatric HIV in Pakistan is transfusion-related. Key populations are children with thalassemia major, hemophilia and other bleeding disorders which necessitate chronic transfusion therapy. Increasingly, HIV health care providers have to deal with sub-optimally managed thalassemic children with multi-organ sequelae of chronic transfusions and avoidable co-infections with HIV, HCV and HBV. Treatment becomes challenging due to baseline liver dysfunction and potential hepatic toxicities of ART.

Caveats to consider:

Iron overload: This is a leading cause of organ injury and death. The aim of chelation therapy is to bind toxic non-transferrin bound iron in plasma and remove it from body. It takes around 3 to 10 years of chronic exposure to high levels of iron before measurable organ dysfunction occurs. End organ dysfunction is multi-system and includes liver dysfunction, endocrinopathies (diabetes mellitus, hypothyroidism and hypoparathyroidism, adrenal insufficiency, osteopenia and osteoporosis, growth hormone deficiency, hypogonadism), cardiac dysfunction (heart failure, pulmonary hypertension), lung dysfunction (transfusion related lung injury-TRALI) and chronic pain syndromes.

The HIV care provider should make an effort to connect the patient with a thalassemia centre of care where his iron overload and chelation status can be monitored and optimized and the patient has exposure to a multi-disciplinary team including a hematologist, a hepatologist, a cardiologist, an endocrinologist, a psychologist, a genetics counselor, a social worker and a dietician.

The HIV health care provider must also be cognizant of side effects of chelation therapy as they may impact treatment choices and outcomes. These include hearing loss, temporary loss of sight, cataracts, renal dysfunction, growth failure and symptoms related to iron deficiency and require a multi-disciplinary team too (audiologist, ophthalmologist, nephrologist, endocrinologist and hematologist).

Infections: This is the second commonest cause of death in thalassemia major patients. Despite multiple alterations in the immune system (reduction in neutrophil numbers, changes in number and function of natural killer cells, increase in number and function of CD8 suppressor cells, impaired macrophage function, chemotaxis, phagocytosis and

interferon gamma production), thalassemia major patients in absence of HIV are generally not considered as immunocompromised. When infection is suspected in thalassemia major patients, common childhood infections, and thalassemia-specific conditions given below must be considered:

- Splenectomy: Post splenectomy patients are extremely susceptible to sepsis due to encapsulated organisms like streptococcus pneumoniae, hemophilus influenza b and Neisseria meningitides. Preventive measures include pre-splenectomy vaccination and post splenectomy penicillin prophylaxis (250 mg twice daily). Other organisms implicated in post-splenectomy sepsis are gram negative organisms like E. coli, K. pneumoniae and P. aeruginosa and protozoal infections like malaria and babesiosis.
- Iron chelation: Potential risk of natural siderophores, as in deferoxamine, is that they may be used by micro-organisms as a source of iron and so become more virulent. This has been established in vitro and in vivo for Yersinia enterocolitica. A clear relationship has also been reported between mucormycosis and rhizopus and desferrioxamine in dialysis patients but only sporadically in thalassemia.
- Iron overload: Many organisms (Y. enterocolitica, Klebsiella sp., E. coli, S.pneumonaie, P.aeruginosa, L.pneumophila and Listeria monocyogenes have been shown to have increased virulence in the presence of excess iron.
- Blood-borne infections:

Parvovirus B19 must be suspected in a transient aplastic crisis. In immunosuppressed patients (HIV infected, post BMT) the infection will be persistent and trigger autoimmune inflammatory disorders. Immune-competant children will generally become immune to further infections by the agent following full recovery.

HIV prevalence in thalassemia varies greatly worldwide, from less than 1% to more than 20%. It is possible to keep the risk of HIV transmission very low by use of standard procedures for prevention and sensitive pre-transfusion screening measures. Patients with thalassemia and HIV should be managed in collaboration with an infectious disease physician with HIV expertise. There is general agreement that iron status influences the outcome of HIV-1 infection. In HIV-1 infected patients with TM, the rate of progression of HIV was significantly faster in patients with low level of chelation with desferoxamine and higher ferritin concentrations. Further to the capacity to remove iron, iron chelators, mainly deferiprone show interesting antiviral properties in vitro. Optimal control of iron overload with iron chelation is therefore recommended in HIV-positive children with thalassemia and the choice of chelator should take into consideration the above data as well as the individual ‘s needs. Because of an increased risk of neutropenia with deferiprone, it should be used with caution in such cases. While there is no direct evidence that splenectomy facilitates the progression of HIV infection, a decision to perform splenectomy in an HIV-positive patient with thalassemia should be made with extreme caution. Of particular concern is the removal of an important fraction of T cells and the potential for overwhelming infection in immune-compromised patients.

Transfusion-associated CMV is usually subclinical and may appear as an infectious mononucleosis-like syndrome in immune-competant patients. In HIV-infected or BMT recipients, CMV infection may cause significant morbidity and mortality.

Yersinia infections present as fever, abdominal pain, diarrhea or vomiting. The most typical picture is of 'acute abdomen'. Atypical presentations may include ARDS, arthralgia and skin rashes. Complications may include abdominal abscesses, intussusception, nephritis, ileo-psoas abscess and meningitis. Treating physicians should inform the laboratory of suspicion of Yersinia to request specific culture conditions (22C for 48 hours). Treatment includes immediate cessation of chelation, and 2 weeks of parenteral or enteral ciprofloxacin, with trimethoprim-sulfomethoxazole or cephalosporins as an adjunct or alternative.

Other micro-organisms that may cause severe infections and should be seriously considered in unwell patients with thalassemia include Klebsiella sp., Pseudomona ssp., vibrio vulnificus, E.coli, Salmonella sp. and Mucor sp. Dengue has also bene reported as more severe in TM patients.

Liver and Gall bladder diseases: Liver toxicity can occur due to iron toxicity, transfusion-acquired hepatitis (HBV, HCV) and other causes of liver disease (medications, autoimmune reactions or metabolic disease like wilson's disease or alpha 1 antitrypsin deficiency). An annual HBV and HCV screen should be done. HBAb should be positive and if not, vaccination should be completed. Every 3 months, AST, ALT, bilirubin and alkaline phosphatase should be measured. The combination of hepatitis and iron overload increases the chances of liver damage. All such children should be referred to a hematologist for optimization of chelation and a hepatologist/gastroenterologist for treatment of viral hepatitis due to HBV or HCV.

5.1.2.2: Malnutrition

Malnutrition remains a major contributor to mortality in both, HIV-uninfected and infected children in developing countries. In HIV-infected children, wasting (i.e. low weight for height/length) has been associated with reduced duration of survival while weight loss increases the rate of infectious complications in children with HIV. Nutritional assessment i.e., the systematic evaluation of current nutritional status, diet, and nutrition-related symptoms is critical in early identification of malnutrition and poor growth as well as for monitoring of HIV disease progression and treatment efficacy for children on ART. Nutritional assessment should be part of routine clinical monitoring of HIV-infected children whether or not receiving ART.

Infants: Two options of infant feeding are recommended for HIV positive mothers: Exclusive breastfeeding (EBF) and exclusive replacement feeding through Breast Milk Substitute (BMS). EBF for the first 6 months is recommended unless BMS is Acceptable, Feasible, Affordable, Sustainable and Safe (AFASS) before that time. Non-breastfed babies are at higher risk of acute respiratory infections, diarrhea and dehydration. The BMS of choice is commercial formula. Home-modified animal milk is generally not recommended in the first six months. It should only be used as a last resort. Mothers should be extended support and counseling on technique (EBF and BMS) throughout the

first 6 months on life. Cup and spoon feeding in BMS may be a safer practice than bottle feeding. In cases where mothers have to discontinue EBF, mixed feeding should be minimized as much as possible and early weaning considered. As for all infants, HIV-infected infants should be measured monthly, ideally using standardized growth curves (http://www.who.int/childgrowth/standards/). Thereafter, children should be weighed at each review and full nutritional assessments be performed every three months unless the child requires particular attention due to growth problems or special nutritional requirements.

Children older than 1 year: HIV infected children have increased energy needs. In asymptomatic HIV-infected children, resting energy expenditure is increased by about 10% while in HIV-infected children who experience growth failure energy needs may be increased 50% and 100% (http://www.who.int/nutrition/publications/hivaids/9789241597524/en/). Increased utilization and excretion of nutrients in HIV infection can also lead to micronutrient deficiencies. Nutritional support should thus include early efforts to assess, classify and decide on a nutritional care plan (Annexure 13), and practically to enable family to implement the appropriate nutritional care plan (Annexures 14-16). This includes ensuring adequate nutrient intake based on easily available nutritious and affordable foods and micronutrients equivalent to Recommended Daily Allowance (RDA). It is recommended to increase the energy intake of HIV-infected infants and children by 10% of the RDA for their age and sex where asymptomatic and by 20-30% of RDA when symptomatic or recovering from acute infections. These are minimal requirements and more may be needed in children with nutritional deficiencies. Model menus for children, practical advice on diet and minimizing drug side effects through timing with food intake is available online (http://www.who.int/nutrition/publications/hivaids/9789241591898/en/)

There is insufficient information at present to make firm recommendations on routine micronutrient supplementation of HIV-infected children. However there is good evidence that large-dose Vitamin A supplementation halves all-cause mortality, has inconsistent impacts on diarrheal and respiratory morbidity, and improves short term growth. Vitamin A supplements should be given according to Pakistan IMCI which recommends high-dose prevention schedule for children at high risk of Vitamin A deficiency (http://www.emro.who.int/child-health/strategy-adaptation/prevention-vitamin-a-and-vitamin-d-supplementation.html). Zinc supplementation during diarrheal episodes reduces morbidity in both HIV-infected and uninfected children and is recommended in Pakistan. Vitamin D and other micronutrient supplementation until hospital discharge has significantly reduced the duration of all hospital admissions in poorly nourished South African children, and supplementation for six months after discharge improved appetite and nutritional indicators. However a stronger evidence base is needed for formal recommendations. Counseling mothers about breastfeeding or safe substitute feeding and all children and their caretakers about food and water hygiene are further core elements of nutritional support. In children experiencing growth failure (i.e. failure to gain weight or weight loss between regular measurements) or feeding difficulties, more intensive evaluation is indicated. Underlying illnesses should be carefully sought and managed according to IMCI guidelines

(http://www.who.int/maternal_child_adolescent/documents/IMCI_chartbooklet/en/). Children should be evaluated for the need to start or switch ART; families should be educated about appropriate food choices and referrals made to outreach service providers for food assistance, if needed. In addition, selection of specific, palatable high-energy foods in children with conditions that interfere with normal ingestion or digestion (such as sore throat or mouth, oral thrush, or diarrhea) may relieve symptoms and at the same time ensure sufficient energy intake.

5.1.3: Management of common childhood illnesses/infections

HIV infected children suffer frequent episodes of common childhood illnesses such as acute respiratory infections and diarrhea. WHO and UNICEF have developed evidence-based guidelines on the Integrated Management of Childhood Illnesses (http://www.who.int/child-adolescent-health/publications/pubIMCI.htm) which have been adapted by Pakistan. Management of these infections in HIV-infected children should follow the same principles as in children without HIV infection.

5.2: Adherence to ART

WHO defines treatment adherence as "the extent to which a person's behavior – taking medications, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider". For ART, a high level of sustained adherence is necessary to (1) suppress viral replication and improve immunological and clinical outcomes; (2) decrease the risk of developing ARV drug resistance; and (3) reduce the risk of transmitting HIV.

5.2.1: General barriers to adherence

Multiple factors related to health care delivery systems, the medication and the person taking ARV drugs may affect adherence to ART.

The **individual factors** may include forgetting doses; being away from home; changes in daily routines; depression or other illness; a lack of interest or desire to take the medicines; and substance or alcohol use, adverse effects, precarious social and economic situation, familial or professional conflicts, etc. Medication-related factors may include adverse events; the complexity of dosing regimens; the pill burden; and dietary restrictions.

Health system factors may include requiring people living with HIV to visit health services frequently to receive care and obtain refills; travelling long distances to reach health services; and bearing the direct and indirect costs of care. Lack of clear information or instruction on medication, limited knowledge on the course of HIV infection and treatment and adverse effects can all be barriers to adherence to ART.

Moreover, uninterrupted ARV drug supply and continuity of care are essential for people to adhere to their medication. Adherence to ART may also be challenging in the absence

of supportive environments for people living with HIV and due to HIV-related stigma and discrimination.

5.2.2: Adherence issues in pregnant and post-partum women

The pregnancy and postpartum period presents significant biological, social and economic challenges that may affect treatment adherence. Pregnancy-related conditions such as nausea and vomiting may negatively affect treatment adherence. Other challenges during this period may include dealing with the diagnosis of HIV infection (especially if the diagnosis was made during pregnancy); concerns about how ART affects the health of the fetus; pill burden; the number of clinic visits during pregnancy; fear of disclosure of HIV status; long waiting times at clinics; and lack of follow-up and transfer to other clinics after delivery.

5.2.3: Adherence issues in adolescence

Adherence challenges faced by adolescents include a potentially large pill burden if they are treatment-experienced; stigma and fear of disclosure; concerns about safety of medications; adverse effects; peer pressure and perceived need to conform; not remembering to take medications; and inconsistent daily routine. The transition from pediatric to adolescent care presents several challenges that may affect treatment adherence in adolescents. These include assuming increased responsibility for their own care (which may lead to treatment interruptions because of forgetfulness); an inability to navigate the health care system; lack of links between adult and pediatric services and inadequately skilled health care providers. Depression and substance use have also been shown to present challenges in adolescents.

5.2.4: Adherence issues in infants and children

Adherence among children is a special challenge. The limited choice of pediatric formulations, poor palatability of liquid formulations, high pill or liquid volume burden, large pill size, frequent dosing requirements, dietary restrictions, loss of primary caregiver, difficulties in swallowing tablets and adverse effects may all affect adherence. Successfully treating a child requires the commitment and involvement of a responsible caregiver. Parents and other family members of children living with HIV may themselves be living with HIV and suboptimal HIV care and treatment for family members could result in suboptimal care for the child.

5.2.5: Adherence issues in mental health disorders and substance abuse (other than PWID)

Adherence to ART is known to be complicated by mental health co-morbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans. Studies have linked uncontrolled depressive symptoms with low levels of adherence to ART and poor treatment outcomes. As a result, several treatment strategies target depression and psychosocial stress to improve adherence to ART, ranging from co-counseling for HIV and depression to appropriate medical therapies for individuals with mental disorders.

Individuals with substance use disorders may have poor adherence to ART. Alcohol and other drug use could be associated with forgetfulness, poor organization and diversion of monetary and time priorities.

5.2.6: Adherence issues in Persons Who Inject Drugs (PWID)

PWID make up a large proportion of patients with HIV in Pakistan, with up to 50% of PWID testing positive in certain cities. Treatment of HIV in this population has its unique difficulties especially as active drug use is directly linked to poor ART compliance. Moreover, there are limited opportunities for drug rehabilitation in the country (including no active OST sites) and a high relapse rate in those who do manage to quit drug use. Also given the limited number of HIV treatment centers in the country coupled with the chaotic lifestyle of these individuals, it is often difficult for PWIDs to access HIV treatment. Even once ART is initiated, PWID often have a weak follow-up and poor adherence leading to a high risk of developing HIV drug resistance.

Initiation of ART in PWID should therefore be carefully planned and never be rushed, especially as HIV treatment is never an emergency. Adherence should be addressed before treatment is started and should keep in account the patient's current social circumstances. For example, with the home-based PWID, identifying a treatment buddy (e.g. spouse, parent, sibling) may be relatively easier as compared to a street based PWID. Other options include linkages with NGOs and/or enrolling in proposed ART adherence units where medical services, counselling services and socio-economic rehabilitation can be provided. Once OST is available, substitution will also help improve adherence. If no provisions to improve adherence are available before starting ART (for example lack of a treatment buddy in a street PWID), then a strong consideration should be made to defer therapy.

Similarly, extra care must be taken in PWID who have already defaulted on ART. These patients are at a very high risk of stopping medications again and given the current lack of third-line ARVs and genotyping capabilities in the country, repeated episode of non-compliance will severely limit treatment options both for the patient as well in newly infected PLHIV. In such patients, ART should be withheld until the active drug use has been addressed or an alternative system to improve adherence has been found.

5.2.7: Monitoring adherence

Objective monitoring of adherence to ARV drugs is necessary for effective and efficient treatment. Therefore adherence must be assessed and supported during each visit. While there is no ideal method to assess adherence, effective monitoring requires a combination of approaches based on human and financial resource capacity and acceptability to people living with HIV and to health workers. The following are four possible methods of assessing adherence. While implementation of all four is not required, a combination of methods should be used depending on the program's and the patient's logistics. A number of these measures also form the basis of the EWI (see section 7)

Viral load monitoring

Viral load monitoring is used to diagnose and confirm treatment response and failure (see section 3.7.3). While lapses in adherence to ART often lead to treatment failure, other factors may also need to be evaluated such as drug stock-outs, drug interactions or malabsorption. Moreover, viral load monitoring does not provide an opportunity for care providers to monitor non-adherence in real time and prevent progression to treatment failure. Viral load monitoring must therefore be combined with other approaches to monitor adherence.

Pharmacy refill records

Pharmacy refill records provide information on when people living with HIV pick up their ARV drugs. When people obtain pharmacy refills at irregular intervals, this may indicate non-adherence to ART and should prompt further investigation. However, care must be taken that patients might pick up their medications irrespective of their adherence level, which may lead to health care providers overestimating adherence if pharmacy refill records are used solely to monitor adherence. Nonetheless, a recent study found pharmacy records to be more reliable than self-reporting.

Self-reporting

Asking people living with HIV or their caregivers about number of doses of medication they have missed since the last visit (or within a specified number of days in the past) can help to estimate non-adherence. Adherence also encompasses incorrectly taken doses and timing of the dosage intake should also be inquired. However, while this method is commonly used because it provides a quick assessment of adherence and easily leads into discussions to improve this, people may not remember missed doses accurately or may not report missed doses because they want to be perceived as being adherent and to avoid criticism. Counseling on the importance of remembering and/or documenting ARV drug doses in an environment that promotes and enables honest reporting of non-adherence are critical components of monitoring adherence to ART in routine care settings.

Pill counts

Counting the remaining pills in bottles may help to assess adherence. Pill counts usually take place at routine health care visits. However, some people may throw away tablets prior to health care visits, leading to overestimated adherence. Counting pills also requires health care personnel to invest significant time and may not be feasible in routine care settings.

5.2.8: Interventions to improve adherence

No single adherence intervention or package of interventions is effective for all populations and all settings. Patient's needs and circumstances may also change over time, and care providers must tailor a combination of feasible interventions to maximize adherence to ART based on individual barriers and opportunities. A team effort of healthcare provider, counselor, outreach support service provider, patient and caregiver is required to ensure longterm adherence and good response to ART. Compassionate care should be provided in a supportive and non-threatening atmosphere and efforts

made to understand the patient's and the family's social and medical needs. Interventions to improve compliance may be implemented both at a program level as well as an individual level.

Program level interventions for improving adherence to ART include: (1) avoiding imposing out-of-pocket payments at the point of care, (2) switching to fixed-dose combination regimens for ART and (3) strengthening drug supply management systems to reliably forecast, procure, and deliver ARV drugs and prevent stock-outs.

Numerous individual level interventions exist, but efforts to support and maximize adherence should begin before ART is initiated. Developing an adherence plan and education are important first steps. Initial patient and care-giver education should cover basic information about HIV; the ARV drugs, expected adverse effects, preparing for treatment and adherence to ART. Patient education and counseling are essential both when ART is initiated and throughout the course of treatment. Informing and encouraging people receiving ART and their families and peers are essential components of chronic HIV care.

Once adherence issues have been identified, solutions are often required to be individualized based on the exact problem. For example, if doses are being missed, reasons for this must be explored (such as if the dosing time is inconvenient, if the pill burden is too high, for children if the medication is not palatable) and appropriate solutions explored mutually with the patient (such as changing the time of the medication, using a pill box or an alarm, changing the formulation to decrease the pill burden or improve taste). Forgetfulness and changes in daily routines are often cited as the main reason for poor adherence to ART in most settings, although the specific reasons for forgetting to take medication could vary. Reminders in the form of SMS, alarms, phone calls, diaries and calendars may be considered. Many individual level adherence interventions have benefits beyond improving adherence to ART. For example, nutritional support, peer support, management of depression and substance use disorders and patient education are vital components of routine health and HIV care and work to both improve adherence as well as the patient's quality of life.

The table below summarizes strategies to improve adherence

Table 5.1: Strategies to improve adherence

Strategies	Examples
Use a multidisciplinary team approach	Nurses, social workers, pharmacists, and medications managers
Establish patient readiness to start ART	Assess and simplify the regimen, if possible
Identify potential barriers to adherence before starting ART	Psychosocial issues Active substance abuse or at high risk of relapse Low literacy Low numeracy Busy daily schedule and/or travel away from home Nondisclosure of HIV diagnosis Scepticism about ART Lack of prescription drug coverage

	Lack of continuous access to medications
Provide resources for the patient	Referrals for mental health and/or substance abuse treatment Resources to obtain prescription drug coverage Pillboxes Occupational Training/women empowerment
Involve the patient in ARV regimen selection	For each option, review regimen potency, potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of non-adherence
Assess adherence at every clinic visit	Ensure that other members of the health care team also assess adherence Ask the patient open-ended questions (e.g., In the last 3 days, please tell me how you took your medicines.)
Identify the type of non-adherence	Failure to fill the prescription(s) Failure to take the right dose(s) at the right time(s) Non-adherence to food requirements
Identify reasons for non-adherence	Adverse effects from medications Complexity of regimen (pill burden, dosing frequency, etc.) Difficulty swallowing large pills Forgetfulness Failure to understand dosing instructions Inadequate understanding of drug resistance and its relationship to adherence Pill fatigue Other potential barriers

5.3: Special requirements for advanced HIV

Patients with advanced HIV require additional support given the higher morbidity and mortality in this population as well as due to higher rates of co-infections and opportunistic infections. Advanced HIV is defined as follows:

- For adults and adolescents, and children older than five years, as CD4 cell count <200cells/mm^3 or WHO stage 3 or 4 event.
- All children younger than five years old with HIV are considered as having advanced HIV disease.

For patients with advanced HIV A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered. The table below summarizes the components of this care package including the sections in the guidelines where further details can be found

Table 5.2: Components of the package of care for people with advanced HIV disease

Intervention	CD4 count	Adult	Adolescent	Childre n	Section in guidelines

Diagnosis	Sputum Xpert® MTB/RIF as the first test for TB diagnosis among symptomatic people	Any	Yes	Yes	Yes	4.2.1
Prophylaxis	Co-trimoxazole Prophylaxis	≤350 cells/mm^3 or clinical stage 3 or 4	Yes	Yes	Yes (in some cases)	4.1
	INH preventative therapy	Any	Yes	Yes	Yes	4.2.2
ART initiation	Rapid ART initiation	Any	Yes	Yes	Yes	3.3
	Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis	Any	Yes	Yes	Yes	3.10
Support	Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible	≤200 cells/mm^3	Yes	Yes	Yes	5.2

The algorithm in annexure 18 describes a step-wise approach to provide the care package

Section 6: Prevention

6.1: Combination HIV prevention strategies

Although ARV drugs play a key role in HIV prevention, they should be used in combination with an appropriate mix of HIV prevention strategies. People's HIV prevention needs change during their lifetime, and a combination approach helps people to access the types of interventions that best suit their needs at different times. Moreover, combining approaches may also result in synergy, which will have a greater impact than a single intervention alone. Interventions to prevent spread of HIV must be addressed at the first visit and reinforced in subsequent visits (for pre and post-test counseling see section 2.1.3). On the other hand, the patient's and the family's fears regarding how HIV may be transmitted should also be addressed by removing commonly held myths such as the lack of risk in associated with hugging, eating together, sleeping together, mosquito bites etc.

HIV preventive strategies may be biomedical, behavioral or structural/supportive.

6.1.1: Biomedical Interventions

Apart from ART, one of the most important biomedical interventions to reduce the probability of HIV transmission per contact is male condoms. When used consistently and correctly, male condoms reduce heterosexual transmission by at least 80% and offer 64% protection in anal sex among men who have sex with men. Other measures include needle and syringe programs which are highly associated with a reduction in HIV transmission in PWIDs. Similarly opioid substitution therapy with methadone or buprenorphine is the most effective form of treatment for opioid dependence and has the additional benefit of effectively reducing HIV risk behavior and transmission through injecting drug use. Opioid substitution therapy in PWID also provides adherence support to people on ART (see section 5.2.6).

6.1.2: Behavioral interventions

Behavioral interventions that reduce the frequency of potential transmission events include targeted information and education. These programs may use various communication approaches for example, school-based sex education, peer counseling and community-level and interpersonal counseling to disseminate behavioral messages designed to encourage people to reduce risk behavior (such as safer drug use, delaying sexual debut, reducing the frequency of unprotected sex with multiple partners, using condoms correctly and consistently and knowing your and your partner's HIV status).

6.1.3: Structural/supportive interventions

Structural and supportive interventions affect access to, uptake of and adherence to behavioral and biomedical interventions. Such interventions address the critical social, legal, political and environmental enablers that contribute to HIV transmission, including legal and policy reform, measures to reduce stigma and discrimination, the promotion of gender equality and prevention of gender-based violence, economic

empowerment, access to schooling and supportive interventions designed to enhance referrals, adherence, retention and community mobilization.

6.2: PMTCT/PPTCT

See section 3.5.5 for complete details of ART during pregnancy and in the infant immediately after birth/during breast feeding.

6.3: Oral PrEP

Oral pre-exposure prophylaxis of HIV (PrEP) is the use of ARV drugs by HIV-uninfected people to block the acquisition of HIV. Clinical trials of oral PrEP have shown evidence of effectiveness in serodiscordant couples, heterosexual men, women, men who have sex with men, people who inject drugs and transgender women. It is important to understand that PrEP does not replace the biomedical and behavioral interventions mentioned above (in particular early treatment of infected partner in a serodiscodant partnership, condom use and safe needle practices), and is currently not recommended for routine use. However, PrEP has been found to be safe across populations and has not been associated with increased drug resistance.

6.3.1: Indications for PrEP

PrEP is now recommended in people at a "substantial risk" of acquiring HIV. This is defined as populations with an HIV incidence of around 3 per 100 person-years. As a result PrEP would be indicated in any high risk populations such as MSM, male commercial sex workers, serodiscordant heterosexual couples, transgendered and in carefully selected cases of IDUs where adherence has been assessed and can be ensured.

6.3.2: Monitoring prior to and while on PrEP

Before initiating PrEP, behavioral and biomedical interventions must be explained and stressed. Clients must be tested for HIV prior to starting PrEP and then tested every 3 months. As PrEP contains tenofovir, serum creatinine must also be checked prior to initiation and then at least quarterly. Similarly, as tenofovir is active against hepatitis B and holding tenofovir in an infected patient may lead to virologic and clinical relapse, Hepatitis-B status must be documented prior to PrEP.

6.3.3: Drugs and timing of PrEP

- PrEP must always contain tenofovir ideally in combination with lamuvidine (3TC) or emtricitabine (FTC) in a fixed drug combination. The frequency of PrEP will depend on the risk of the person. For exposure which are likely to be frequent (e.g. a CSW), PrEP must be given daily. Moreover, as the penetration of tenofovir in to the vaginal issue is less than rectal tissue, women (e.g. those wishing to conceive) should also receive daily PrEP. Moreover, PrEP must be started a few days before the exposure is likely to occur (e.g. in couples trying to conceive) and continued till the exposure period ends (add the reference). In MSM, on-demand PrEP can be used as follows: 2 tablets of tenofovir two to 24 hours prior to the exposure, 1 tablet after sex and one tablet 24 hours later. In all other patients TDF+3TC should be given in the standard once daily dosing. Overall, on

demand PreP is recommended for MSM and daily PreP for heterosexual couples. Therefore, PrEP should be offered as **an additional prevention choice** for people at risk of HIV infection **as part of combination HIV prevention approaches.**

Donnell D et. al. JAIDS. 2014;66(3):340-348.;

Anderson et al. Sci Transl Med Sep 12, 2012; 4(151): 151ra125.

6.4: PEP

Post-exposure prophylaxis (PEP) is short-term ART to reduce the likelihood of acquiring HIV infection after a potential exposure which may be either occupationally or through sexual intercourse. Persons who may require PEP include health care workers (such as doctors, paramedics, house staff, medical students, lab workers), individuals sharing needles during injecting drug user, waste-disposal workers, law enforcement personnel, victims of sexual assault or after consensual sex.

An HIV exposure is defined as exposure to infectious materials, including body substances (e.g. blood, tissue, and specific body fluids), contaminated medical supplies and equipment, and contaminated environmental surfaces. Significant exposure is defined as a percutaneous injury (e.g. a needle-stick or cut with a sharp object) or contact of mucous membrane or non-intact skin (e.g. exposed skin that is bruised, abraded or afflicted with dermatitis) with blood, tissue, or other body fluids that are potentially infectious. In addition to blood and visibly bloody body fluids, semen and vaginal secretions are also considered potentially infectious. Faeces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered infectious unless they are visibly bloody.

In case of a suspected exposure, a detailed history must be taken to assess if this was a significant exposure on not. The source person (from which the exposure occurred) should be identified (if possible) and an HIV test obtained of both the source and the exposed persons. In cases where the source is unknown or the status cannot be ascertained, PEP must be individualized, based on the risk (e.g. exposure in a general ward with no HIV patients vs. in a needle exchange centre).

PEP should be started as early as possible and ideally within 02 hours of the exposure and a can be given up to a maximum of 72 hours. Once started, ARVs needs to continue for 28 days and an HIV serology rechecked 6 weeks after the exposure. For PEP, TDF+3TC with LPV/r is recommended with adherence support. However, if the source patient is already known to have HIV and has failed first-line and second-line therapy, the PEP must be tailored to match the current regimen on which VL suppression has been achieved.

Health care workers should also be educated about the steps which need to be taken immediately after an occupational exposure to blood and body fluid. These include not to squeeze or rub the injury site of a needle-stick injury and to wash the site immediately

using soap and water. Irritant solutions, such as bleach or iodine, should not be used to clean the site. Similarly, after a splash of blood or body fluids, the area should be immediately washed and in the case of splashes in the eye the exposed eye should be irrigated with water or normal saline.

6.5: Management of serodiscordant couples who wish to conceive

Serodiscordant couples should be counselled to use barrier precautions, especially if the infected partner is not virally suppressed. Those couples who wish to have children should be counseled that, as long as the infected partner is virally suppressed, the risk of acquiring the infection is low. However this risk can be reduced further by using PrEP and timed intercourse (see section 6.3.3)

Section 7: Program Monitoring and Early Warning Indicators

The rapid scaling up of ART by the WHO has allowed a greater number of PLHIV to receive therapy, improving both AIDS-related morbidity and mortality. This scaling up also has the potential of eventually reducing new cases of HIV (treatment as prevention). On the other hand, an increased population of patients on ART also raises concern of the possibility of emergence and transmission of HIVDR (Drug Resistance). In response to this concern, WHO created HIVResNet, a global network of over 50 institutions to support development and implementation of a global drug resistance surveillance strategy. This strategy includes 5 key components: surveillance of transmitted HIVDR in recently infected populations, surveillance of HIVDR in populations initiating ART, surveillance of HIVDR in children less than 18 months of age, surveillance of acquired HIVDR in populations failing first line ART and monitoring of Early Warning Indicators (EWI) at all ART sites.

The EWI are quality of care indicators which assess factors associated with the emergence of HIVDR and are central to the HIVResNet strategy. These indicators should be monitored and reported routinely to the provincial program managers in order to provide an alert if situations are favorable to development of resistance. The indicators also provide an opportunity for corrective action as well as means of assessing each center's performance in relation to others in the country.

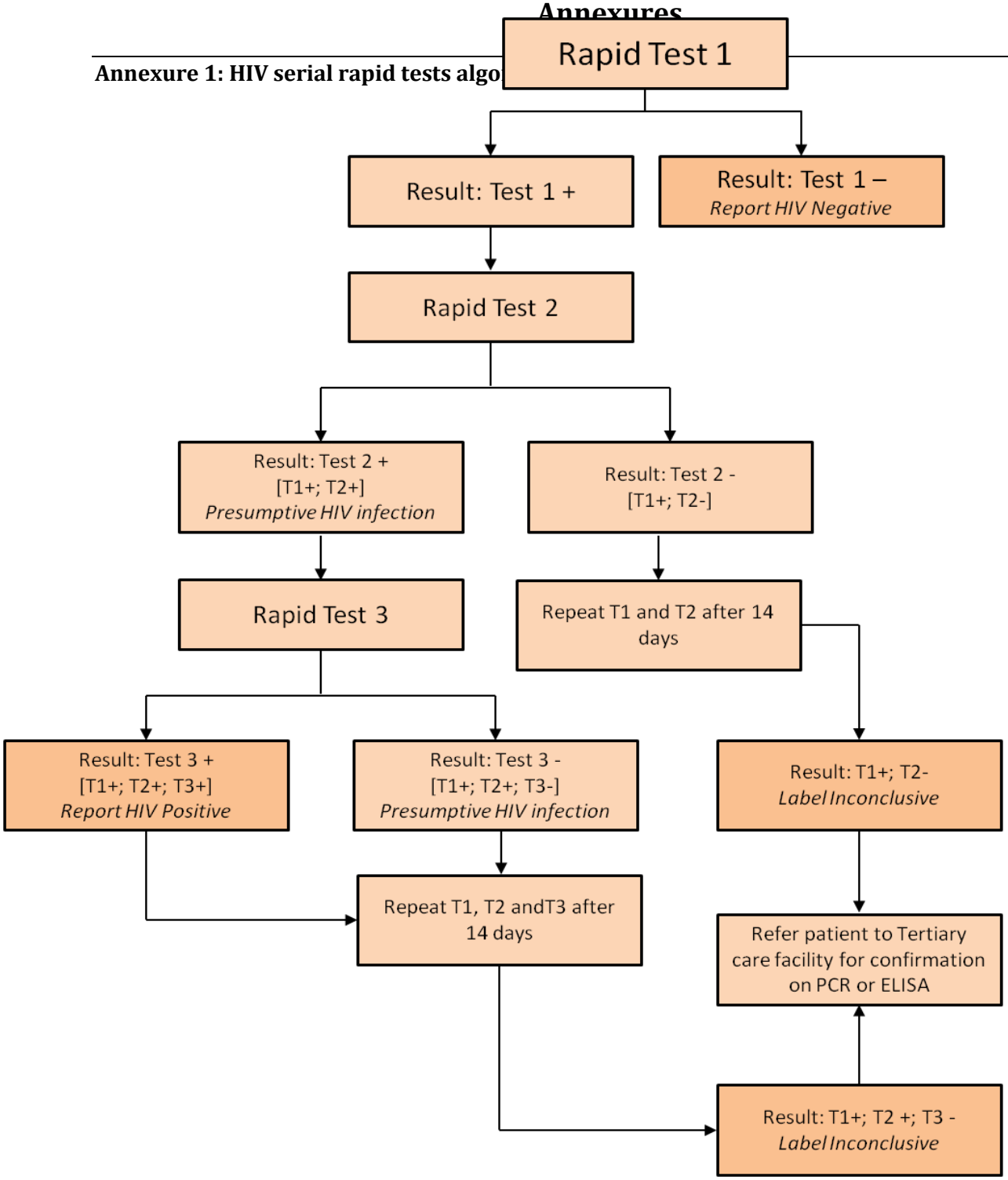
The table below details the EWI which each program should be monitoring and reporting

Table 7.1: Early Warning Indicators

Early warning Indicator	Target
1. On-time pill pick-up	Red: <80% Amber: 80–90% **Green: >90%**
2. Retention in care	Red: <75% retained after 12 months of ART Amber: 75–85% retained after 12 months of ART **Green: >85% retained after 12 months of ART**
3. Pharmacy stock-outs	Red: <100% of a 12-month period with no stock-outs **Green: 100% of a 12-month period with no stock-outs**
4. Dispensing practices	Red: <75% started on national recommended first line ART Amber: 75–85% started on national recommended first line therapy **Green: >85% started on recommended national first line therapy**
5. Viral load suppression at 12 months	Red: <70% viral load suppression after 12 months of ART Amber: 70–85% viral load suppression after 12 months of ART **Green: >85% viral load suppression after 12 months of ART**

Annexures

Annexure 1: HIV serial rapid tests algo



Annexure 2: WHO clinical staging and criteria for diagnosis in adults and adolescents

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

Clinical event	Clinical diagnosis	Definitive diagnosis
Fungal nail infections	Paronychia (painful red and swollen nail bed) or onycholysis (separation of nail from nail bed) of the fingernails (white discolouration, especially involving proximal part of nail plate, with thickening and separation of nail from nail bed)	Fungal culture of nail / nail plate material
Clinical stage 3		
Severe unexplained weight loss (more than 10% of body weight)	Reported unexplained weight loss (over 10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index below 18.5. In pregnancy, weight loss may be masked.	Documented loss of more than 10% of body weight
Unexplained chronic diarrhoea for longer than 1 month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than 1 month	Not required but confirmed if three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens
Unexplained persistent fever (intermittent or constant and lasting for longer than 1 month)	Reports of fever or night sweats for more than 1 month, either intermittent or constant with reported lack of response to antibiotics or antimalarials, without other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented fever exceeding 37.6 ^{o}C with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection
Oral candidiasis	Persistent or recurring creamy white curd-like plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Clinical diagnosis
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue, which do not scrape off	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive diagnosis
Pulmonary TB (current)	Chronic symptoms (lasting at least 2 to 3 weeks): cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats, plus EITHER positive sputum smear OR negative sputum smear AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, cavitation, pulmonary fibrosis and shrinkage). No evidence of extrapulmonary disease.	Isolation of *M. tuberculosis* on sputum culture or histology of lung biopsy (together with compatible symptoms)
Severe bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)	Fever accompanied by specific symptoms or signs that localize infection, and response to appropriate antibiotic	Isolation of bacteria from appropriate clinical specimens (usually sterile sites)
Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, rapid loss of bone and/or soft tissue	Clinical diagnosis
Unexplained anaemia (below 8g/dl), neutropenia (below 0.5×10^9/l) or chronic (more than 1 month) thrombocytopenia (under 50×10^9/l)	No presumptive clinical diagnosis	Diagnosed on laboratory testing and not explained by other non-HIV conditions. Not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in relevant national treatment guidelines, WHO IMCI guidelines or other relevant guidelines.
Clinical stage 4		
HIV wasting syndrome	Reported unexplained weight loss (over 10% of body weight) with obvious wasting or body mass index below 18.5, plus EITHER	Documented weight loss (over 10% of body weight) plus two or more unformed stools negative for pathogens

Clinical event	Clinical diagnosis	Definitive diagnosis
	unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than 1 month OR reports of fever or night sweats for more than 1 month without other cause and lack of response to antibiotics or antimalarials. Malaria must be excluded in malarious areas.	OR documented temperature exceeding 37.6 ^{o}C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged CXR
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past 3 months), tachypnoea and fever; AND CXR evidence of diffuse bilateral interstitial infiltrates, AND no evidence of bacterial pneumonia. Bilateral crepitations on auscultation with or without reduced air entry.	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue
Recurrent severe bacterial pneumonia (this episode plus one or more episodes in last 6 months)	Current episode plus one or more episodes in last 6 months. Acute onset (under 2 weeks) of symptoms (e.g. fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or CXR. Response to antibiotics.	Positive culture or antigen test of a compatible organism
Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal) of more than 1 month, or visceral of any duration	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrent HSV infection and reported for more than one month. History of previous episodes. Visceral HSV requires definitive diagnosis.	Positive culture or DNA (by PCR) of HSV or compatible cytology/histology
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty in swallowing (food and fluids) together with oral candidiasis	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy/histology
Extra-pulmonary TB	Systemic illness (e.g. fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated TB varies by site: pleural, pericardial, peritoneal	*M. tuberculosis* isolation or compatible histology from appropriate site, together with compatible symptoms/signs (if culture/histology is from

Clinical event	Clinical diagnosis	Definitive diagnosis
	involvement, meningitis, mediastinal or abdominal lymphadenopathy, osteitis. Miliary TB: diffuse uniformly distributed small miliary shadows or micronodules on CXR. Discrete cervical lymph node *M. tuberculosis* infection is usually considered a less severe form of extra-pulmonary tuberculosis.	respiratory specimen there must be other evidence of extra-pulmonary disease)
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat patches with a pink or blood-bruise colour, skin lesions that usually develop into violaceous plaques or nodules	Macroscopic appearance at endoscopy or bronchoscopy, or by histology
CMV disease (other than liver, spleen or lymph node)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Compatible histology or CMV demonstrated in CSF by culture or DNA (by PCR)
CNS toxoplasmosis	Recent onset of a focal neurological abnormality or reduced level of consciousness AND response within 10 days to specific therapy.	Positive serum toxoplasma antibody (usually Ig G) AND (if available) single/multiple intracranial mass lesion on neuroimaging (CT or MRI). If lumbar puncture is safe and feasible: Positive CSF toxoplasma antibody and CSF Toxoplasma PCR.
HIV encephalopathy	Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or	Diagnosis of exclusion, and, if available, neuroimaging (CT or MRI)

Clinical event	Clinical diagnosis	Definitive diagnosis
	condition, other than HIV infection, which might explain the findings	
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasingly severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Isolation of *Cryptococcus neoformans* from extra pulmonary site or positive cryptococcal antigen test (CRAG) on CSF/blood (sensitivity 92% to 95%, India-Ink stains (positivity: 80%)
Disseminated non-tuberculous mycobacteria infection	No presumptive clinical diagnosis	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding lung
Progressive multifocal leukoencephalopathy (PML)	No presumptive clinical diagnosis	Progressive neurological disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuroimaging or positive polyomavirus JC (JCV)PCR on CSF
Cryptosporidiosis (with diarrhoea lasting more than 1 month)	No presumptive clinical diagnosis	Cysts identified on modified ZN microscopic examination of unformed stool
Chronic isosporiasis	No presumptive clinical diagnosis	Identification of *Isospora*
Disseminated mycosis (coccidiomycosis, histoplasmosis)	No presumptive clinical diagnosis	Histology, antigen detection or culture from clinical specimen or blood culture
Recurrent non-typhoid salmonella bacteraemia	No presumptive clinical diagnosis	Blood culture
Lymphoma (cerebral or B cell non-Hodgkin) or other solid HIV- associated tumours	No presumptive clinical diagnosis	Histology of relevant specimen or, for CNS tumours, neuroimaging techniques

Clinical event	Clinical diagnosis	Definitive diagnosis
Invasive cervical carcinoma	No presumptive clinical diagnosis	Histology or cytology
Visceral leishmaniasis	No presumptive clinical diagnosis	Histology (amastigotes visualized) or culture from any appropriate clinical specimen
HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

Annexure 3: WHO clinical criteria and criteria for diagnosis in infants and children

	Clinical diagnosis	Definitive diagnosis
Primary HIV infection		
Asymptomatic infection Acute retroviral syndrome	Acute febrile illness 2–4 weeks post-exposure, often with lymphadenopathy, pharyngitis and skin rashes	In children 18 months or over: 1. seroconversion from HIV antibody negative to antibody-positive 2. A positive virological test for HIV virus or its components (RNA or DNA or TNA or HIV p 24 antigen) confirmed by a second virological test obtained from a separate determination 3. Profound temporary lymphopaenia and other transient blood abnormalities may occur
Clinical Stage 1		
Asymptomatic	No HIV related symptoms reported and no signs on examination	Not required
Persistent generalized lymphadenopathy (PGL)	Swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites, without known cause	Not required
Clinical Stage 2		
Unexplained persistent Hepatosplenomegaly	Enlarged liver and spleen without obviouscause	Not required
Papular pruritic eruptions	Papular pruritic vesicular lesions. Also common in uninfected children: scabies and insect bites should be excluded	Not required
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed). Proximal white subungual onchomycosis is uncommon without immunodeficiency	Not required
Angular cheilitis	Splits or cracks on lips at the angle of the mouth with depigmentation, usually responding to antifungal treatment but may recur	Not required
Lineal gingival Erythema (LGE)	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding	Not required
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring	Not required

Extensive molluscum contagiosum infection	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths, may be inflamed or red; facial, more than 5% of body area or disfiguring	Not required
Recurrent oral ulcerations (two or more in six months)	Aphthous ulceration, typically with a halo of inflammation & yellow-grey pseudomembrane	Not required
Unexplained parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless	Not required
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent. Does not cross the midlines	Not required
Recurrent upper respiratory tract infection (URTI)	Current event with at least one episode in past 6 months. Symptom complex; fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough. Persistent or recurrent ear discharge	Not required
Clinical Stage 3		
Unexplained moderate malnutrition	Weight loss: low weight-for-age, up to −2 standard deviations (SDs), not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management	Confirmed by documented loss of body weight of – 2SD, failure to gain weight on standard management and no other cause identified during investigation
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment	Confirmed by stools observed and documented as unformed. Culture and microscopy reveal no pathogens
Unexplained persistent fever (intermittent or constant, for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas	Confirmed by documented fever of >37.5 0C with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease
Oral candidiasis(outside first 6-8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off	Confirmed by microscopy or culture

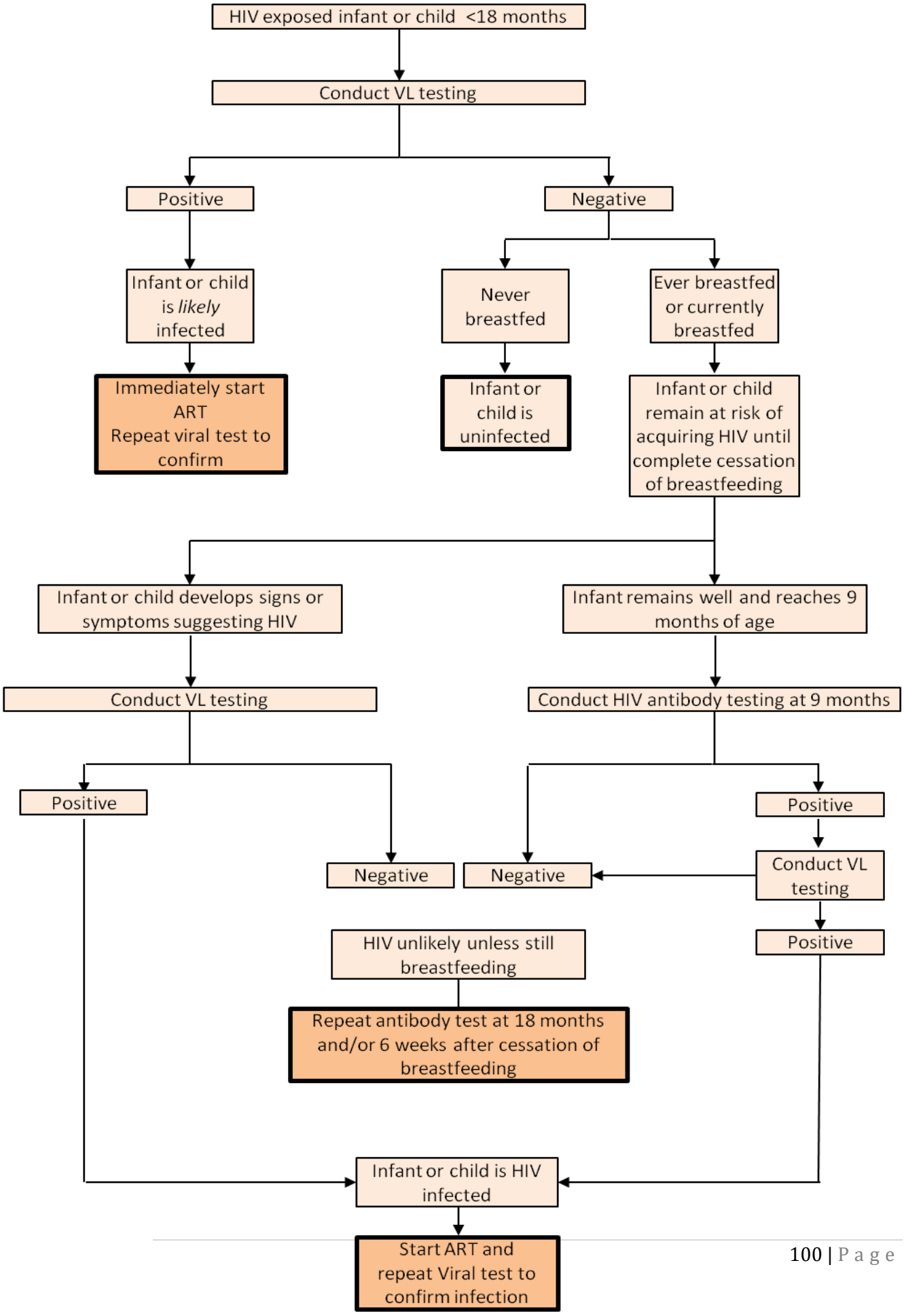
	(pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off	None
Lymph node TB	Non acute, painless "cold" enlargement of lymph nodes, usually matted, localized to one region. May have draining sinuses. Response to standard anti-TB treatment in one month	Confirmed by histology or fine needle aspirate for Ziehl Neelsen stain and/or Culture
Pulmonary TB	Nonspecific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. Abnormal CXR. Response to standard anti-TB treatment in one month	Confirmed by positive sputum smear or culture GenXpert if available
Severe recurrent presumed bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months	Confirmed by isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate)
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue	None
Symptomatic LIP	No presumptive diagnosis	Diagnosed by CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may have increased exercise-induced fatigue. Characteristic histology
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation	Confirmed by CXR may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume

Unexplained anaemia (<8g/dl), or neutropenia (<1000/mm3) or chronic thrombocytopenia (<50 000/ mm3)	No presumptive diagnosis	Diagnosed on laboratory testing, not explained by other non-HIV conditions, or not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in IMCI
Clinical Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of –3 SDs, as defined by WHO IMCI guidelines	Confirmed by documented weight loss of >-3 SD +/- oedema
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI). Usually of rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole +/- prednisolone	Confirmed by: CXR typical bilateral perihilar diffuse infiltrates; microscopy of induced sputum or BAL or NPA, or histology of lung tissue
Recurrent severe presumed bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months	Confirmed by culture of appropriate clinical specimen
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month	Confirmed by culture and/or histology
Oesophageal candida (or candida of trachea, bronchi or lungs).	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids), or retrosternal pain worse on swallowing (food and fluids) responds to specific treatment. In young children, suspect particularly if oral candida observed and food refusal occurs and/or difficulties/crying when feeding	Confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology
Extra pulmonary/disseminated TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis.	Confirmed by positive microscopy showing AFB or culture of Mycobacterium TB from blood or other relevant specimen except sputum or BAL. Biopsy and histology

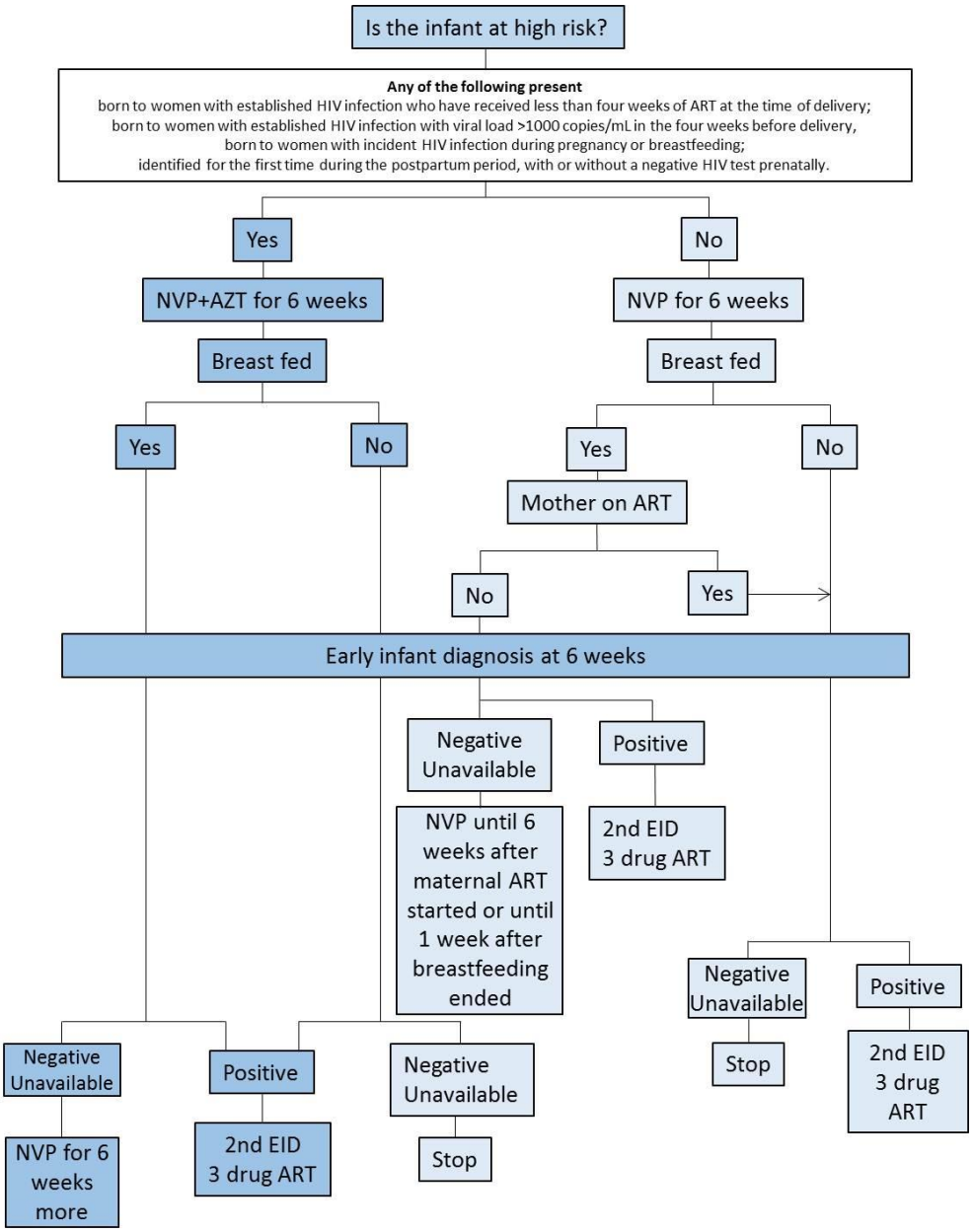
	Responds to standard anti-TB therapy	
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules	Not required but may be confirmed by: • Typical red-purple lesions seen on bronchoscopy or endoscopy • Dense masses in lymph nodes, viscera or lungs by palpation or radiology • Histology
CMV retinitis or CMV infection affecting another organ, with onset at age over 1 month.	Retinitis only. CMV retinitis may be diagnosed by experienced clinicians: progressive floaters in field of vision, light flashes and scotoma; typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis	Definitive diagnosis required for other sites. Histology. CSF polymerase chain reaction (PCR)
CNS toxoplasmosis with onset at age over 1 month.	Fever, headache, focal neurological signs, convulsions. Usually responds within 10 days to specific therapy.	Not required but confirmed by computed tomography (CT) scan showing single/multiple lesions with mass effect/enhancing with contrast.
Extra-pulmonary cryptococcosis including meningitis	Meningitis: usually sub-acute, fever with increasing severe headache, meningism, confusion, behavioural changes that responds to cryptococcal therapy.	Confirmed by CSF microscopy (India ink or Gram stain), serum or CSF CRAG or culture.
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: - failure to attain, or loss of, developmental milestones, loss of intellectual ability; or - progressive impaired brain growth demonstrated by stagnation of head circumference; or - acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances.	Confirmed by brain CT scan or MRI demonstrating atrophy and basal ganglia calcification and excluding other causes.
Disseminated mycosis (coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive diagnosis.	Diagnosed by: Histology: usually granuloma formation. Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture.
Chronic Disseminated nontuberculous	No presumptive diagnosis.	Nonspecific clinical symptoms including progressive weight

mycobacteriosis		loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung.
Chronic cryptosporidiosis	No presumptive diagnosis.	Confirmed in children with chronic diarrhoea lasting longer than one month by microscopic examination.
Chronic Isosporiasis	No presumptive diagnosis.	Confirmed in children with chronic diarrhoea by microscopic examination.
Cerebral or B cell non-Hodgkin lymphoma	No presumptive diagnosis.	Diagnosed by CNS imaging: at least one lesion with mass effect on brain scan; histology of relevant specimen
Progressive multi focal leukoencephalopathy (PML)	No presumptive diagnosis.	Diagnosed by MRI or CT scan, and biopsy. Viral PCR for Jacob Creutzfeldt virus.

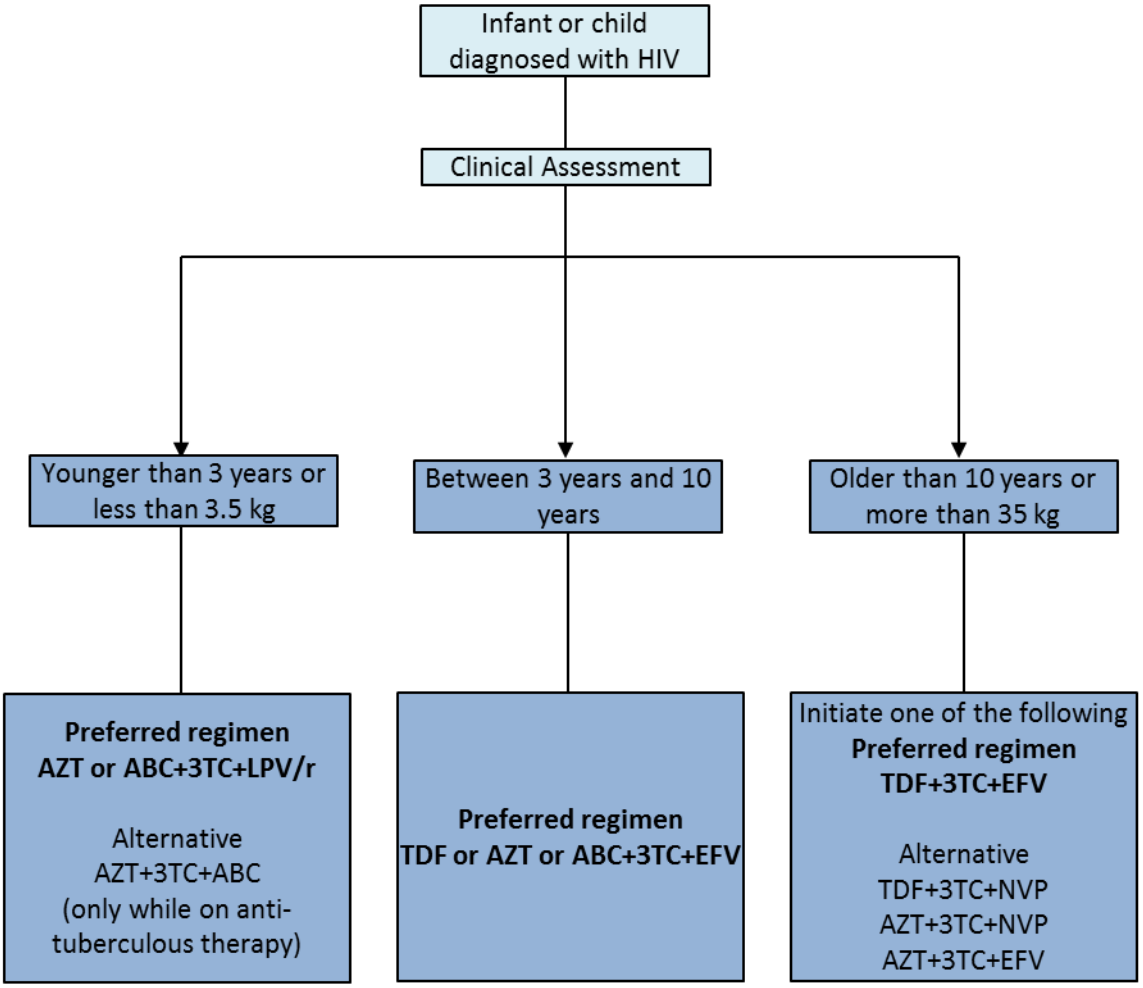
Annexure 4: Algorithm diagnosis of HIV in infants



Annexure 5: Algorithm for PPTCT



Annexure 6: What to start in children with HIV



Note: CPT indicated for CD4 <200 cells/mm^3 and MAC prophylaxis is indicated for CD4 <100 cell/mm^3

Annexure 7 Dosages of antiretroviral drugs for adults and adolescents (>35 kg)

Generic name	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Didanosine (ddI)	400 mg once daily (>60 kg) 250 mg once daily (≤60 kg)
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Stavudine (d4T)	30 mg twice daily
Zidovudine (AZT)	250–300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	600 mg once daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily
Protease inhibitors (PI)	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg once daily
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily Considerations for individuals receiving TB therapy In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin, adjusted dose of LPV/r (LPV 800 mg + RTV 200 mg twice daily or LPV 400 mg + RTV 400 mg twice daily)
Raltegravir	
FDCs EFV+3TC+TDF (ABC+3TC) co packaged with EFV	

Annexure 8: Dosages of antiretroviral drugs for infants, children and adults <35 kg

Drug	Strength of tablets (mg) or oral liquid (mg/ml)	Number of tablets by weight band morning and evening											
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	
Dosing for Solid Formulations (Fixed Drug Combinations) currently available through NACP for children													
ABC-3TC	(ABC600 3TC300)											1	
Co-pack	(ZDV300 3TC150) + (EFV600)											1+0	
EFV-3TC-TDF	(EFV600 3TC300 TDF300)											1	
Duovir-N	(3TC150 ZDV300 NVP200)											1	
ZDV/3TC	(ZDV300 3TC150)							0.5	0.5	1	0.5	1	
3TC/NVP/AZT	3TC30+NVP50+ZDV60 (dispersable)	1	1	2	1	2	2	3	2	4	3.5		
Simplified Dosing for urgently needed ARV (FDCs) for children recommended by the Pediatric Antiretroviral Drug Optimization Group													
ABC-3TC-LPV/r	(ABC30/3TC15/LPV40/r10)	2	2	3	3	4	4	5	5	6	6	-	
AZT-3TC-LPV/r	(AZT30/3TC15/LPV40/r10)	2	2	3	3	4	4	5	5	6	6		
DRV/r	(DRV120/r20)					2	2	3	3	3	3	4	
ATV/r	(ATV100/r33)					1		2		2		-	
ABC-3TC-EFV	(ABC150/3TC75/EFV150)					1.5		2		2.5		3	
Dosing for Solid Formulations currently available for children at NACP													
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	
ABC	Tab 300 mg (adult)							0.5	0.5	1	0.5	1	
3TC	Tab 30 mg (dispersable)	1	1	2	1	2	2	3	2	3	3	5	
	Tab 150mg (adult)	-	-	-	-			0.5	0.5	1	0.5	1	
AZT	Tab 60 mg (dispersable)	1	1	2	1	2	2	3	2	3	3	5	
	Tab 300mg (adult)							0.5	0.5	1	0.5	1	
NVP	Tab 200mg (Induction)					0.5	-	1	-	1	-	1	

NVP	Tab 200mg (Maintenance)					0.5	0.5	1	0.5	1	0.5	1	
LPV/r	Tab 200/50 (adult)					1	0.5	1	1	1	1	2	
LPV/r	Tab 100/25					2	1	2	2	2	2	3	
RAL	Tab 400 mg											1	
Dosing for Solid Formulations in children													
Drug	Weight Band	3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–34.9 kg	
	Frequency	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	
EFV	Tab 200 mg					1	-	1	-	1	0.5	1	
	Tab 600mg					0.5	-	0.5	-	0.5	-	[c]	
DDI	Cap 250 mg					0.5	-	1	-	1	-	1	
TDF	Tab 300mg							0.5 tab OD		0.5 tab OD		1	
	Tab 150 mg or 200 mg							150 mg tab OD		200 mg tab OD		-	
	Powder 40 mg per scoop	-		-		3 scoops OD		4 scoops OD		5 scoops OD		-	
Dosing for Liquid Formulations in children													
Drug	Weight Band	3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–34.9 kg	
	Frequency	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	
AZT	10 mg/ml	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	15 ml	15 ml	18 ml	18 ml	–	
ABC	20 mg/ml	3 ml	3 ml	4.5 ml	4.5 ml	6 ml	6 ml	7.5 ml	7.5 ml	9 ml	9 ml	–	
3TC	10 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–	
NVP[a]	10 mg/ml	5 ml	5 ml	7.5 ml	7.5 ml	10 ml	10 ml	12.5 ml	12.5 ml	15 ml	15 ml	–	
LPV/r	80/20 mg/ml	1ml	1 ml	1.5ml	1.5ml	2 ml	2 ml	2.5ml	2.5ml	3 ml	3 ml	–	
Drug	Weight Band	3-3.9 kg		4-5.9 kg		6-7.9 kg		8-10.9 kg		11-13.9 kg		14-19.9 kg	20-24.
	Frequency	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM+PM	PM
RAL	20 mg/ ml	1	1	1.5	1.5	2	2	3	3	4	4	5+5	7.5
Drug	Weight Band	3.5-4.9 kg		5-7.4 kg		7.5-14.9 kg		15-19.9 kg		20-24.9 kg		25-32.4 kg	32.5-39.9 kg
	Frequency	OD		OD		OD		OD		OD		OD	OD
EFV	Susp 30 mg/ml , tab 600mg	3.5 ml		5 ml		6.5 ml		8.5 ml		10ml or ½ tab		12ml or ½ tab	13.5 ml
Infant Prophylaxis													
Drug	Age	Birth to 6 weeks										>6 weeks to 12 wee	

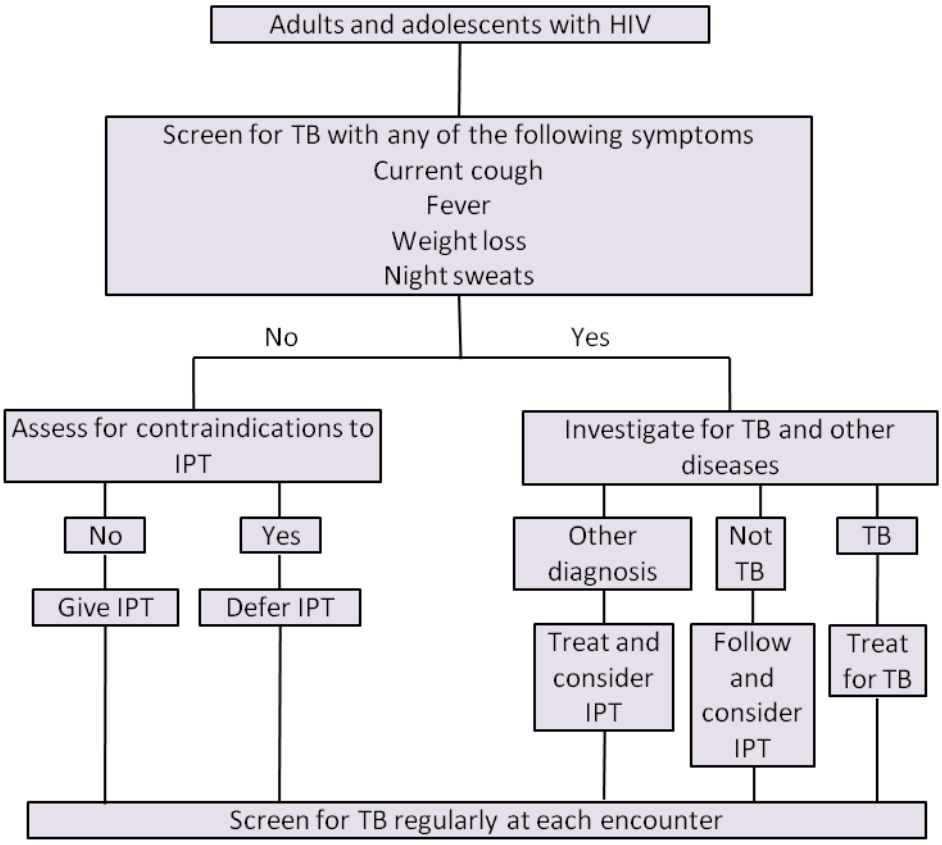
	Weight band	2- 2.49 kg		>2.5 kg			
AZT	Susp 10 mg/ml	1 ml twice daily		1.5 ml twice daily		6 ml twice daily	
NVP	Susp 10 mg/ml	1 ml once daily		1.5 ml once daily		2 ml once daily	
Isoniazid Preventive Therapy (IPT)							
Weight band		<5 kg	5.1-9.9 kg	10-13.9 kg	14-19.9 kg	20-24.9 kg	>2
INH	Tab 100 mg	½ tab OD	1 tab OD	1 ½ tab OD	2 tab OD	2 ½ tab OD	3 ta
Weight band		5-7 kg		8-14 kg		≥15 kg	
Vita 6	Tab 50 mg	¼ tab OD		½ tab OD		1 tab OD	
Cotrimoxazole Preventive Therapy (CPT)							
Weight band		<5 kg		5-15 kg		15-30 kg	>3
CTX	Susp 200/40 per 5 ml	2.5 ml OD		5 ml OD		10 ml OD	
	Tab(disper) 100/20 mg	1 tab OD		2 tab OD		4 tab OD	
	Tab(scored) 400/80mg	¼ tab OD		½ tab OD		1 tab OD	2 ta
	DS Tab(scored) 800/160mg	-		-		½ tab OD	1 ta
MAC Prophylaxis							
Clarithromycin Azithromycin	Susp 250mg per 5ml Susp 200mg per 5ml	Clarithromycin 7.5 mg/kg body weight (maximum 500 mg) by mouth orally twice daily, or Azithromycin 20 mg/kg body weight (maximum 1200 mg) orally once weekly					

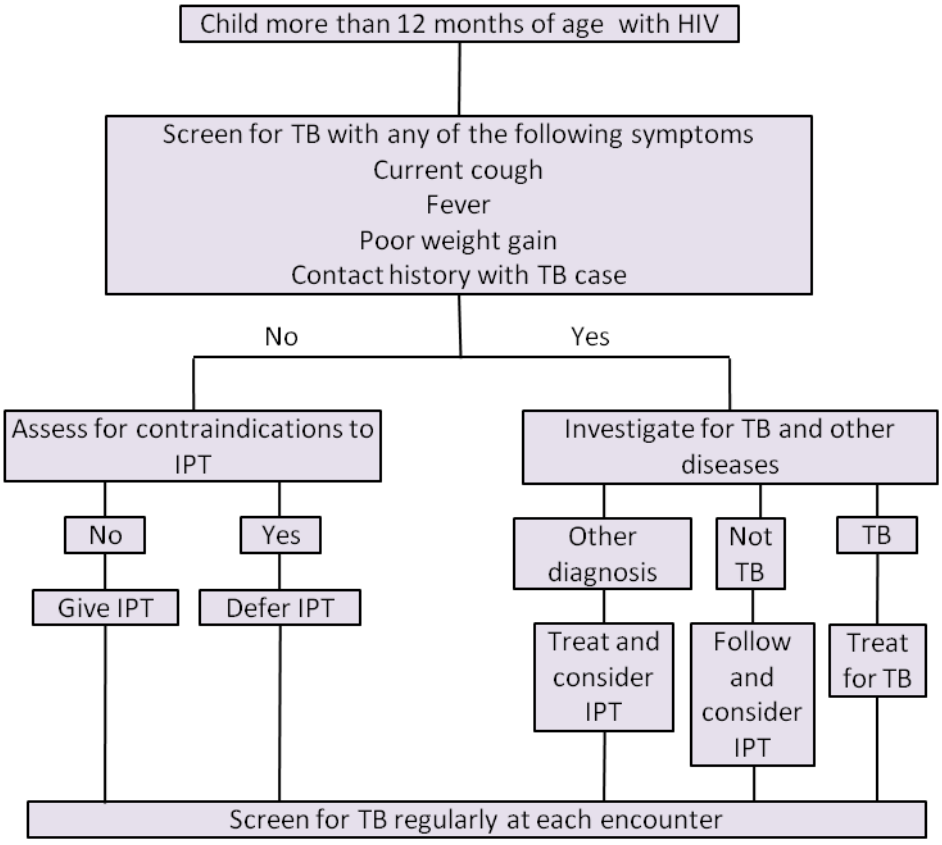
a: Dose escalation is recommended by giving half the dose for the first 2 weeks

b: Do not crush or split

c: Consult a pediatric infectious disease specialist for dosage for less than 17kg

Annexure 9: INH Preventative therapy algorithm





Annexure 10: Side-effects and suggested management of commonly used ARVs used in Pakistan

ARV Drug	Major types of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 Gene	If ABC is being used in first-line ART, substitute with TDF or AZT. If ABC is being used in second line ART, substitute with TDF
ATV/r	Electrocardiographic abnormalities (PR interval prolongation)	Pre-existing conduction disease Concomitant use of other drugs that may prolong the PR interval	LPV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider integrase inhibitors
	Indirect hyperbilirubinaemia (clinical jaundice)	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs	
	Nephrolithiasis and risk of prematurity	Risk factors unknown	
AZT	Anaemia, neutropaenia, myopathy, lipoatrophy or lipodystrophy	Baseline anaemia or neutropaenia CD4 count ≤200 cells/mm^3	If AZT is being used in first-line ART, substitute with TDF or ABC If AZT is being used in second-line ART, substitute with ABC
	Lactic acidosis or severe hepatomegaly with steatosis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	
d4T	Peripheral neuropathy, lipoatrophy or lipodystrophy	Older age CD4 count ≤200 cells/mm^3 Concomitant use of isoniazid or ddI	If d4T is being used in first-line ART, substitute with TDF or AZT or ABC If d4T is being used in second-line ART (after TDF or ABC are used in first-line ART), substitute with AZT
	Lactic acidosis or severe hepatomegaly with steatosis, acute pancreatitis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	
EFV	Persistent central nervous system toxicity (such as abnormal dreams,	Depression or other mental disorder (previous or at baseline) Daytime dosing	NVP. If the person cannot tolerate either NNRTI, use boosted PIs

	depression or mental confusion)		
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drug	
	Convulsions	History of seizure	
	Hypersensitivity reaction Stevens-Johnson syndrome Male gynaecomastia	Risk factors unknown	
LPV/r	Electrocardiographic abnormalities (PR and QT interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR interval	If LPV/r is used in first-line ART for children, use an age-appropriate NNRTI (NVP for children younger than 3 years and EFV for children 3 years and older). ATV can be used for children older than 6 years If LPV/r is used in second-line ART for adults, use ATV/r or DRV/r. If boosted PIs are contraindicated and the person has failed on treatment with NNRTI in first-line ART, consider integrase inhibitors
	QT interval prolongation	Congenital long QT syndrome Hypokalaemia Concomitant use of drugs that may prolong the QT interval	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	
	Pancreatitis	Advanced HIV disease	
	Risk of prematurity, lipoatrophy or metabolic	Risk factors unknown	

	syndrome, dyslipidaemia or severe diarrhoea		
NVP	Hepatotoxicity	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs CD4 >250 cells/mm^3 in women CD4 >400 cells/mm^3 for men First month of therapy (if lead-in dose is not used)	EFV. If the person cannot tolerate either NNRTI, use boosted PIs
	Severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome)	Risk factors unknown	
TDF	Tubular renal dysfunction, Fanconi syndrome	Underlying renal disease Older age BMI <18.5 (or body weight <50 kg) Untreated diabetes mellitus Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	If TDF is being used in first-line ART, substitute with AZT or d4T or ABC If TDF is being used in second-line ART (after d4T + AZT use in first line ART), substitute with ABC or ddI
	Decreases in bone mineral density	History of osteomalacia and pathological fracture Risk factors for osteoporosis or bone loss	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity	

	Exacerbation of hepatitis B (hepatic flares)	Discontinuation of TDF due to toxicity	Use alternative drug for hepatitis B treatment (such as entecavir)
DTG	Hepatotoxicity Hypersensitivity reactions	Hepatitis B or C coinfection Liver disease	If DTG is used in first-line ART, and there are hypersensitivity reactions, substitute with another therapeutic class (EFV or boosted PIs).

Annexure: Summary of ART Regimens for children who need TB treatment (from WHO 2016 guidelines)

Recommended regimens for children and adolescents initiating ART while on TB treatment[a,b]		
Younger than 3 years		Triple NRTI (AZT + 3TC + ABC)[c]
3 years and older		Two NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC)[c]
Recommended regimen for children and infants initiating TB treatment while receiving ART[a]		
Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP)	Younger than 3 years	Continue NVP, ensuring that the dose is 200 mg/m^2 or Triple NRTI (AZT + 3TC + ABC)[c]
	3 years and older	If the child is receiving EFV, continue the same regimen If the child is receiving NVP, substitute with EFV or Triple NRTI (AZT + 3TC + ABC)[c]
Recommended regimen for children and infants initiating TB treatment while receiving ART[a]		
Child on standard PI-based regimen (two NRTIs + LPV/r)	Younger than 3 years	Triple NRTI (AZT + 3TC + ABC)[c] or Continue LPV/r, adding RTV to achieve the full therapeutic dose[d]
	3 years and older	If the child has no history of failure of an NNRTI-based regimen: Substitute with EFV[e] or Triple NRTI (AZT + 3TC + ABC)[c] or Continue LPV/r, adding RTV to achieve the full therapeutic dose[d] If the child has a history of failure of an NNRTI-based regimen: Triple NRTI (AZT + 3TC + ABC)[c] or Continue LPV/r, adding RTV to achieve the full therapeutic dose[d] Consider consultation with experts for constructing a second- line regimen

[a] Ensure optimal dosing of rifampicin based on dosing guidelines (Annex 11c).

[b] Substitute ARV drugs based on an age-appropriate ART regimen in line with nationally recommended first-line ART.

[c] Triple NRTI is only recommended for the duration of TB treatment; an age-appropriate PI- or NNRTI-based regimen should be restarted when rifampicin-based therapy ends. Based on the findings from the ARROW trial *(174)*, this regimen should be considered as the preferred option for children younger than 3 years who are receiving an LPV/r-based regimen when starting TB treatment. The US FDA approval for the use of EFV in children 3 months to 3 years old weighing more than 3.5 kg offers a potential alternative to the triple-NRTI approach *(358)*. An EFV-based regimen in children under 3 years is still not recommended because pharmacokinetic data are needed to ensure that the co-administration of rifampicin does not decrease drug levels below the therapeutic level. Triple NRTI should also be considered as the preferred regimen for children older than 3 years with a history of failure on an NNRTI-based regimen.

Annexure 11: Renal adjustment and hepatic adjustment for commonly used ARV in Pakistan

ARV	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
Abacavir (ABC)	300 mg PO BID	No dosage adjustment necessary	Child-Pugh Score Dose 5–6 200 mg PO BID (use oral solution) >6 Contraindicated
Lamivudine (3TC)	300 mg PO once daily or 150 mg PO BID	CrCl (mL/min) Dose 30–49 150 mg q24h 15–29 150 mg x1, then 100mg qd 5–14 150 mg x1, then 50 mg qd <5 or on HD* 50 mg x1, then 25 mg q24h *On dialysis days, take dose after HD session	
Stavudine (d4T)	Body weight ≥60 kg: 40 mg PO BID Body weight <60 kg: 30 mg PO BID	CrCl (mL/min) ≥60 kg <60 kg 26–50 20 mg q12h 15 mg q12h 10–25 or HD* 20 mg q24h 15 mg q24h *On dialysis days, take dose after HD session	
Tenofovir (TDF)	300 mg PO once daily	CrCl (mL/min) Dose 30–49 300 mg q48h 10–29 300 mg twice weekly (every 72–96 hours) <10, not on HD Not recommended On HD* 300 mg q7d	
Zidovudine (AZT)	300 mg PO BID	CrCl (mL/min) Dose <15 or HD* 100 mg TID or 300 mg once daily *On dialysis days, take dose after HD session	
Efavirenz (EFV)	600 mg PO once daily, at or before bedtime	No dosage adjustment necessary	
Nevirapine (NVP)	200 mg PO BID	Patients on HD: limited data; no dosage Recommendation	Child-Pugh Class A: No dosage adjustment Child-Pugh Class B or C: Contraindicated

Lopinavir/ritonavir (LPV/r)	400/100 mg PO BID or 800/200 mg PO once daily	Avoid once-daily dosing in patients on HD	No dosage recommendation; use with caution in patients with hepatic impairment.

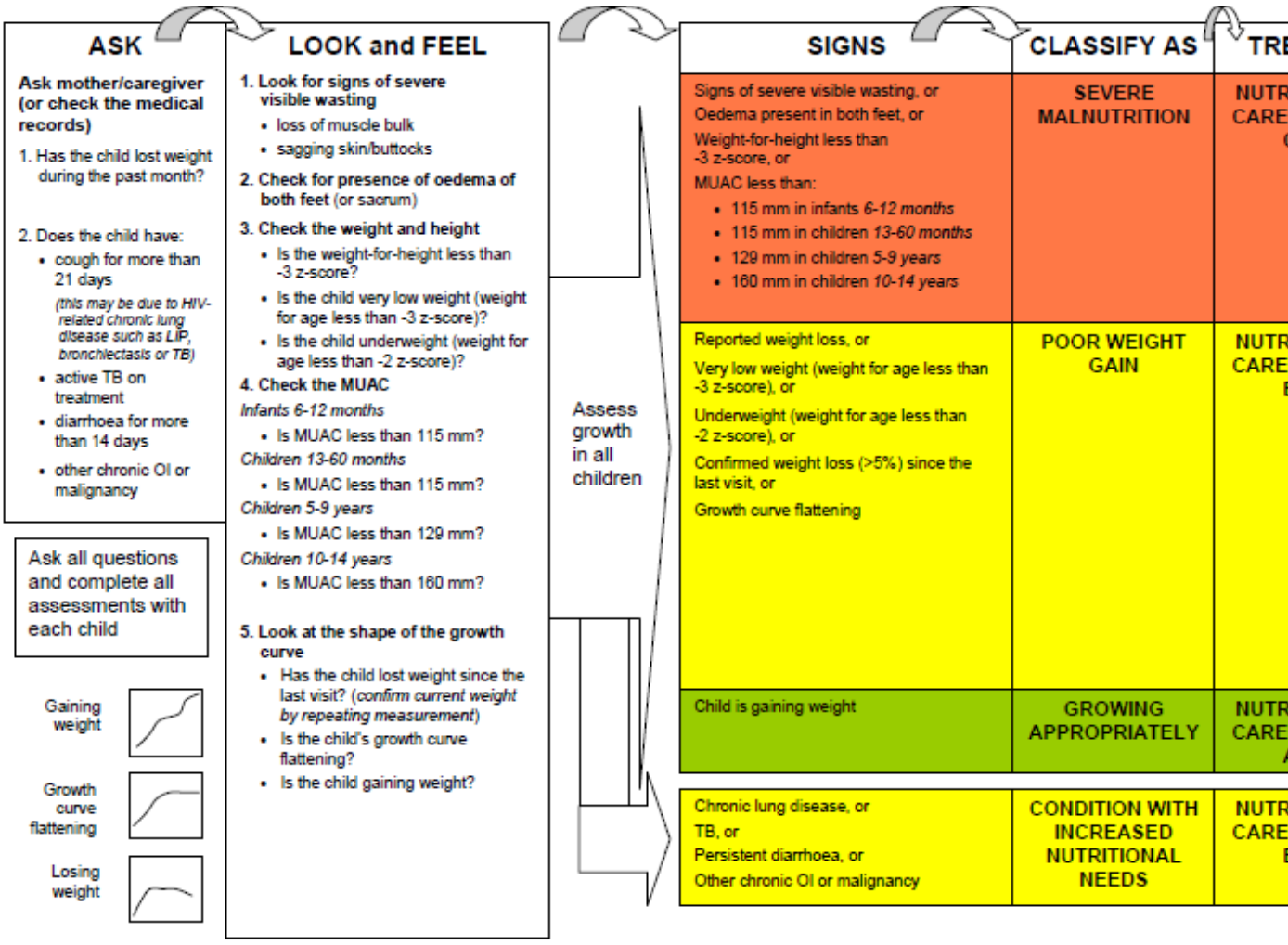
* eGFR can be calculated for adults as follows: $\frac{(age-140) \times weight}{72 \times creatinine}$ (multiply by 0.85 if female)

* eGFR (ml/min/1.73m^2) can be calculated for childrenas follows: k× (length in cm) / Serum Creatinine in mg/dL)

Where k: 0.33 (low birth weight infant), 0.45 (term infant), 0.55 (children and girls aged 13-21y), 0.70 (boys aged 13-21y)

Annexure 12: Nutritional Care of HIV-infected children

from: Guidelines for an integrated approach to the nutritional care of HI V-infected children (6 months–14 years)



Annexure 13: Nutrition Care Plan A for the child who is growing well ± ART

from: Guidelines for an integrated approach to the nutritional care of HI V-infected children (6 months–14 years) 2009

1st Action. Ask about general condition and if child is on any treatment including ART and TB medicine?

- Also check immunizations (Step 7)
- Is the child at school?
- If child is on ART then also complete Step 10. Check if ART dose needs to be adjusted up.

2nd Action. Check mother's health (+ need for ART) and care of other children

3rd Action. Nutrition counselling

- Encourage mother/caregiver that the child is growing well. Explain growth chart and how to follow progress.
- Ask, have there been any major changes in the child's circumstances from the last visit that might put the care of the child at risk, including access to food?
- Advise mother/caregiver why additional food (energy) is needed in children (and adults) with HIV infection (approx 10%).
- Counsel on continued breastfeeding if mother is well (check national guidelines related to breastfeeding policy and age of the child).
- Counsel on complementary feeding and replacement feeding (frequency of meals, amount and type of food per meal, responsive feeding – see Appendices VI and VII). Reinforce and encourage good practices.
- Counsel on feeding a variety of foods such as milk, fruit, vegetables, whole grains, cereals and meat/chicken or fish based on local diets i.e. food sources that are high in vitamin A, iron, calcium, etc. and other locally produced foods.
- Review safe food preparation, food and water storage methods and hygiene issues (keep hands, utensils and food preparation area clean; separate raw and cooked foods; cook food thoroughly; keep food at safe temperature; use safe water and food).
- Check if there are other sources of good foods such as garden projects or other community resources.

4th Action. Meet age-specific needs and additional 10% energy based on actual weight

Examples of ways to increase energy intake by 10% using food GIVE IN ADDITION TO THE MEALS AND SNACKS APPROPRIATE FOR THE CHILD'S AGE
6-11 months [additional 60-75 kcal = Total ~760 kcal/day] • LOCAL ADAPTATION – Give examples and quantities of local foods that can be used to increase energy density of other foods e.g. 2 tsp margarine/oil and 1-2 tsp sugar to porridge or that can be given in addition to normal diet.
12 -23 months [additional 80-95kcal = Total ~990 kcal/day] • LOCAL ADAPTATION – Give examples and quantities of local foods that can be used to increase energy density of other foods e.g. margarine/oil and sugar to porridge or that can be given in addition to normal diet.
2-5 years [additional 100-140 kcal = Total ~1390 kcal/day] • LOCAL ADAPTATION – Give examples and quantities of local foods that can be used to increase energy density of other foods or that can be given in addition to normal diet e.g. extra cup of full cream milk/fermented milk.
6-9 years [additional 130-190 kcal = Total ~1815 kcal/day] • LOCAL ADAPTATION – Give examples and quantities of local foods that can be used to increase energy density of other foods or that can be given in addition to normal diet e.g. extra cup of full cream milk/fermented milk.
10-14 years [additional 170-230 kcal = Total ~2200 kcal/day] • LOCAL ADAPTATION – Give examples and quantities of local foods that can be used to increase energy density of other foods or that can be given in addition to normal diet. e.g. extra cup of fruit yoghurt or cheese/peanut butter sandwich

5th Action. Ensure adequate micronutrient intake

- If the child's diet is not balanced and does not contain a variety of animal sourced foods, fruits and vegetables then give a daily micronutrient supplement that provides 1 Recommended Daily Allowance of a wide range of vitamins and other micronutrients. Refer to national guidelines.

6th Action. Vitamin A supplements every 6 months

- 6-12 months 100 000 IU 1-5 years 200 000 IU

Do not give if child has received dose within the past month e.g. from hospital

For children >5 yrs, vitamin A should be provided through regular daily micronutrient supplements

7th Action. De-worm every 6 months (Step 7)

- Albendazole (oral) 400 mg single dose every 6 months after first year of life.

8th Action. Cotrimoxazole prophylaxis (Step 7)

- Provide from 6 weeks of age 5 mg/kg/day. See step 7 for guidance on when to stop.

9th Action. Ensure mother/caregiver understands care plan and ask if she/he has any questions

10th Action. Review in 2-3 months (tell caregiver to return earlier if problems arise).

Annexure 14: Nutrition Care Plan B with poor weight gain or increased nutritional needs

from: Guidelines for an integrated approach to the nutritional care of HI V-infected children (6 months–14 years) 2009

1st Action. Clinically stage the child (Appendix I) and assess for ART. Check for treatable conditions. If on ART, assess, clinical and immunological response (complete Step 10). Refer if indicated

2nd Action. Check mother's health (+ need for ART) and care of other children

3rd Action. Nutrition counselling

- What does the child eat and drink? (Step 4)
- Who gives the child his/her food and how does the child eat? (Step 5)
- Is there food at home? (Step 6)
- Advise mother/caregiver why additional food (energy) is needed in children (and adults) with HIV + complications.
- Review safe food preparation, food and water storage methods and hygiene issues. (Step 7)
- Ask, have there been any major changes in the child's circumstances from the last visit that might put the care of the child at risk, including access to food? (Step 6)

4th Action. Meet age-specific needs and additional 20- 30% food (energy) based on actual weight

These needs may be achieved either through a food-based approach or through specific nutritional supplements – either form of support should be provided by the service/programme

Food-based approach or Nutritional Supplement*

GIVE IN ADDITION TO MEALS AND SNACKS

6-11 months [additional 120-150 kcal per day]

- **LOCAL ADAPTATION**: Give examples of quantities and frequency of local foods that can be used to increase energy density of other foods e.g. 2 tsp margarine/oil and 1-2 tsp sugar to porridge. Aim to add 3 times daily

12-23 months [additional 160-190 kcal per day]

- **LOCAL ADAPTATION**: Give examples of quantities and frequency of local foods that can be used to increase energy density of other foods e.g. extra cup of full cream milk or cheese/peanut butter sandwich (1 slice)

2–5 years [additional 200-280 kcal per day]

- **LOCAL ADAPTATION**: Give examples of quantities and frequency of local foods that can be used to increase energy density of other foods e.g. extra cup of enriched milk or cheese/peanut butter sandwich (4 slices)

6–9 years [additional 260-380 kcal per day]

- **LOCAL ADAPTATION**: Give examples of quantities and frequency of local foods that can be used to increase energy density of other foods e.g. extra cup of enriched milk or cheese/peanut butter sandwich (6 slices)

10-14 years [additional 340-400 kcal per day]

- **LOCAL ADAPTATION**: Give examples of quantities and frequency of local foods that can be used to increase energy density of other foods e.g. 3 cheese/peanut butter/egg sandwiches (6 slices)

See Appendix III in the Handbook for examples of foods than can provide additional 20-30% energy.

5th Action. Ensure adequate micronutrient intake

- If the child's diet is not balanced then give a daily micronutrient supplement that provides 1 RDA of a wide range of vitamins and other micronutrients. Refer to national guidelines).
- Check if any prescribed nutritional supplement provides micronutrient intake. Additional supplements may not be needed.
- If recent diarrhoeal illness, give zinc supplement (20 mg daily for 2 weeks).

6th Action. Vitamin A supplements every 6 months

- 6-12 months 100 000 IU >12 months 200 000 IU

Do not give if child has received dose within the past month e.g. from hospital

For children >5 yrs, vitamin A should be provided through regular daily micronutrient supplements

7th Action. De-worm every 6 months (Step 7)

- Albendazole (oral) 400 mg single dose every 6 months after first year of life.

8th Action. Cotrimoxazole prophylaxis (Step 7)

- Provide from 6 weeks of age 5 mg/kg/day. See step 7 for guidance on when to stop.

9th Action. Ensure mother/caregiver understands care plan and ask if she/he has any questions

10th Action. Review 1st visit 1-2 weeks. If responding, then review every 1-2 months depending on response. Change to Nutrition Care Plan A when nutritional recovery achieved

* The term nutritional supplement is used to refer to fortified processed foods

Annexure 15: Nutrition Care Plan C for the severely malnourished HIV-infected child

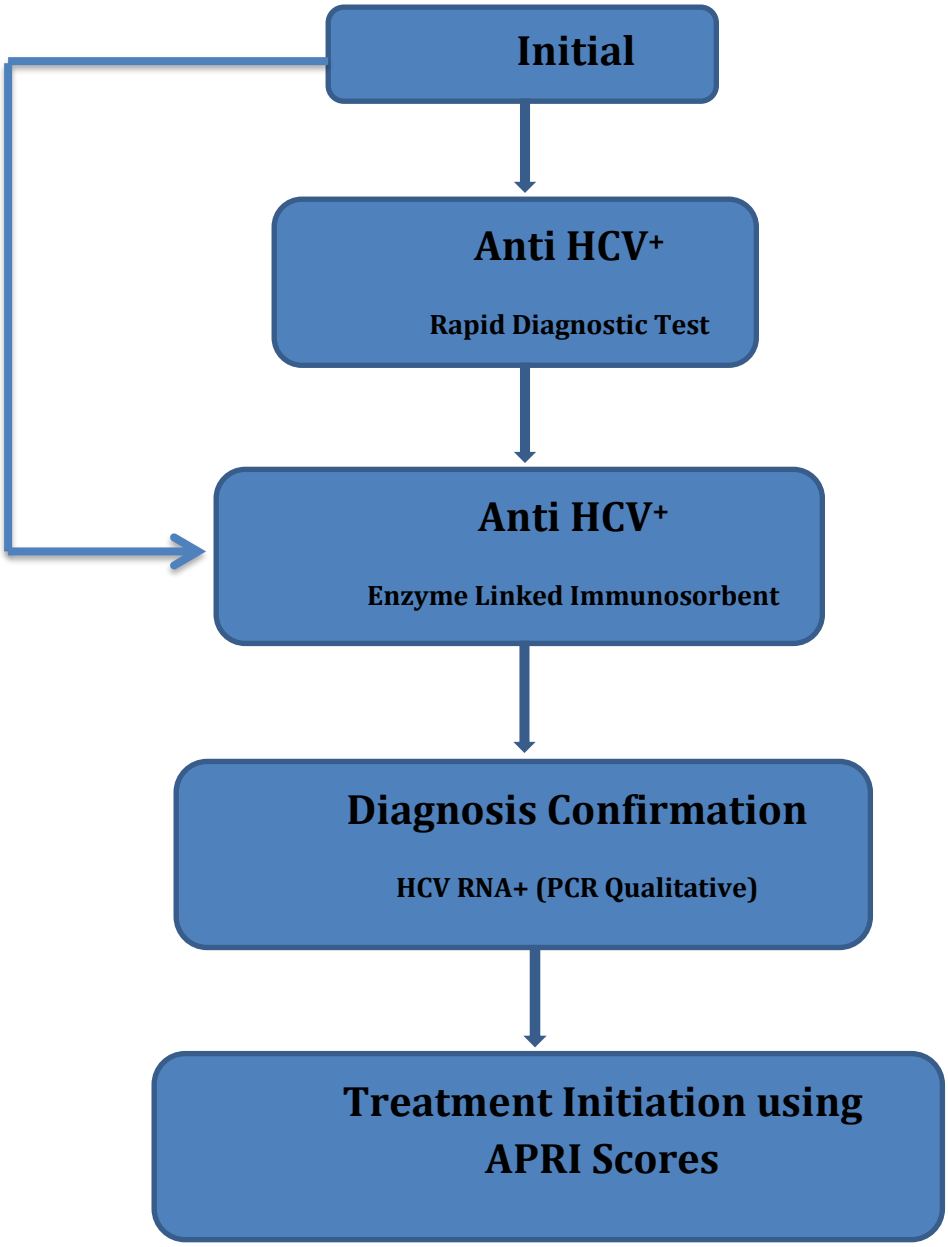
from: Guidelines for an integrated approach to the nutritional care of HI V-infected children (6 months–14 years) 2009

1st Action. Assess if the child needs to be admitted "CHECK FOR GENERAL DANGER SIGNS"

- Assess if there are signs of a concurrent opportunistic infection. If yes, then Admit and Treat accordingly.
- Assess if the child wants to eat. **Conduct a test feed (Step 4)**. If the child will not eat (suggestive of underlying complications) then Refer tor specialised care for management as per WHO Management of Children with Severe Malnutrition.
- If the child eats well then plan home (community-based) management according to table below. Prescribe feeds.
- Assess if there have been any major changes in the child's circumstances? (Step 6).

2nd Action. Clinically stage the child (Appendix I). Assess for ART, clinical and immunological response to ART including adherence and refer if indicated.

Annexure 16: Treatment cascade for management of Hepatitis C



Annexure 17: Eligibility Criteria for HCV Treatment Using APRI Score

APRI Score	Staging of Fibrosis & Cirrhosis	Treatment Decision	Treatment	
			Preferred Treatment	Alternate Treatment
<0.5	**No Fibrosis**	Defer for treatment	***Though these patients have viremia but they don't have significant fibrosis, therefore, their treatment can be delayed for a few years. But if the patient insists for treatment and resources are available, use the following regimen;*** **24 weeks Treatment:** Sofosbuvir 400 mg (one tablet per day) **Plus** Ribavirin(1000 mg a day for <75 kg and 1200 mg a day for >75 kg)	***Though these patients have viremia but they don't have significant fibrosis, therefore, their treatment can be delayed for a few years. But if the patient insists for treatment and resources are available, use the following regimen;*** **12 weeks Treatment:** Sofosbuvir 400 mg (one tablet per day) **Plus** Daclatasvir 60 mg/day (one tablet per day)
0.5 – 2	**Significant Fibrosis**	If resources are available, could be treated	Same treatment as above	Same treatment as above
>2	**Cirrhosis without decompensation**	Prioritize for Treatment	Same treatment as above	**24 weeks Treatment:** Sofosbuvir 400 mg (one tablet per day) **Plus** Daclatasvir60 mg/day (one tablet per day) **Plus** Ribavirin (1000 mg a day for <75 kg and 1200 mg a day for >75 kg)
	Cirrhosis with decompensation	Refer to tertiary care hospital/liver specialist		
Complicated cases and Patients with co-infections like HIV, Renal Failure, TB etc. should be referred to tertiary care hospital/liver specialist				

Note: APRI Score = [{AST (IU/L)/ Lab's AST_ULN (IU/L)} ×100]/ platelet count (109/L)

ALT - alanine aminotransferase AST - aspartate aminotransferase

IU - international unit ULN - upper limit of normal

Annexure 18: Algorithm for providing a package of care for people with advanced HIV disease