NATIONAL CLINICAL PROTOCOL ON ANTI RETROVIRAL THERAPY (ART)

National AIDS Control Program

Ministry of Public Health
Afghanistan

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Acknowledgements

The Afghan progress towards ART (anti retroviral therapy) began in 2007 when WHO and NACP agreed to begin. Dr. Zubair Harooni, resident physician at the national infection hospital, was inducted into ART at a two-week Belgian training program. By late year, Dr. Veronique Bortolotti, EMRO WHO, assisted the national ART working group to review an Afghan specific framework which was presented to the national HIV services group in 2008. In addition, the MOPH included first line ART drugs onto the licensed drug list in December 2007. Dr. Zubair then adapted the national clinical guidelines for ART in 2008.

Many paragraphs in this protocol have been borrowed from the WHO Antiretroviral treatment of HIV infection in infants and children in resource-limited settings, towards universal access: Recommendations for a public health approach, WHO, 2003

List of Abbreviations

3TC	lamivudine
ABC	abacavir
AIDS	Acquired Immunodeficiency Syndrome
ANC	antenatal care
APV	amprenavir
ART	antiretroviral treatment (therapy)
ARV	Anti-Retroviral
ASI	Addiction Severity Index
ATS	amphetamine type stimulants
BPRS	Brief Psychiatric Rating Scale
BPHS	Basic Package of Health Services
CBT	Cognitive Behavioural Therapy
CMV	cytomegalovirus
CYP 450	cytochrome P450
CTX	CTX
d4T	stavudine
DAART	directly administered antiretroviral treatment
ddI	didanosine
DIC	Drop inCenter
DNA	dezoxyribonucleic acid
DOT	Directly Observed Treatment
DVT	deep venous thrombosis
EFV	efavirenz
FDC	fixed dose combinations
FTC	emtricitabine
GHB	gamma-hydroxybutyrate
Hb	haemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICD10	International Classification of Disease 10th revision
ICU	intensive care unit
IDU	injecting drug use
IDU	Injecting Drug Users
IDV	indinavir
INH	isoniazid
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
LSD	lysergic acid diethylmide
MAC	mycobacterium avium complex
MADRS	Montgomery Asberg Depression Rating Scale
MAP	Maudsley Addiction Profile
MDM	Medicins du Monde
MDMA	methylenedioxymethamphetamine
MDR	multi-drug resistance
MMT	methadone maintenance treatment

MOCN	Ministry of Counter Narcotics
MOPH	Ministry of Public Health
MTCT	mother to child transmission
NFV	nelfinavir
NGO	non-governmental organization
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTIs	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
OD	once daily
OI	opportunistic infection
OST	Opioid Substitution Therapy
OTI	opioid treatment index
PCP	pneumocystis pneumonia
PE	pulmonary embolism
PI	protease inhibitor
PLHA	people living with HIV and AIDS
PML	progressive multifocal leucoencephalopathy
PMTCT	prevention of mother to child transmission
QID	four times daily
RMP	rifampicin
RNA	ribonucleic acid
RTV	ritonavir
SQV	saquinavir
STIs	sexually transmitted infections
TB	Tuberculosis
TDF	tenofovir
TE	toxoplasma encephalitis
THC	tetrahydrocannabinol
TLC	total lymphocyte count
T/O	tincture of opium
UGT	uridine 5'-diphosphate glucuronosyltransferase
UNAIDS	United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drug and Crime
WBC	white blood count
WHO	World Health Organization
ZDV	zidovudine (also known as AZT)

Table of Contents

National ART Clinical Protocol

1. GOALS AND PRINCIPLES OF ART IN HIV PREVENTION, TREATMENT, CARE, AND SUPPORT SERVICES

1. This protocol for ART (anti retroviral therapy) for Afghanistan should be considered by all providers of HIV prevention, treatment, care, and support services operating under the Ministry of Public Health, Afghanistan, including HIV diagnostics for targeted interventions, TBHIV, reproductive health and ANC, as well as blood screening by CBB (Central Blood Bank), BPHS (Basic Package of Health Services), EPHS (Essential Package of Hospital Services) and private providers, and for HIV surveillance. This protocol is also to be considered for the HIV program of the ANA (Afghan National Army).

2. The purpose of this document is to provide guidance for the range of service providers operating at multiple health facilities in Afghanistan on HIV prevention, treatment, care, and support services. The target audience is professionals, both specialists and care providers, working in the field of HIV, whether in blood banks, for surveillance, and for TB (tuberculosis), reproductive health and ANC (antenatal care), harm reduction or other targeted interventions in communities and prisons, in BPHS and EPHS facilities, and the private sector.

3. Afghanistan is a low HIV prevalence country in which HIV could rise due to incidence of injecting drug use (IDU) that partially intersects with sex work (SW)[1]. The available HIV prevalence data includes 3% among IDUs with additional report of 10% among prisoners as well as 0.2% among TB patients in 2006 (Todd, 2007). Blood safety screening indicates higher rates of HCV among IDUs. Out of more than 400,000 blood screening test since 1989, there have been 487 HIV positive results (NACP, 2008). According to UNAIDS and WHO estimates, there are 1,000 to 2,000[2] HIV positive cases.

4. The country exhibits key vulnerability factors that may fuel the HIV epidemic.[3] Almost 23 million people in Afghanistan suffered 25 years of war, conflict, displacement, tremendous human loss, and severe impoverishment. Approximately 7.8 million Afghans spent some time living abroad as refugees, primarily in Pakistan (6.1 million) and partially in Iran (1.7 million). Today, about 2 million widows, 2 million orphans, almost 2 million disabled, over 1.7 million returnees and 500,000 IDPs reside in Afghanistan, while almost 4 million Afghan refugees still live in Pakistan and Iran. Poverty became extreme for the most part of the country while access to social services, including education, health, and basic infrastructure has substantially deteriorated. Many lost their family members to war (widows and orphan children) or were stripped off their social, economic and human rights as they fled the country in the search of a refuge (i.e. refugees in Pakistan). Serious gender and age discrimination, including gender segregation and low mobility of women, trafficking, violence against women, labor and sexual exploitation of girls and children have been also marked.

[1] AIDS in South Asia: Understanding and Responding to a Heterogeneous Epidemic, The World Bank, 2006; UNAIDS, 2006
[2] Afghanistan Epidemiological Fact Sheets on HIV/AIDS and STIs, UNAIDS, 2006
[3] UNAIDS, 2006, UNODC, 2005, ORA International, 2006, Action Aid, 2006

5. Other structural determinants or amplifiers of HIV have been also reported in Afghanistan, such as: (a) limited blood safety, (b) unsafe surgical practices and basic physical care; (c) limited awareness and correct knowledge about HIV/AIDS among the general population; (d) almost no use of preventive measures, including condoms; (e) extreme poverty; (f) most at level of illiteracy, especially among women; (g) most at prevalence of TB, malaria, Hepatitis A, B, and C in the context of (h) limited health care services and competing health priorities; (i) serious deterioration of key human development indicators. Additionally, lack of income-generating opportunities in the country resulted in (a) significant out-migration of rural population to urban areas; and (b) male seasonal and long-term migration, largely for the purposes of illegal and/or unregistered migrant work to Pakistan, Iran, and the countries of the Persian Gulf, the countries that exhibit HIV prevalence rates and more widely available commercial sex and injecting drugs.

6. In the absence of an effective surveillance system and robust prevention programs, the transmission of HIV may become a serious threat among the country's most at risk groups such as: (i) injecting drug users (IDUs); (ii) sex workers (SWs), (iii) men who have sex with men (MSM), (iv) prisoners, and (v) sexual partners/clients of these populations. Vulnerable populations include: (i) seasonal and long-term migrant workers such as long-distance truck and bus drivers, (ii) mobile populations such as refugees, returnees and internally displaced populations (IDPs), and (iii) persons in uniform (police and military). Among general population, the following groups are believed to be also particularly vulnerable to HIV infection: (i) women; (ii) youth; and (iii) street children.

7. Throughout the many monthly evaluations-including CD4 count, viral load, routine laboratory, genotypic and phenotypic resistance testing, and drug plasma levels- the ultimate goal of antiretroviral therapy should always be borne in mind. This paradigm suggests that not only opportunistic infections and malignancies, but also side effects of therapy, should be prevented. Ideally, antiretroviral treatment should have little or no negative influence on daily life.

Figure 1. Paradigm of Care

To prolong the patient's life, while maintaining the best possible quality of health and life.

8. All HIV testing and counseling services will be provided according to the ethical principles in the national HIV Service Code of Ethics (HIV Services Code, 2007)

Figure 2. HIV Service Code of Ethics

All persons seeking HIV prevention, treatment, care, and support services should be treated with respect and have their well-being and security safeguarded. All persons will be assured of voluntary and confidential access to the information, diagnosis, and testing they need to protect themselves against HIV infection. No one may disclose the HIV status of any individual except the person him or herself. This includes laboratory reports to other medical professionals. People living with HIV and AIDS will have the same rights as all other citizens, and will not be discriminated against or stigmatized on the basis of their HIV status, gender, socioeconomic status, or HIV-risk behaviors.

HIV prevention, treatment, care, and support practices will follow evidence-based, international best practices in the context of Afghanistan's religious and cultural values.

9. Quality HIV testing and counseling services require active laws and policies that guard against discrimination on the basis of HIV status, risk behavior, and gender. Good laws and policies enhance privacy, autonomy and gender equality, which in turn strengthen client confidence in service provision. Ethical disclosure and partner notification and counseling should be done in accordance with the HIV service code of ethics.

10. Community preparedness and participation are integral aspects of HIV testing and counseling services to promote the rights of people living with HIV and to provide information about available services for HIV prevention, treatment, care and support. PLHA and affected communities should be involved in the formulation, implementation, and monitoring of such services.

11. HIV testing and counseling services require mutual referral systems for patients, especially for TB, but also for anti-retroviral treatment (ART), OI and STI care, harm reduction, drug treatment, counseling, and mental health services. In order to decrease the burden of HIV in TB patients, TB patients living with HIV should be recommended to access HIV testing and counseling in BPHS and in urban HIV settings.

2. RAPID TESTING OF HIV INFECTION

12. Diagnosis of HIV is an important component of HIV/AIDS care. Please refer to the MOPH HIV Rapid Testing Protocol 2008. A diagnosis of HIV should be based on a positive HIV test. The "3 Cs" advocated since 1985 remain the cornerstone of HIV testing of the individual. The UNAIDS/WHO policy Statement on HIV testing says that testing should be:

- Confidential
- Accompanied by counseling
- Only be conducted with informed consent

13. The rationale behind the "3Cs" is that it may reinforce preventive behaviour in sero-negative and sero-positive people. When patients know their HIV serostatus, they can take measures to prevent the development of some opportunistic infections, to prevent further HIV transmission and prepare themselves and their families for the future. The chance for behavioural change in someone who is tested by coercion is minimal. Behavioural change will only occur if testing is integrated into a comprehensive HIV prevention and care package.

14. Rapid HIV tests should be used in order to be able to provide "same-day results" to patients, and appropriate post test counseling has to be in place for patients who test positive or negative. It is very important that we understand the meaning of a positive and negative HIV test to give correct information to our patients. Especially in infants it can be complicated to diagnose HIV. UNAIDS and WHO recommendations for HIV testing strategies according to test objectives and prevalence of infection in the sample population.[4] (with adaptations according to Respess et al)[2] Rapid tests

[4] WHO. Antiretroviral treatment of HIV infection in infants and children in resource-limited settings, towards universal access: Recommendations for a public health approach

should be used for blood screening, transfusion and transplant safety according to a single test algorithm, for surveillance according to two step test algorithm, and for diagnosis according to a three step algorithm (National HIV Testing Protocol, Afghanistan, 2008)

Figure 3. HIV Rapid Testing Strategy

Objective of testing strategy	Prevalence of infection	Testing
Transfusion and transplant safety	All prevalences	I
Surveillance	>10% ≤10%	I II
Diagnostic		
• Clinical signs of HIV infection	>30% ≤30%	II II
• Asymptomatic	>10% ≤10%	II III

3. DIAGNOSIS OF HIV IN ADULTS AND CHILDREN

15. The gold standard for the diagnosis of HIV is detecting antibodies against HIV (serologic test). Several rapid serologic assays for HIV exist and allow for on-site testing, including confirmatory testing. Currently, the procedure to diagnose HIV includes screening first with a simple/rapid test which is then confirmed by a second rapid test. In case of indeterminate results a third rapid test has to be done. The testing strategy used will depend on: test objectives, HIV prevalence and the age of the individual. Diagnostic HIV testing is performed after individual pretest counseling, client-initiated testing, where patients actively choose to be tested ("opt-in").

16. With the improved access to antiretroviral therapy, increasingly provider-initiated approaches to testing are promoted, where a patient is informed that routine testing is being done, but that he has a choice to "opt-out" of this systematic offer of testing.[5] For provider-initiated testing, whether for purposes of diagnosis or PMTCT patients retain the right to refuse testing ("opt-out). In the 2004 UNAIDS/WHO policy statement on HIV testing, besides VCT and testing for diagnostic reasons in patients who show signs of HIV infection or who have tuberculosis, they also consider routine HIV testing of asymptomatic patients in all health care settings where HIV is prevalent and antiretroviral therapy available, in antenatal clinics and in STD clinics.

17. **For children <18 months** it is impossible to use a serologic test, because of the persistence of maternal antibodies up to 18 months. The antibodies of the mother gradually decrease and are usually immeasurable by 7 up to 10 months of age, but can sometimes persist as long as 18 months: the antibody test can thus be positive until 18 months, whether the infant is infected or not. So the method of diagnosis is age-dependent as well. The lack of appropriate diagnostic tests for early detection of HIV infection in infants born to HIV-positive mothers is one of the bottle necks in scaling up access to ART to HIV-positive infants.

[5] UNAIDS and WHO. 2004 UNAIDS/WHO Policy Statement on HIV testing.
Available at: http://www.who.int/hiv/pub/vct/en/

18. **Children < 18 months**. Definitive diagnosis of HIV infection in this group can only be made by virological testing. Virological tests that can be used for diagnosis in infants include assays to detect plasma HIV DNA, plasma HIV RNA, heat-denaturated p24 antigen assays or viral cultures. HIV DNA PCR is the preferred method but technically demanding. The real time PCR is cheaper and easier to standardise. The heat-denaturated p24Ag detection test (Schüpbach) is a reliable assay, but less sensitive than the HIV DNA/RNA assays. Whole blood is difficult to collect from young infants. Use of dry blood spots (DBS) can overcome this problem, because blood can be obtained using a heel-stick. DBS for HIV DNA and RNA testing has proved reliable.

19. It is recommended to perform the first virological testing after 6-8 weeks, at the first postnatal visit (by this time also children infected intrapartum or peripartum, will be positive on PCR). Reactive tests in duplicate (twice on the same specimen) confirm the diagnosis. Ideally a second sample should be tested, but for public health purposes, in symptomatic HIV-exposed children only one positive result is enough to confirm the diagnosis and to start antiretroviral therapy. The heat-denaturated p24 antigen testing can be used to diagnose HIV infection in infants 4-6 weeks old, but cannot be used to exclude it, because of a lower sensitivity than the DNA or RNA PCR assays. At the age of 18 months HIV antibody testing should be done to confirm the diagnosis. Negative virological testing should also be confirmed after 18 months by a negative antibody test.

20. **Diagnosis of HIV in breastfeeding infants.** As long as an infant or child receives breast feeding from an HIV-infected mother, there is a risk to acquire HIV through breast feeding. WHO recommends that HIV virological testing should be performed at least 6 weeks after complete cessation of breast feeding. If the child is already between 9-18 months old, a HIV antibody test could be performed first. In case it is negative there is no need to do virological testing.

21. **Diagnosis of HIV in infants who have received antiretrovirals as prophylaxis of MTCT.** HIV DNA assays can be reliably done. No data exist on the reliability of HIV RNA assays or p24 antigen testing in this group. It is recommended that in case of a negative HIV RNA test or p24 antigen test, this test is repeated 4 weeks after the completion of the prophylaxis.

22. Diagnosis in infants where the mother is on ART. These infants are at low risk of acquiring infection, when not breastfed. Two virological tests are recommended when the infant is asymptomatic.

23. Children > 18 months. At that age the same testing strategies as in adults can be used. A child is considered HIV + in case of a positive result by two different simple/rapid tests.

4. SELECTION OF PATIENTS FOR ART (Adults and Adolescents)

24. When to start In resource-limited settings the decision to initiate ART in adults and adolescents relies on:

- Clinical assessment
- Immunological assessment

25. Clinical assessment of HIV-infected adults and adolescents

The WHO classification of HIV-associated clinical disease has recently been revised in order to provide greater consistency between the adult and pediatric classification systems (Table 1).

Figure 4. WHO classification of HIV-associated clinical disease

Classification of HIV-associated clinical disease	WHO clinical stage
Asymptomatic	1
Mild	2
Advanced	3
Severe	4

26. Clinical staging is intended for use where HIV infection has been confirmed by HIV antibody testing. It should form part of the baseline assessment (first visit) on entry into a care and treatment programme and is used to guide decisions on when to start CTX prophylaxis and when to start and switch ART in situations where CD4 testing is not available. Figure 5 will provide further details of the specific staging events and the criteria for recognizing them.

27. Immunological assessment of HIV-infected adults and adolescents. The optimum time to commence ART is before patients become unwell or present with their first opportunistic infection. Immunological monitoring (CD4 testing) is the ideal way to approach this situation. A baseline CD4 cell count not only guides the decision on when to initiate ART but is also essential if CD4 counts are to be used to monitor ART. Table 2 summarizes the immunological criteria for the initiation of ART.

Figure 5. CD4 criteria for the initiation of ART in adults and adolescents

CD4 (cells/mm3) [1]	Treatment recommendation [2]	
<200	Treat irrespective of clinical stage	
200 – 350	Consider treatment and initiate before CD4 count drops below 200 cells/mm3 [3,4,5]	[1] CD4 cell count should be measured after stabilization of any intercurrent condition. [2]CD4 cell count supplements clinical assessment and should therefore be used in combination with clinical staging in decision-making. [3] A drop in the CD4 cell count below 200 cells/mm3 is associated with a significant increase in opportunistic infections and death. [4] The initiation of ART is recommended for all patients with any WHO clinical stage 4 disease and some WHO clinical stage 3 conditions, notably pulmonary TB and severe bacterial infections.

		[5] The initiation of ART is recommended in all HIV-infected pregnant women with WHO clinical stage 3 disease and CD4 <350 cells/mm3
>350	>350 Do not initiate treatment	

Figure 6. Indications for Starting and Delaying ART

Indications for ART	• Confirmed HIV infection • WHO stage 4 disease irrespective of CD4 cell count • WHO stage 3 disease o if CD4 count is available with CD4<350 o if CD4 not available irrespective of CD4 • WHO stage 1 or 2 o if CD4 available <= 200 o If CD4 not available, do not treat if WHO stage 1, consider treatment if WHO stage 2 and TLC<1200 • Patient ready to start
Conditions delaying ART	• if the patient is not motivated • patient with poorly controlled psychological illness • patient with active alcoholism/substance abuse • without intensive counseling • terminal disease / incurable disease e.g. cerebral lymphoma • during an acute treatable Opportunistic infection

28. The process of initiating ART involves assessing patient readiness to commence therapy and an understanding of its implications (lifelong therapy, adherence, toxicities) access to nutritional and psychosocial support groups is important when decisions are being made about the initiation of ART.

Figure 7. WHO Clinical Staging of HIV Disease in Adults and Adolescents

CLINICAL STAGE 1	• Asymptomatic • Persistent generalized lymphadenopathy
CLINICAL STAGE 2	• Unexplained moderate weight loss (under 10% of presumed or measured body weight)[b] • Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrhoeic dermatitis • Fungal nail infection
CLINICAL STAGE 3	• Unexplained severe weight loss (over 10% of presumed or measured body weight) • Unexplained chronic diarrhoea for longer than one month • Unexplained persistent fever (intermittent or constant for longer than one month) • Persistent oral candidiasis • Oral hairy leukoplakia • Pulmonary tuberculosis (current) • Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia, severe pelvic in amatory disease) • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anaemia (below 8 g/dl), neutropenia (below 0.5 x 10^9/l) and/or chronic thrombocytopenia (below 50 x 10^9/l)
CLINICAL STAGE 4	• HIV wasting syndrome • Pneumocystis pneumonia • Recurrent bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Extrapulmonary cryptococcosis including meningitis • Disseminated non-tuberculous mycobacteria infection • Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis • Chronic isosporiasis • Disseminated mycosis (coccidiomycosis or histoplasmosis) • Recurrent septicaemia (including non-typhoidal Salmonella) • Lymphoma (cerebral or B cell non-Hodgkin) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis • Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Figure 8. Assessment before starting ART

Clinical Assessment at baseline	• Clinical staging of HIV disease • Determination of concomitant medical conditions (e.g. HBV, HCV, TB, pregnancy, IDU, major psychiatric illness) • Concomitant medications (including traditional & herbal medicines) • Weight • Assessment of patient readiness for therapy
Laboratory assessment at baseline	• Confirmation of HIV infection status • Measurement of CD4 where available • Haemoglobin measurement if initiation of AZT is being considered • Pregnancy test in women if initiation of EFV is being considered • Screening for TB and malaria (and diagnostic testing for other co-infections and opportunistic diseases where clinically indicated)

29. Infants and Children. **When to start** The decision-making process for initiating ART in infants and children relies on clinical and immunological assessment.

30. Clinical assessment of HIV-infected children The WHO Paediatric Clinical Classification of HIV-related disease has recently been revised and is now harmonized with the adult classification system Figure 8.

31. Clinical staging is for use where HIV infection has been confirmed (i.e. serological and/or virological evidence of HIV infection). It is informative for assessment at baseline or entry into HIV care and can also be used to guide decisions on when to start CPT (CTX preventive therapy) in HIV-infected children and other HIV-related interventions, including when to start, switch or stop ART in HIV-infected children, particularly in situations where CD4 is not available.

32. Immunological assessment of HIV-infected children It is also possible to measure the immunological parameters of the HIV-infected child and assess the severity of HIV-related immunodeficiency in order to guide decision-making on the initiation of ART. The results of CD4 measurement should be used in conjunction with clinical assessment. The CD4 and the total lymphocyte count (TLC) in healthy infants who are not infected with HIV are considerably higher than those observed in uninfected adults and slowly decline to adult values by the age of about 6 years.

Figure 9. Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and availability of immunological markers

WHO paediatric stage	Availability of CD4 cell measurements	Age-specific treatment recommendation	
		<11 months	>12 months
4[a]	CD4[b]	Treat all	
	No CD4		
3[a]	CD4[b]	Treat all	Treat all, CD4-guided in those children with TB,[c] LIP, OHL,

			thrombocytopenia
	No CD4		Treat all[c]
2	CD4[b]	CD4-guided[d]	
	No CD4	TLC-guided[d]	
1	CD4[b]	CD4-guided[d]	
	No CD4[b]	Do not treat	

a) Stabilize any opportunistic infection before initiation of ART.
b) Baseline CD4 is useful for monitoring ART even if it is not required to initiate ART.
c) In children with pulmonary or lymph node tuberculosis the CD4 level and clinical status should be used to determine the need for and timing of initiation of ART in relation to tuberculosis treatment (see Section XII).
d) Refer to Figure 10 for CD4 and Figure 11 for TLC values.

Figure 10. CD4 criteria for severe HIV immunodeficiency

Immunological marker[a]	**Age-specific recommendation to initiate ART[b]**			
	<11 months	**12 months to 35 months**	**36 months to 59 months**	**>5 years**
%CD4+[c]	<25%	<20%	<15%	<15%
CD4 count[c]	<1500 cells/mm3	<750 cells/mm3	<350 cells/mm3	<200 cells/mm3

a) Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging. CD4 is preferably measured after stabilization of acute presenting conditions.
b) ART should be initiated by these cut-off levels, regardless of clinical stage; a drop of CD4 below these levels significantly increases the risk of disease progression and mortality.
c) % CD4+ is preferred for children aged <5 years.

Figure 11. TLC criteria for severe HIV immunodeficiency requiring initiation of ART; suggested for use in infants and children with clinical stage 2 and where CD4 measurement is not available

Immunological marker[a]	**Age-specific recommendation to initiate ART[b]**			
	<11 months	**12 months to 35 months**	**36 months to 59 months**	**5 to 8 years[c]**
TLC	<4000 cells/mm3	<3000 cells/mm3	<2500 cells/mm3	<2000 cells/mm3

a) Immunological markers supplement clinical assessment and should therefore be used in combination with the clinical staging.
b) A drop of TLC below these levels significantly increases the risk of disease progression and mortality.
c) There are fewer data available on which to base recommendations on the use of TLC for decision-making in children aged over 8 years.

33. Indications for ART in infants and children Infants and children with established HIV infection should be started on ART if they have:

- WHO paediatric clinical stage 4 disease (irrespective of CD4);
- WHO paediatric clinical stage 3 disease (irrespective of CD4, although it may add guidance); for children aged over 12 months with tuberculosis, lymphocytic interstitial pneumonia, oral hairy leukoplakia or thrombocytopaenia, ART initiation may be delayed if CD4 is available and above threshold values for initiating ART;
- WHO paediatric clinical stage 2 disease and CD4 or TLC value at or below threshold;
- WHO paediatric clinical stage 1 disease and CD4 value at or below threshold.

If virological testing is not available to confirm HIV infection, HIV antibody-positive infants and children aged under 18 months should be considered for ART if they have clinically diagnosed presumed severe HIV disease.

Figure 12. WHO Clinical Staging of HIV/AIDS for Infants and Children

CLINICAL STAGE 1	Asymptomatic Persistent generalized lymphadenopathy
CLINICAL STAGE 2	• Extensive molluscum contagiosum • Recurrent oral ulceration • Unexplained persistent parotid enlargement • Herpes zoster • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) • Unexplained persistent hepatosplenomegaly • Papular pruritic eruptions • Fungal nail infections • Angular cheilitis • Lineal gingival erythema • Extensive wart virus infection
CLINICAL STAGE 3	• Acute necrotizing ulcerative gingivitis or periodontitis • Pulmonary tuberculosis • Severe recurrent bacterial pneumonia • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease including bronchiectasis • Unexplaineda anaemia (below 8 g/dl), neutropenia (below 0.5 x 10^9/l) and/ or chronic thrombocytopenia (below 50 x 10^9/l) • Oral hairy leukoplakia • Unexplained moderate malnutrition or wasting not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5 ºC, intermittent or constant, for longer than one month) • Persistent oral candidiasis (after first 6-8 weeks of life) • Lymph node tuberculosis
CLINICAL STAGE 4	• Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy • Pneumocystis pneumonia • Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) • Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration, or visceral at any site) • Extrapulmonary tuberculosis • Kaposi sarcoma • Oesophageal candidiasis (or Candida of trachea, bronchi or lungs) • Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month

5. ANTIRETROVAL DRUGS, GENERAL CONSIDERATIONS

34. ART or Anti Retroviral Therapy is used successfully to lower the viral load in an HIV infected patient. It has been found that due to the frequency of HIV virus mutation only combinations of 3 or 4 different drugs therapy are successful at suppressing the virus and preventing the emergence of drug resistance. There are many different combinations available, but for a resource poor setting consideration needs to be given to combinations that are easy to use, with a low pill burden and that require minimal monitoring. There are three major classes of ARV drugs. Each class affects different components of the HIV virus replication

35. The first-line regimen for adults and adolescents contain two NRTIs plus one NNRTI. This recommendation is based on available evidence, clinical experience and programmatic feasibility for the wider introduction of ART in resource -limited settings. Regimens based on combination of two NRTIs plus one NNRTI are efficacious, are generally less expensive than other regimens, have generic formulations, are often available as FDCs and do not require a cold chain. In addition, they preserve a potent new class (protease inhibitors) for second-line treatments. Disadvantages include different drug half-lives which complicate ART stopping procedures, the fact that a single mutation is associated with resistance to some drugs (3TC and the NNRTIs), and cross-resistance within the NNRTI class.

36. Currently life-long treatment is required. The best chance at sustained viral suppression of HIV is with strict adherence to first line therapy. Therefore it is important to initiate appropriate first line ART only in the right setting ensuring adequate understanding of therapy by the patient.

Figure 13. ART Drugs

<table>
<tr><th colspan="4">Drug class/drug</th></tr>
<tr><th>Nucleoside RTIs</th><th>Nucleoside RTIs</th><th>Non-nucleoside RTIs</th><th>Protease inhibitors</th></tr>
<tr><td>Abacavir (ABC)</td><td rowspan="6">Tenofovir (TDF)</td><td>Efavirenz (EFV)</td><td>Lopinavir/ritonavir (LPV/r)</td></tr>
<tr><td>Didanosine (ddI)</td><td rowspan="5">Nevirapine (NVP)</td><td rowspan="2">Nelfinavir (NFV)</td></tr>
<tr><td>Lamivudine (3TC)</td></tr>
<tr><td>Stavudine (d4T)</td><td rowspan="2">Saquinavir/ritonavir (SQV/r)</td></tr>
<tr><td>Zidovudine (AZT)</td></tr>
</table>

37. ARV treatment in Infants and Children Studies of antiretroviral therapy in children demonstrate that similar improvements to those obtained in adults are seen in morbidity, mortality and surrogate markers with many different potent ARV regimens. The preferred option when choosing a first-line regimen for infants and children is two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI). These drugs prevent HIV replication by inhibition of the action of reverse transcriptase, the enzyme that HIV uses to make a DNA copy of its RNA. The technical reference group based this decision on available evidence, clinical experience and programmatic feasibility for the wider introduction of ART to infants and children

in resource-limited settings. NRTI/NNRTI-based regimens are efficacious and generally less expensive; generic formulations are more often available and a cold chain is not required.

Figure 14. ART in Adults and Adolescents

Fixed Dose Combinations (FDC):
AZT+3TC = Combivir ABC+AZT+3TC=Trizivir D4T/3TC=Coviro D4T+3TC+NVP =Triviro
Recommended first line regimen
AZT+3TC+EFV or NVP (Zidovudine+Lamivudine+Efavirenz or Nevirapine)
Alternative first line regimen
d4T+3TC+EFV or NVP (Stavudine+Lamivudine+Efavirenz or Nevirapine) (AZT+3TC+ABC) (Zidovudine+Lamivudine+Abacavir)

Figure 15. Choice of NRTI

AZT	• well tolerated and widely available • initial drug side effects are nausea and vomiting • can cause severe anemia but Hb monitoring before and during treatment is recommended particularly in areas with a high prevalence of malaria where anemia is common
3TC	• it is a core component of the dual NRTI backbone in all ARVs combinations • it has proved safe • favorable toxicities profile • effective against Hepatitis B • cheap to produce and widely available • included in fixed dose combinations
D4T	• Widely available in fixed-dose combinations • Preferred over AZT because of the requirement for limited or no laboratory monitoring • Having side effects like lactic acidosis, lipoatrophy and peripheral neuropathy • The latter toxicities are cumulative and often irreversible • The stigmatization associated with lipoatrophy can result in withdrawal from or refusal to enroll in ART programmes
ABC	• Alternative NRTI in first-line therapy • Has the least effect on mitochondrial DNA depletion (associated with lipoatrophy, peripheral neuropathy and lactic acidosis) • One of the possible substitutes for d4T or AZT • Associated with a severe hypersensitivity reaction in approximately 2−5% of patients who receive the drug • It is one of the few drugs available in a paediatric formulation

	• Clinical trial results in naive patients have demonstrated efficacy

Figure 16. Choice of NNRTI

NVP	• Is widely available and is less costly than EFV • Can cause rash therefore other drugs like CTX that can also cause rash the initiation should be avoided • It is the preferred NNRTI for women if there is potential for pregnancy or during the first trimester
EFV	• is the NNRTI of choice in individuals with TB/HIV co infection who are receiving rifampicin based TB therapy • should be avoided in patients with a history of sever psychiatric illness • should be avoided in women when there is potential for pregnancy and during the first trimester of pregnancy • avoid with fatty meal • should be given before going to sleep due to dizziness

Figure 17. Dosages of Antiretroviral Drugs for Adults and Adolescents:

Drug class/drug	Dosage
Nucleoside RTIs	
Abacavir (ABC)	300 mg twice daily
Didanosine (ddI)	400 mg once daily (250 mg once daily if <60 kg)
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Stavudine (d4T)	30 mg twice daily
Zidovudine (AZT)	300 mg twice daily
Nucleotide RTI	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside RTIs	
Efavirenz (EFV)	600 mg once daily
Nevirapine (NVP)	200 mg once daily for 14 days, then 200 mg twice daily
Protease inhibitors	
Lopinavir/ritonavir (LPV/r)	**Tablets**, heat-stable formulation (Lopinavir 200 mg / ritonavir 50 mg) **Treatment-naive patients:** Two tablets twice daily irrespective of coadministration with EFV or NVP (400/100 mg twice daily) **Treatment-experienced patients:** Three tablets twice daily when combined with EFV or NVP (600/150 mg twice daily)
	Capsules (Lopinavir 133.3 mg / ritonavir 33.3 mg): Three capsules twice daily (400/100 mg twice daily) Four capsules twice daily when combined with EFV or NVP (533/133.33 mg twice daily)
Nelfinavir (NFV)	1250 mg twice daily
Saquinavir/ritonavir (SQV/r)	1000 mg/100 mg twice daily or 1600 mg/200 mg once daily

Atazanavir + ritonavir (ATV/r)	300 mg +100 mg once daily
Fos-amprenavir + ritonavir (FPV/r)	700mg + 100 mg twice daily
Indinavir + ritonavir (IDV/r)	800 mg + 100 mg twice daily

38. Normally ARV doses have to be calculated according to weight or body surface and **doses have to be adjusted when children grow**. To be more practical here we have decided to give doses according to weight bands and taking into account the increased metabolism of drugs in children. But we have to be aware that for some weights this means that medicines are a bit overdosed or underdosed. In general it is better to overdose medicines a bit to prevent resistance, but we have to be aware of higher risk of side effects if we overdose.

Figure 18. Recommended preferred first-line ART regimens for infants and children

AZT [b] + 3TC[c] + NVP[d]/ EFV[e]
d4T [b] + 3TC[c] + NVP [d]/EFV[e]
ABC + 3TC[c] + NVP[d]/ EFV[e]

a) The use of AZT, d4T, ABC with 3TC results in several possible dual nucleoside combinations (see following section on choice of NRTI).
b) AZT should not be given in combination with d4T.
c) Where available, FTC can be used instead of 3TC in children over 3 months of age.
d) NVP should be used with caution in postpubertal adolescent girls (considered as adults for treatment purposes) with baseline CD4 absolute cell counts >250/mm3.
e) EFV is not currently recommended for children under 3 years of age and should be avoided in postpubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active and not receiving adequate contraception.

Figure 19. Recommended Alternative ART regimen for infants and children to simplify management of toxicity, comorbidity and drug-drug interaction

Regimen of triple NRTI: AZT/ d4T[a] + 3TC[b] + ABC

[a] AZT should not be given in combination with d4T.
[b] Where available, FTC can be used instead of 3TC in children over 3 months of age.

Figure 20 . Pediatrics Dosing for: < 8 years old

Weight	1st 14 days	Maintenance
5-9 kg	**3TC[6]:** 2.5ml bd **d4T[7]:** 7.5mg bd **NVP[8]:** 6ml **od**	**3TC:** 2.5ml bd **d4T:** 7.5ml bd **NVP:** 6ml **bd**

[6] Syrup 10mg/ml
[7] Capsules 15 mg, given diluted in water

10-14 kg	**Am**: ½ tab Coviro 30 **Pm**: ½ tab Triviro 30	½ tab Triviro 30 bd
15-19 kg	½ tab Triviro 30 bd	½ tab Triviro 30 bd + 5ml NVP bd (**or** ½ tab NVP od)
20-24 kg	½ tab Triviro 40 bd	½ tab Triviro 40 bd + 7ml NVP bd (**or** ½ tab NVP od)
25-60 kg	**Am**: 1 tab Coviro 30 **Pm**: 1 tab Triviro 30	1 tab Triviro 30 bd

Figure 21. Pediatrics Dosing for: > 8 years old

Weight	1st 14 days	Maintenance
5-9 kg	**3TC**[9]**:** 2.5ml bd **d4T**[10]**:** 7.5ml bd **NVP**[11]**:** 6ml **od**	**3TC:** 2.5ml bd **d4T:** 7.5ml bd **NVP:** 6ml **bd**
10-14 kg	**Am**: ½ tab Coviro 30 **Pm**: ½ tab Triviro 30	½ tab Triviro 30 bd
15-19 kg	½ tab Triviro 30 bd	½ tab Triviro 30 bd + 5ml NVP bd (**or** ½ tab NVP od)
20-24 kg	½ tab Triviro 40 bd	½ tab Triviro 40 bd + 7ml NVP bd (**or** ½ tab NVP od)
25-60 kg	**Am**: 1 tab Coviro 30 **Pm**: 1 tab Triviro 30	1 tab Triviro 30 bd

39. Notes on ARV combinations to be avoided or used with caution: Monotherapy or dual therapy should not be used to treat chronic HIV infection; they may only be used in the setting of PMTCT and post-exposure prophylaxis. Certain dual NRTI backbone combinations should not be used within three -drug therapy. These are d4T + AZT (proven antagonism), d4T + ddI (overlapping toxicities) and 3TC + FTC (interchangeable, but should not be used together). The combinations of TDF + 3TC + ABC and TDF + 3TC + ddI select for the K65R mutation and are associated with high incidences of early virological failure. The combinations of TDF + ddI + any NNRTI are also associated with high rates of early virological failure. However, the use of ddI should be reserved for second-line treatment, in which situation it is possible to consider TDF + ddI with boosted PIs, provided that caution and close monitoring are practised, until more data become available. The ddI dose should be adjusted when used concomitantly with TDF in order to reduce the toxicity risk

6. ART FOR INJECTING DRUG USERS

40. Principles for initiating ART in IDUs. ART should not be excluded or unnecessarily delayed in current or former IDUs. Issues related to comorbidities, treatment priorities and readiness to start ART should be adequately addressed from the scientific, social and ethical perspectives. A comprehensive approach to care and treatment of IDUs is recommended but the

[8] Syrup

absence of specific components (e.g. opioid substitution therapy) should not be a barrier to starting ART in those who need it. In some settings, often in those countries where the HIV epidemic is largely driven by IDUs, this arises because of a lack of provision of ART in general and to IDUs in particular. In settings where ART is available, disordered lives, criminalization and social marginalization are the major factors that adversely affect the provision of HIV care. There are data indicating that IDUs may have lower and suboptimal access to HIV care and may be less likely to receive antiretroviral therapy than other populations.

41. Patients often present complicated pictures to care providers, involving psychiatric illness, coinfection with TB, HBV and HCV, high incidences of bacterial infection, and polysubstance abuse. In addition, health care programmes often fail to recognize that drug dependence is a medical condition and frequently have a perception that drug users do not adhere to ART, overlooking the confounding effects of social instability, poverty, psychiatric morbidity, human rights violations and poor patient-physician relationships which characterize many drug users' lives. The need to improve adherence among IDUs is recognized but there is evidence suggesting that when engaged in stable care with experienced staff and adequate support, IDUs can adhere to ART and have clinical outcomes comparable to those of HIV patients who do not use drugs. Active drug use is therefore not a valid reason for denying IDUs access to treatment and care.

42. Thus, from the biomedical, epidemiological and ethical points of view, drug use should not be used as an argument for withholding antiretroviral therapy from persons for whom treatment would otherwise be recommended. A comprehensive approach to care and treatment of drug dependence is recommended, but the absence of specific components (e.g. opioid substitution treatment − OST) should not be a barrier to starting antiretroviral therapy in patients for whom it is indicated.

43. Choice of ART in IDUs. The basic WHO-recommended first-line and second-line drug formulary can be used in selecting ART for the vast majority of IDUs.. The choice of specific antiretroviral drugs should also take into consideration that the prevalence of hepatic, renal, neurological, psychiatric, gastrointestinal and haematological comorbidities is higher in IDUs. • Potential drug interactions with other legal or illicit drugs should be considered.

44. The criteria for initiating ART and the first-line and second-line therapies in substance-dependent patients are the same as for the general population. The management of ART in IDUs may pose some challenges because of comorbidities, drug side-effects and toxicities, the need for substance dependence treatment, drug interactions, psychosocial problems and legal issues.

45. Support is needed such that IDUs can fully access available treatment services and adhere strictly to treatment regimens. Adherence support should be part of the routine clinical care provided by health professionals and peer support groups involved in dealing with HIV-positive individuals.The development of programmes that integrate care of drug dependence (including OST) and HIV is therefore encouraged where approaches such as directly observed therapy (DOT) can be considered. Harm reduction strategies are highly effective for IDUs in supporting HIV prevention, treatment and care. Appropriate support, provided by an accessible and nonjudgemental health care team and delivered through community-based programmes and outreach strategies, has proved effective. Comprehensive harm reduction programmes also reduce new HIV infections among IDUs.

46. Whenever possible, preference should be given to antiretroviral regimens that include the drugs least likely to cause hepatic, renal, haematological or neuropsychiatric side-effects. Simple dosing schedules and the absence of interactions with, for example, methadone or buprenorphine, are also desirable characteristics. The use of specific strategies (fixed-dose combinations, once-daily drugs, directly supervised treatment, psychosocial support, case management) should be strongly considered in order to improve adherence to treatment. It is important to note that methadone and buprenorphine are now on the WHO Essential Drugs List, a reflection of the world body's commitment to the health rights of IDUs. Patients receiving methadone replacement therapy and NNRTI-based ART require a stepwise increase in the daily dose of methadone of 5−10 mg to maintain pre-NNRTI methadone levels. The dosage adjustment of methadone is normally required approximately seven days after commencing methadone and NNRTI coadministration.

47. Methadone is the most commonly used replacement drug for the treatment of opiate dependence. Since methadone interferes with gastric emptying and with metabolism by major cytochrome P450 isoenzymes, interactions with ART are common and may lead to symptoms of opiate withdrawal or overdose and/or to increased toxicity or to decreased efficacy of antiretroviral drugs. From the perspective of ART provision, important drug interactions exist between some ARVs and methadone, particularly the NNRTIs and certain PIs which can lower the levels of methadone and precipitate withdrawal symptoms. The latter normally occur after several days of coadministration and can be treated with stepwise increases in the daily doses of methadone.

48. The use of EFV or NVP is associated with significant decreases in methadone levels, which can lead to opiate withdrawal symptoms. On the other hand, methadone does not affect NNRTI levels. With regard to the PIs, the use of amprenavir, NFV or LPV can result in decreases in methadone levels. NFV does not seem to be associated with opiate withdrawal but LPV/r has been associated with opiate withdrawal symptoms. SQV and ATV do not seem to affect methadone levels. Except for amprenavir, whose levels can be reduced by up to 30%, the available data indicate that the use of methadone does not significantly affect PI levels. Although the pharmacokinetics of methadone seem to be unaffected by NRTIs, methadone increases the area under the curve of AZT by 40%, which in turn may lead to a higher incidence of AZT-related side-effects. Methadone leads to a significant decline in levels of the buffered tablet formulation of ddI, but not of the enteric-coated formulation. Interactions with other NRTIs are not likely to be clinically relevant.

49. Buprenorphine is increasingly used for the treatment of opiate dependence. There are limited data on interactions with antiretroviral drugs. However, it appears that AZT in conjunction with buprenorphine does not increase AZT levels as is the case with methadone. Interactions with EFV, LPV/r and NFV can occur but do not seem to be clinically significant.

50. Although HIV infection is most commonly associated with people who inject opiates, effective treatment options for dependence on other substances, e.g. cocaine and amphetamine-type stimulants (ATSs) should also be provided. At present there is no proven substitution therapy for stimulant injectors. Interventions that have been shown to be beneficial in the treatment of cocaine and ATS use and dependence include psychological interventions, cognitive behavioral therapy (CBT), the community reinforcement approach, contingency management

and 'twelve step programmes'. Challenges faced in the provision of ART to cocaine and ATS injectors are similar to those facing services dealing with opioid injectors. Special efforts to reinforce ART adherence should also be considered in this population.

7. ART FOR TBHIV COINFECTION

51. Tuberculosis is an important entry point into HIV care and a common opportunistic infection among persons already diagnosed with HIV, particularly in resource-limited settings. HIVinfected persons with TB often require ART, and WHO recommends that ART be given to all patients with extrapulmonary TB (stage 4) and all those with pulmonary TB (stage 3) unless the CD4 count is above 350 cells/mm3. ART reduces both case-fatality rates and the incidence of TB and recurrent TB.

52. When to start first-line ART in patients with active tuberculosis For patients with active TB in whom HIV infection is diagnosed and ART is required the first priority is to initiate standard antituberculosis treatment (in accordance with national TB policy and guidelines). The optimal time to initiate ART is not known. Case-fatality rates in patients with TB during the first two months of TB treatment are high, particularly in settings where there are high prevalences of HIV suggesting that ART should begin early. On the other hand, considerations of pill burden, drug-drug interactions, toxicity and IRIS support the later initiation of ART.

Figure 22. Initiating first-line ART in relationship to starting anti-TB therapy

CD4 cell count	**ART recommendations**	Timing of ART in relation **to start of TB treatment**
CD4 <200 cells/mm^3	Recommend ART [a]	Between two and eight weeks [b]
CD4 between 200 and 350 cells/mm^3	Recommend ART	After eight weeks
CD4 >350 cells/mm^3	Defer ART [c]	Re-evaluate patient at eight weeks and at the end of TB treatment
Not available	Recommend ART [d]	Between two and eight weeks

a) An EFV-containing regimen is the preferred first-line regimen. Alternative first-line treatment regimens include NVP and triple NRTI (based on TDF or ABC) regimens. For NVP-containing regimens, ALT should be checked at 4, 8 and 12 weeks; treatment should be decided on the basis of symptoms thereafter.
b) ART should start as soon as TB treatment is tolerated, particularly in patients with severe immunosuppression.
c) ART should be started if other non-TB stage 3 or 4 events are present.
d) For some TB diagnoses that generally respond well to anti-TB therapy (i.e. lymph node TB, uncomplicated pleural effusion), deferral of ART should be considered.

53. **Women of childbearing potential or pregnant women with TB who require ART** An EFV-containing regimen is the first-line treatment recommendation for patients with TB and HIV but should not be used during the first trimester of pregnancy or in women of childbearing potential unless effective contraception is ensured. If a pregnant woman is in the second or third trimester, an EFV-containing ART regimen can be considered. Effective contraception would have to be assured postpartum if the regimen were continued. An alternative in women with active TB is a triple NRTI regimen, e.g. AZT + 3TC + ABC. A change from an EFV-containing to an NVP-containing regimen can be considered when TB treatment has been completed.

54. Tuberculosis in patients already receiving ART. There are two issues to consider in patients who are diagnosed with TB while on ART. The first concerns the modifications of ART, if any, which should be recommended for patients developing active TB within six months of initiating first-line or second-line ART.

Figure 23. ART recommendations for patients who develop TB within six months of starting a first-line or second-line ART regimen

First-line or second- line ART	ART regimen at the **time TB occurs**	**Options**
First-line ART	Two NRTIs + EFV	Continue with two NRTIs + EFV
	Two NRTIs + NVP	Substitute to EFV [a b] OR Substitute to triple NRTI regimen [a] OR Continue with two NRTIs + NVP [c]
	Triple NRTI regimen	Continue triple NRTI regimen
Second-line ART	Two NRTI s + PI	Substitute to or continue (if already being taken) LPV/r- or SQV/r-containing regimen and adjust dose of RTV [a]

a) Substituting back to the original regimens once the rifampicin-containing regimen is completed can be considered. When switching back from EFV to NVP, no lead-in dose is required.
b) The use of EFV-containing regimens is not recommended in women of childbearing potential, if adequate contraception cannot be ensured, and during the first trimester of pregnancy.
c) Careful clinical and laboratory monitoring (ALT) is advised when NVP or boosted PIs are administered concurrently with rifampicin.

The second issue is whether the presentation of active TB on ART constitutes ART failure. In cohort studies, ART decreases the incidence of TB in treated patients by approximately 80%. Rates of TB among treated patients nevertheless remain persistently higher than among HIV negative individuals.An episode of TB can occur across a wide range of CD4 cell counts and does not necessarily herald ART failure and the need to switch to second-line regimens. In addition, subclinical or undiagnosed TB often presents within the first six months after the initiation of ART, frequently as part of IRIS.
WHO therefore recommends that the following principles be applied when determining whether the development of TB on ART constitutes treatment failure. If an episode of TB occurs during the first

six months following the initiation of ART, this should not be considered a treatment failure event and the ART regimen should be adjusted for coadministration with rifampicin-containing regimens. If an episode of TB develops more than six months after the initiation of ART and data on the CD4 cell count and viral load are available, the decision about whether the TB diagnosis represents ART failure is based on the CD4 cell count and, if available, the viral load. If a CD4 cell count is not available the decision on whether the TB diagnosis constitutes ART failure depends on whether the TB is pulmonary or extrapulmonary and whether there are other non-TB stage 3 or 4 events. While awaiting more data, WHO recommends that the development of an episode of pulmonary TB after six months of ART, without other clinical and immunological evidence of disease progression, should not be regarded as representing ART failure. Extrapulmonary TB should be considered as indicating ART failure, although simple lymph node TB or uncomplicated pleural disease may be less significant than disseminated TB.
If there is a good response to TB therapy the decision to switch to a second-line regimen can be delayed until short-course TB therapy has been completed.

8. ART WITH HEPATITIS B OR HEPATITIS C OR CO-INFECTION

55. Hepatitis B infection is endemic in many resource-limited countries. Shared modes of transmission lead to high rates of coinfection with HIV and hepatitis B virus (HBV) and/or hepatitis C virus (HCV) in many parts of the world. It is estimated that between 370 million and 400 million people are chronic carriers of HBV and that 180 million are chronically infected with HCV. The prevalence of coinfection varies widely between geographical regions and between modes of HIV transmission. Rates of HIV/HCV coinfection are highest in areas where injecting drug use and unsafe blood practices are the dominant modes of HIV transmission. HIV modifies the natural history of HBV infection: higher rates of progression to advanced liver disease occur among persons with HIV/HBV coinfection. The presence of HIV infection is associated with greater rates of progression to cirrhosis. The impact of HBV on the natural history of HIV is less certain.

56. HBV infection Treatment of HBV. WHO advocates more widely available HBsAg testing, especially in areas of high hepatitis B prevalence. There are several antiviral agents with activity against HBV. Three of these drugs (3TC, FTC and TDF) also have activity against HIV and are recommended as first-line agents; they should be used in patients with HIV/HBV coinfection. 3TC and FTC share the same anti-HBV and anti-HIV activity and are interchangeable. *They should not be used together.*

57. Lamivudine (3TC) is efficacious against HBV in patients with and without HIV. The efficacy of 3TC is limited by the occurrence of HBV drug resistance, which develops in 50% of patients after two years of 3TC monotherapy for HBV and in 90% after four years of treatment. HBV seroconversion (loss of HBeAg and development of HBe antibody) occurs in 11% to 22% of HBeAg-positive HIV-1-infected patients who are treated with lamivudine for one year. The discontinuation of 3TC without the inclusion of other anti-HBV drugs may be associated with hepatitis flares and rapid clinical deterioration.

58. Emtricitabine (FTC) appears to have similar rates of suppression of HBV DNA, a similar safety profile and a similar resistance pattern to those of 3TC.

59. Tenofovir (TDF) is effective against wild-type and 3TC-resistant HBV. On the basis of small studies in HIV patients the efficacy of TDF against HBV appears superior to that of 3TC.There is growing interest in the use of combination therapy for HBV with TDF and either 3TC or FTC. The virological superiority of combination therapy with TDF and 3TC over monotherapy with 3TC in both 3TC-naive and 3TC-experienced HIV coinfected patients has recently been demonstrated in preliminary studies. However, the impact of combination therapy on the development of HBV resistance is currently under evaluation.

60. Selection of ART in patients with HIV/HBV coinfection. In situations where both HIV and HBV require treatment, the ART regimens must contain 3TC and/or TDF. It is preferable to use 3TC and TDF together as both drugs have anti HIV and anti-HBV activity and the use of TDF or 3TC as the only anti-HBV drug can result in more rapid development of resistance.

61. For treatment-naive HIV-1-infected persons who require ART, either 3TC at 150 mg twice daily or 300 mg daily or FTC at 200 mg daily is recommended for the treatment of chronic HBV infection as part of the ART regimen. Because of the high rate of development of HBV resistance to 3TC monotherapy, and because preliminary data have demonstrated a superior virological response to combination therapy, the inclusion of TDF, where available, should be considered as part of the ARV regimen. ARV programmes in areas of the world with a high HBV seroprevalence and no capacity to screen for HBV may consider the use of TDF plus either FTC or 3TC as the preferred initial NRTI combination. EFV is the preferred NNRTI option, or a triple NNRTI combination may be used.

62. It is recommended that NVP be used with care and regular monitoring in patients who have known HIV/HBV coinfection and grade 3 or lower elevation of ALT. NVP is not recommended for those with ALT elevations of grade 4 or higher.

63. HCV infection. Treatment of HCV. Irrespective of whether a patient has HIV infection, the optimal treatment for hepatitis C virus infection is pegylated interferon alpha and ribavirin (RBV).These drugs are complex to deliver, costly and not generally available through the public sector in resource-limited settings. Guidelines on the use of these drugs have recently been published.

64. The initiation of ART in HIV/HCV-coinfected patients should follow the same principles and recommendations as for the initiation of ART in HIV-monoinfected patients. However, the patients should be followed up more closely because of the major risk of drug-related hepatotoxicity and for specific drug interactions of some ARVs with anti HCV drugs.
The major interactions are:

- Ribavirin and ddI –> pancreatitis/lactic acidosis (do not give concomitantly).
- Ribavirin and AZT –> anaemia (monitor closely).
- Interferon and EFV –> severe depression (monitor closely).

65. In patients with high CD4 cell counts it is preferable to treat HCV infection before HIV. While concurrent treatment of both infections is feasible, it may be complicated by pill burden (RBV +ARV drugs), drug toxicities and drug interactions. In patients who need ART it may be

preferable to initiate ART and delay HCV therapy in order to obtain better anti-HCV response rates after immune recovery.

66. Selection of ART in HCV coinfection In general, recommendations for the selection of ART are not different for patients with HCV coinfection. Patients with HCV coinfection may experience increased rates of hepatotoxicity during ART compared to patients without HCV. Several studies have examined the impact of specific ART regimens on toxicity in HCV/HIV coinfection.

67. EFV is the NNRTI of choice in patients with HIV/HCV coinfection. A triple NRTI regimen is also an option. It is recommended that NVP be used with care; if it is used in patients with HIV/HCV coinfection who have grade 3 or lower elevation of ALT, regular monitoring is recommended. NVP is not recommended in patients with ALT elevations of grade 4 or above.

68. ART in patients with baseline elevation of ALT and unknown HBV/HCV status. In resource-limited settings, baseline ALT may be available but HBV/HCV status may be unknown. Ideally, serological testing for viral hepatitis should be pursued when elevations of ALT are noted.As stated above, NVP-based ART should be used with caution in patients (whether their HBV/HCV status is known or not) who have baseline grade 1, 2 or 3 elevations of ALT, and regular monitoring should take place. NVP should not be used in patients with ALT elevations of grade 4 or above.

69. The introduction of an EFV-containing regimen is recommended after the withdrawal of NVP (for grade 4 ALT elevation and/or clinical hepatitis) and the stabilization of clinical status and ALT. If EFV is withdrawn (for grade 4 ALT elevation and/or clinical hepatitis), NVP should not be initiated; a triple NRTI regimen can be used.

9. ADHERENCE TO ART

70. Adherence to ART is well recognized as an essential component of individual and programmatic treatment success. Studies on drug adherence in the developed world have demonstrated that higher levels of drug adherence are associated with improved virological, immunological and clinical outcomes and that adherence rates exceeding 95% are necessary in order to maximize the benefits of ART. It is desirable to achieve rates of this order over a long period. Numerous approaches to improving adherence have been investigated in the developed world and have begun to be explored in resource-limited settings. Particularly in the absence of HIV-RNA (viral load) for detecting early ART failure, adherence is even more crucial for delaying or avoiding the development of drug resistance and ensuring maximum durability of the first-line ARV regimen.

71. The contribution of dose timing is less well studied. A recent study demonstrated that a mean dose-timing error (DTE) of less than three hours over a one-month period was independently associated with virological suppression. A review of the efficacy of 24 adherence intervention studies published between 1996 and 2004 revealed that interventions targeting people with poor ART adherence had better outcomes. The most frequently reported interventions in this review were reminder systems and counseling support. The success of any adherence strategy depends

on the education of patients before the initiation of ART, an assessment of their understanding of the therapy, and their readiness for treatment.

72. Adherence counseling includes giving basic information on HIV and its manifestations, the benefits and side-effects of ARV medications, how the medications should be taken and the importance of not missing any doses. Peer counselors and visual materials can be particularly useful in this process.

73. Once treatment has begun the keys to success include trying to minimize the number of pills (in part through the use of FDCs), the packaging of pills (coblister packs when available), the frequency of dosing (no more than twice-daily regimens), the avoidance of food restrictions, fitting the ARVs into the patient's lifestyle, and the involvement of relatives, friends and/or community members in supporting the patient's adherence.

74. After therapy has begun it is essential to continue with support for adherence. This should involve adherence assessments during every health centre visit, the emphasizing of adherence principles to the patient by treatment supporters, and the continuous involvement of relatives, friends and/or community support personnel. Although the coverage of ART in the developing world remains low in relation to the burden of disease, important lessons have been learnt which can be incorporated into newly developing or expanding programmes, as outlined below.

- Medications should be provided free of charge for people who can least afford treatment, through subsidized or other financing strategies. Free access to ARVs at the point of delivery may assist adherence.
- Family or community members should be engaged in adherence education and maintenance programmes. Home visits can be useful if the patient's status is known by family members. It is essential to minimize stigma through psychosocial support.
- Family-based care is desirable if more than one family member is HIV-infected. This is particularly true when mother and child are infected.
- Pillboxes or coblister packs can be used.
- Directly observed therapy (DOT) or modified DOT strategies can be adopted. This approach is resource-intensive and difficult to introduce on a large scale and for the lifelong duration of ART. However, it may be helpful for certain groups (IDUs) and for early patient training.
- Strategies are required for reaching isolated communities.

75. At the programmatic level it is vital to ensure adequate stocks and storage of ARVs and to provide necessary resources for culturally appropriate adherence counseling.

76. Adherence in women in the postpartum period may be particularly problematic and require special support for them, as the stresses of caring for a newborn baby may lead a woman to pay insufficient attention to her own health care.

77. Adherence in children is a special challenge, particularly if the family unit is disrupted by health, economic or political conditions. Family-based HIV care programmes are some of the best approaches to assuring childhood health. It is imperative that paediatric formulations be

improved and made widely available. They should match the adult regimens, where possible, so that family-based care can be pursued effectively.

78. Follow up of patients on ARVs

- All HIV+ patients, diagnosed seropositive in VCT and referred to ART clinic, get a regular initial screening there;
- Regular screening includes staging and baseline lab investigations: Hb, ALT, pregnancy test, and CD4.
- Patients of stage 1 & 2 are referred to OPDs for their health problems and are scheduled for follow up visit in ART clinic after 6 months.
- Patients with the CD4< 500 start CTX prophylaxis wherever they will be getting other services (OPD, ART clinic, etc.);
- Patients in stage 3 & 4 stay in ART clinic where management of OIs, CTX prophylaxis and preparation for ART starts;
- Patients on ART without HIV/AIDS related disorders or stable patients are referred to OPD for further monitoring and are scheduled for follow up visits in ART clinic every 6 months. If meanwhile HIV/AIDS related problems or ARV side effects appear, patients are referred to ART clinic;
- Adherence Counselors do the adherence counseling and ARV Nurses do ARV refill and side effect monitoring. Adherence system consists of:
  01. Pre ART
      a. Group adherence, one week before ART initiation;
      b. One to one adherence counseling, on the day of ART initiation;
  02. During ART
  03. Two weeks after ART initiation:
      a. ARV regimen change, pill count and refill
      b. Side effect monitoring
      c. Group adherence counseling
  04. Four weeks after ART initiation:
      a. ARV pill count refill
      b. Side effect monitoring
      c. Group adherence counseling
  05. Monthly pill count, drug refill and monitoring of ARV side effects. If the side effects are more advanced than ARV nurse can handle, the patients are referred to a clinician in ART clinic.
  06. After 6 months, stable patients with good adherence are switched to quarterly drug refill. Group adherence counseling is monthly until 6 months.
  07. ARV group adherence counseling is every 6 months after the first 6 months.

79. Delivery of ART in Afghanistan Health Care Setting. The proposed model presented to the ART working group is a one-stop (user-friendly) service provincially provided range of services, with strong referral mechanisms within distributed outreach and referral points, such as harm reduction programs in community and prisons, as well as BPHS and EPHS service points for ANC and TB. It is possible to start HIV care and treatment services in a phased approach (first Kabul, then extension to Herat and other provinces) and in close partnership with main stakeholders. The proposed model is a one stop service providing comprehensive care and linked with local lab

services, mostly based on existing VCT sites which will be upgraded as "HUB" (HIV/AIDS care Urban Based centers).

80. Kabul, as capital city, requires a more complex organization of services, taking into account medical and public health services, as well as community-based organization providing services for most at risk populations, and based on networking and referral mechanisms. In Kabul, taking into account the existence of a national reference hospital, the provision of HIV treatment services could start through a network of linked sites: e.g. infectious diseases hospital, VCT center based in the polyclinic for mainstream PLHA, MDM drop-in center for most at risk PLHA. The National TB Institute (NTI) may start activities such as patients' awareness and education on TBHIV, staff training and HIV testing and counseling. Inclusion of other sites in the capita, such as for PMTCT, should be done only after consolidation of the initial ones and based on careful assessment of needs, case management practice, and feasibility. Further scaling up in provinces should be based on GFATM R7 plan (7 sites), first in Herat. Implementation should be done as phase 2 (i.e. after Kabul), and prioritized according to needs.

Figure 24. Example of Package of services for ART care and treatment in Kabul, 2008

	(NACP / MoPH) Provincial Health Department	**Infectious Diseases Hospital**	**Central Public Health Lab**	**VCT centre - Polyclinic**	**MDM - DIC**	**National TB institute**
Main role	• Coordination, • monitoring, • supply and equipment, • human resource management	• National Reference centre for clinical management of HIV/AIDS • Primary ART prescriber	Lab diagnostics for drug monitoring, CD4, and OI	HUB center for PLHA (mainstream) Primary ART prescriber	HuB for IDU and most at risk HIV+ (may be primary prescriber or not)	Coordination, monitoring of TBHIV
Staff structure Activities	•	• Clinical expert • IPD: managemenf of severe OI • OPD: management of OI, ART (initiation and follow up) • Provider initiated HIV testing and		adherence	adherence	- education and awareness of TB patients - Training of staff on TB/HIV - Provider initiated testing and counseling -

		counseling • Linkages with Harm Reduction services, social support services • Involvement of PLHA				
Remarks					Other NGOs offering Harm Reduction services Non directly medical-related	Second phase: initiate and follow up of ART during TB treatment

Figure 25. Patients flow within HUB (HIV Urban Base)

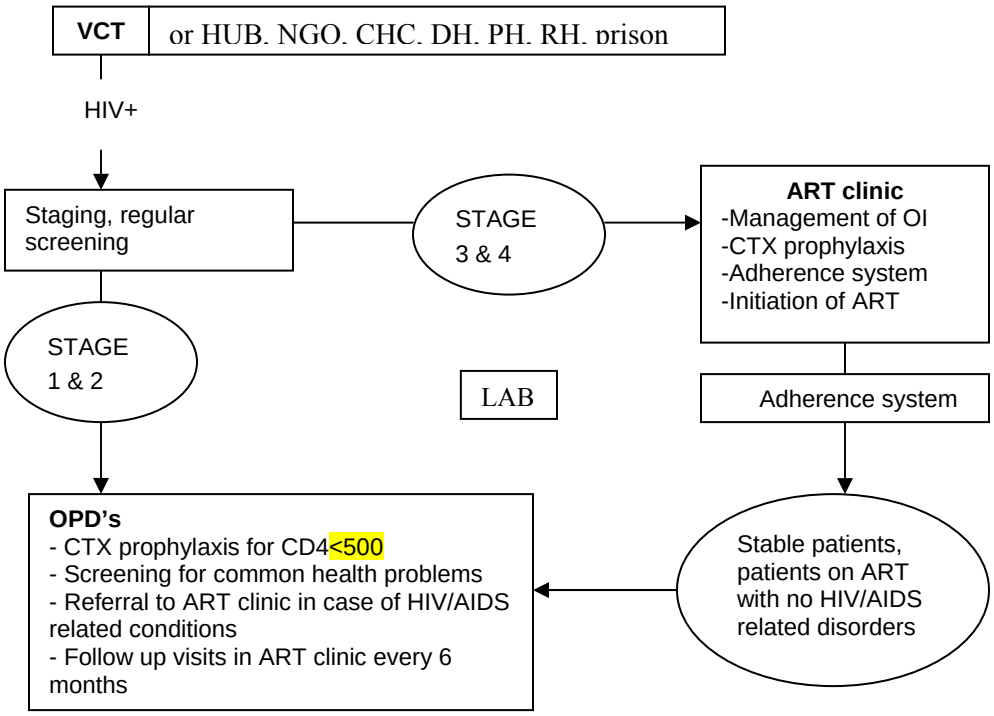

Figure 26. Patients follow up

	One week before ART	ART initiation	2 weeks after ART	4 weeks after ART	Months 2,3,4,5 after ART	Month 6 after ART	Every 3 months after the first 6 months	Every 6 months after the first 6 months
Adherence Counsellor	X	X	X	X	X	X		X
ARV Nurse		X	X	X	X	*X*	*X*	*X*
CO (MD when needed)		X				X		X
Medical Doctor		X				X		X

This schedule regarding adherence counseling may be modified in the RHC due to human resource capacity The infant patient follow up schedule is also modified

81. Stable patient:

- Reaches asymptomatic stage within 3-6 months after initiating ART
- After reaching the asymptomatic stage:
  - No occurrence of new OI
  - No reoccurrence of previous OI
  - No deterioration of clinical conditions down to WHO stage 3 or further
- CD4 reaches ≥500 and remains such for 6 months or longer
- CD4 does not decline ≥30% from its maximal value without any detectable acute infection or any other condition that would explain the decrease.

Figure 27. Referral from OPD to ART clinic

Patients **not on ART** (stage 1 & 2)	Patients **on ART** (stable and with non HIV/AIDS related disorders)
• Appearance of OI • Patient requires TB treatment • 6 monthly follow up	• Major ARV side effect • New OI • 6 monthly follow up

Figure 28. Laboratory monitoring:

	Baseline	2 weeks	4 weeks	3 months	6 months	12 months
Hb at non AZT regimen	**X**				**X**	**X**
Hb at AZT regimen	**X**		**X**	**X**	**X**	**X**
ALT	**X**	**X**	**X**			
Preg test	**X**					
CD4	**X**				**X**	**X**

10. MANAGEMENT OF ADVERSE EFFECTS

82. Adverse effects can be classified as:

- **Minor (grade 1 or 2 toxicity)** where the side effects may bother the patient, but they are not very serious and often disappear with time (usually within the first 4 to 6 weeks) or the patient learns to tolerate them. However it is important to support the patient by reinforcing the reasons for adhering to ART. Intensive ongoing counseling is necessary. Minor side effects very often have bad effects on adherence.

- **Major (grade 3 or 4 toxicity)** where significant toxicity is experienced which is disabling or life threatening the patient. Change of therapy is indicated.

Figure 29. Estimation of Severity and Grade

GRADE 1	**Mild**	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisations possible
GRADE 4	**Life**	Extreme limitation in activity, significant assistance required;

	threatening	significant medical intervention/therapy required, hospitalisation or hospice care probable

Figure 30. Grades of ART side effects according to severity

GRADE 1	**Mild**	• Transient or mild discomfort • No limitation in activity • No medical intervention or therapy required • Continue with ARVs • Monitor
GRADE 2	**Moderate**	• Mild to moderate limitation in activity • Some assistance may be needed • Usually minimal medical intervention or therapy required • Try to avoid change of treatment by controlling the symptoms • Close monitoring
GRADE 3	**Severe**	• Marked limitation in activity • Assistance usually required • Medical Intervention or therapy required • Hospitalisation possible • Potentially life threatening • Management depends on clinical setting • Change of causing drug possible
GRADE 4	**Life threatening**	• Extreme limitation in activity • Significant assistance required • Significant medical intervention or therapy required • Hospitalisation or hospice care probable • Discontinue all drugs • Offer supportive therapy

83. SERIOUS OR LIFE-THREATENING, AEs ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 adverse effect. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis.

1. MISCELLANEOUS

- When two values are used to define the criteria for each parameter, the lowest values will appear first.
- Parameters are generally grouped by body system.
- Some protocols may have additional protocol-specific grading criteria.

Figure 31. Grading of side effects						
Side effect	**Drug**	**Required Lab Investigation**	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Live treatening**
Mucocutaneous Skin Rash	NVP EFV	NONE	Erythema with or without pruritis. No urticaria	Diffuse macular or maculopapular rash or dry desquamation. No constitutional Symptoms Urticaria can exist	Diffuse maculopapular Rash or moist desquamation & Oral or Eye lesion Constitutional findings <10% body surface	Diffuse cutaneous reaction and Cutaneous bullae with widespread sheet like detachment. >10% body surface
Hepatic Toxicity	NVP D4T EFV	ALT	1.25 to 2.5 times normal upper limit	>2.5 – 5 times normal Cont therapy but repeat ALT after 7, 14, 28 days	5 – 10 times upper limit Hospitalise. Seek expert help to stop offending drug	>10 times normal Hospitalise. Seek expert help to stop offending drug
Pancreatitis	DDI 3TC D4T	Amylase	1.0 to 1.5 times normal upper limit	>1.5 – 2 times normal Continue therapy but repeat Amylase after 7, 14, 28 days	>2 – 5 times upper limit and abdominal pain. Hospitalise. Seek expert help to stop offending drug	>5 times normal with or without shock Hospitalise. Seek expert help to stop offending drug
Renal failure	TDF	Serum Cr	1.25 to 2.5 times normal upper limit	>2.5 – 5 times normal	5 – 10 times upper limit	>10 times normal

Diarrhoea	LPV	NONE	3-4 loose stools a day OR mild diarrhoea lasting less than one week	5-7 loose stools a day OR mild diarrhoea lasting more than one week	Bloody diarrhoea OR Over 7 loose stools a day OR Needing IV treatment OR Feeling dizzy when standing	Hospitalisation required. Possible also for grade 3
Fatigue	AZT	NONE	Normal activity reduced by less than 25%	Normal activity reduced by 25-50 %	Normal activity reduced by over 50 % Individual can not work	Unable to care for your self.
Mood disturbance	EFV	NONE	Mild anxiety Able to continue daily tasks	Moderate anxiety/disturbance, interfering with ability to work	Severe mood changes requiring medical treatment.Unable to work	Acute psychosis Suicidal thoughts
Nausea	3TC DDI AZT SQV TNF		Mild OR transient. Reasonable intake Maintained.	Moderate discomfort OR Intake decreased for less than 3 days	Severe discomfort OR Minimal intake for more than 3 days	Hospitalization required
Vomiting	3TC DDI TNF AZT SQV	NONE	Mild OR transient; 2-3 episodes per day OR mild vomiting lasting <1 week	Mod OR persistent; 4-5 episodes per day; OR vomiting lasting >1 week	Severe vomiting of all food/fluids in 24 hrs OR orthostatic hypotension OR IV treatment required	Hypotensive shock OR hospitalization required for IV treatment

Neuromotor	D4T DDI	NONE	Mild weakness in muscle of feet but able to walk AND/OR mild increase OR decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes) OR, mild weakness in hands, still able to do most hand tasks AND/OR loss of previously present reflex OR development of hyperreflexia AND/OR unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), AND mod proximal weakness e.g., in hands interfering with routine activities AND/OR requiring assistance to walk AND/OR unable to rise from chair unassisted	Confined to bed OR wheelchair because of muscle weakness.
Neuro-sensory	D4T DDI	NONE	Mild impairment (dec sensation, e.g.,Vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution OR Mild discomfort. No treatment required	Mod impairment (mod dec sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position sensation of at least or mild impairment that is not symmetrical. OR Moderate discomfort Analgesia required	Severe impairment (dec or loss of sensation to knees or wrists) or loss of mod degree in multiple different body areas (i.e., upper and lower extremities) OR Severe discomfort	Sensory loss involves limbs and trunk. OR Incapacitating Discomfort.

Neuro-cerebellar	D4T DDI	NONE	Slight incoordination OR dysdiadochokinesia	Intention tremor OR dysmetria OR slurred speech OR nystagmus interfering with ADLs	Ataxia requiring assistance to walk or arm incoordination	Unable to stand
Paresthesia (burning, tingling, etc.)	D4T DDI	NONE	Mild discomfort, no treatment required	Moderate discomfort, non-narcotic analgesia required	Severe discomfort, OR narcotic analgesia required with symptomatic improvement	Incapacitating, OR not responsive to narcotic analgesia

11. CTX (CO-TRIMOXAZOLE) PROPHYLAXIS FOR HIV-RELATED INFECTIONS AMONG CHILDREN ADOLESCENTS AND ADULTS

84. **Children among whom CTX prophylaxis is contraindicated.** Children with a history of severe adverse reaction to CTX or other sulfa drugs and children with glucose-6-phosphate dehydrogenase deficiency should not be prescribed CTX prophylaxis. In resource-limited settings, routine testing for glucose-6-phosphate dehydrogenase deficiency is not recommended. Dapsone 2 mg/kg once daily, if available, is an alternative. Some children cannot tolerate either CTX or dapsone. No alternative recommendation can be made in resource-limited settings for children who cannot tolerate either.

85. HIV-exposed infants and children. In resource-limited settings, CTX prophylaxis 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. CTX is also recommended for HIVexposed breastfeeding children of any age, and CTX prophylaxis 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. Programme efforts should focus on CTX prophylaxis in the first six months of life, when the risk of PCP is greatest.

86. Infants and children documented to be living with HIV. All children younger than one year of age documented to be living with HIV should receive CTX prophylaxis regardless of symptoms or CD4 percentage. After one year of age, initiation of CTX prophylaxis is recommended for symptomatic children (WHO clinical stages 2, 3 or 4 for HIV disease) or children with CD4 <25%. All children who begin CTX prophylaxis (irrespective of whether CTX was initiated in the first year of life or after that) should continue until the age of five years, when they can be reassessed. Adult clinical staging and CD4 count thresholds for CTX initiation or discontinuation apply to children older than five years of age.

87. In some countries with a high burden of mortality and morbidity due to other infectious diseases (such as malaria and bacterial infections), CTX prophylaxis may be offered to children living with HIV in all clinical stages, including asymptomatic children irrespective of their CD4 level. The universal option of providing CTX prophylaxis to all children is an adaptation issue for individual countries. Among children with presumptive symptomatic HIV disease, CTX prophylaxis should be started at any age and continued until HIV infection status can be excluded.

Figure 32. Initiation of CTX prophylaxis in infants and children

Situation			
HIV-exposed infants and children[a]	Infants and children confirmed[b] to be living with HIV		
	<1 Year	1–4 Years	>5 Years
CTX prophylaxis is universally indicated, starting at four to six weeks after birth and maintained until cessation of risk of	CTX prophylaxis is indicated regardless of CD4 percentage or clinical status[c]	WHO clinical stages 2, 3 and 4 regardless of CD4 percentage OR	Follow adult recommendations

HIV transmission and exclusion of HIV infection		Any WHO stage and CD4 <25%	

a) Defined as a child born to mother living with HIV or a child breastfeeding from a mother living with HIV until HIV exposure stops (six weeks after complete cessation of breastfeeding) and infection can be excluded.
b) Among children younger than 18 months, HIV infection can only be confirmed by virological testing.
c) Once a child is started on CTX, treatment should continue until five years of age regardless of clinical symptoms or CD4 percentage. Specifically, infants who begin CTX prophylaxis before the age of one year and who subsequently are asymptomatic and/or have CD4 levels >25% should remain on CTX prophylaxis until they reach five years of age

Figure 33. CTX formulations and dosage for infants and children living with HIV or exposed to HIV

Recommended daily dosage[a]	**Suspension (5 Ml of syrup 200 mg/ 40 mg)**	**Child tablet (100 mg/20 mg)**	**Single strength adult tablet (400 mg/80 mg)**	**Double strength Adult tablet (800 mg/160 mg)**
<6 months 100 mg sulfamethoxazole/ 20 mg trimethoprim	2.5 ml	One tablet	¼ tablet, possibly mixed with feeding[b]	-
6 months–5 years 200 mg sulfamethoxazole/ 40 mg trimethoprim	5 ml[c]	Two tablets	Half tablet	-
6–14 years 400 mg sulfamethoxazole/ 80 mg trimethoprim	10 ml[c]	Four tablets	One tablet	Half tablet
>14 years 800 mg sulfamethoxazole/ 160mg trimethoprim	-	-	Two tablets	One tablet

A Some countries may use weight bands to determine dosing. Age and the corresponding weight bands (based on the children with HIV antibiotic prophylaxis trial are:

Ages	**Ages**
<6 months	<5 kg
6 months–5 years	5–15 kg
6–14 years	15–30 kg
>14 years	>30 kg

b Splitting tablets into quarters is not considered best practice. This should be done only

if syrup is not available.

c Children of these ages (6 months–14 years) may swallow crushed tablets.

88. Secondary CTX prophylaxis in infants and children Children with a history of treated PCP should be administered secondary CTX prophylaxis with the same regimen recommended for primary prophylaxis.

89. HIV-exposed infants and children confirmed to be HIV uninfected. CTX prophylaxis can be discontinued when HIV infection has been definitely excluded by a confirmed negative HIV virological test six weeks after complete cessation of breastfeeding in an infant <18 months of age or a confirmed negative HIV antibody test in a child >18 months of age and six weeks after complete cessation of breastfeeding.

90. Children living with HIV in the context of antiretroviral therapy–related immune recovery. Given that children living with HIV have a high risk of bacterial infections, the general recommendation is that, among children confirmed to be living with HIV in resource-limited settings, CTX should be continued irrespective of immune recovery in response to antiretroviral therapy.

91. Data suggest that the risk of developing PCP after immune restoration in response to antiretroviral therapy is sufficiently low to withdraw CTX if it was initiated primarily for PCP prophylaxis. Children older than five years who are stable on antiretroviral therapy, with good adherence, secure access to antiretroviral therapy and with CD4 and clinical evidence of immune recovery can be reassessed and consideration can be given to discontinuing CTX prophylaxis in accordance with the recommendations for adults and adolescents. If children have been prescribed dapsone prophylaxis, the same discontinuation recommendations apply.

92. CTX prophylaxis (or dapsone if the child cannot tolerate CTX) should be recommenced if the CD4 percentage falls below the age-related initiation threshold or if new or recurrent WHO clinical stage 2, 3 or 4 conditions occur.

Figure 34. Summary of recommendations for discontinuing primary CTX among infants and children

Target population	Recommendations
HIV-exposed children	Discontinue CTX prophylaxis after HIV infection is excluded
Infants and children living with HIV	Maintain on CTX prophylaxis until age five years irrespective of clinical and immune response Children older than five years can be reassessed and consideration can be given to discontinuing CTX prophylaxis in accordance with the recommendations for adults and adolescents

93. Discontinuation for CTX adverse reactions. CTX prophylaxis may need to be discontinued in the event of an adverse drug reaction. Although severe reactions to CTX are uncommon, these may include extensive exfoliative rash, Stevens-Johnson syndrome or severe anaemia or pancytopaenia. There are insufficient data on CTX desensitization (rechallenge following an adverse reaction to CTX commencing with low doses of CTX and gradual dose escalation) among children to make any recommendations on its use in resource-limited settings. Everyone starting CTX and their guardians and caregivers should be provided with verbal or written information on potential adverse effects and advised to stop the drug and report to their nearest health facility if CTX-related adverse events are suspected.

94. Discontinuation of secondary CTX prophylaxis. The safety of discontinuing secondary CTX prophylaxis among children living with HIV has had limited assessment and has been studied only in high–income countries. The general recommendation is that secondary CTX prophylaxis should not be discontinued, irrespective of clinical and immune response to antiretroviral therapy.

95. Based on evidence that secondary CTX prophylaxis can be safely stopped among adults and adolescents guided by immune recovery in response to antiretroviral therapy assessed using CD4 cell count, discontinuation of secondary CTX prophylaxis may be considered among children older than five years with evidence of immune recovery in response to antiretroviral therapy in accordance with the recommendation for discontinuation of primary prophylaxis.

96. Adults and adolescents among whom CTX prophylaxis is contraindicated. Adults and adolescents with a history of severe adverse reaction (grade 4) to CTX or other sulfa drugs should not be prescribed CTX prophylaxis. In situations in which CTX cannot be continued or should not be initiated, dapsone 100 mg per day, if available, can be used as an alternative. Dapsone is less effective than CTX in preventing PCP and also lacks the broad antimicrobial activity of CTX.

97. It is therefore desirable to attempt desensitization (section 7.4.3) to CTX, if feasible in the clinical setting, among individuals with a previous non-severe reaction, before substituting dapsone. However, CTX desensitization should not be attempted among individuals with a previous severe (grade 4) reaction to co trimoxazole or other sulfa-containing drugs.

98. Initiation of primary CTX prophylaxis among adults and adolescents. These recommendations include a degree of flexibility to enable decisions on the most appropriate threshold of CD4 count or clinical disease stage for initiation of CTX prophylaxis to be made at the country level or even the local level, taking into account variation in the burden of HIV, disease spectrum and the capacity and infrastructure of health systems. In settings in which CTX prophylaxis is initiated based on WHO clinical staging criteria only, CTX prophylaxis is recommended for all symptomatic people with mild, advanced or severe HIV disease (WHO clinical stages 2, 3 or 4). Where CD4 cell testing is available, CTX prophylaxis is recommended for everyone with a CD4 cell count <350 per mm3, particularly in resource-limited settings where bacterial infections and malaria are prevalent among people living with HIV.

99. Some countries may choose to adopt a CD4 threshold of 200 cells per mm3 below which CTX prophylaxis is recommended. This option is especially recommended if the main targets for

CTX prophylaxis are PCP and toxoplasmosis. However, bacterial infections are prevalent in individuals living with HIV in all settings, which supports the use of the 350 cells per mm3 threshold. People with WHO clinical stage 3 or 4 HIV disease (including people with pulmonary as well as extrapulmonary TB) should, however, still initiate CTX prophylaxis irrespective of the CD4 cell count.

100. Some countries may also opt to treat everyone living with HIV (universal option), because of operational simplicity and data suggesting a reduction of severe events irrespective of CD4 count or clinical stage. This strategy may be considered in settings with high prevalence of HIV and limited health infrastructure. However, lifelong use of CTX prophylaxis for all people living with HIV needs to be weighed against the challenges of maintaining long-term adherence and the potential for emergence of drug-resistant pathogens.

Figure 35. Initiation of CTX prophylaxis among adults and adolescents living with HIV

Based on who clinical staging criteria alone (when CD4 count is not available)	Based on who clinical staging and CD4 cell count criteria[a]
WHO clinical stage 2, 3 or 4	Any WHO clinical stage and CD4< 350 cells per mm3 [b] OR WHO clinical stage 3 or 4 irrespective of CD4 level
Universal option: Countries may choose to adopt universal CTX for everyone living with HIV and any CD4 count or clinical stage. This strategy may be considered in settings with high prevalence of HIV and limited health infrastructure.	
a) Expanded access to CD4 testing is encouraged to guide the initiation of antiretroviral therapy and to monitor the progress of antiretroviral therapy. b) Countries may choose to adopt a CD4 threshold of <200 cells per mm3 .	

101. **CTX prophylaxis among pregnant women**. Although pregnant women living with HIV widely use CTX, there is no evidence of an increase in CTX-related adverse events among pregnant women versus non-pregnant women. Since the risk of life-threatening infections among pregnant women with low CD4 count or clinical features of immunosuppression outweighs the theoretical risk of CTX-induced congenital abnormalities, women who fulfill the criteria for CTX prophylaxis should stay on CTX throughout their pregnancy. If a woman requires CTX prophylaxis during pregnancy, it should be started regardless of the stage of pregnancy.

102. If a woman living with HIV is receiving CTX prophylaxis and resides in a malarial zone, it is not necessary for her to have additional sulfadoxine/pyrimethamine–based intermittent presumptive therapy for malaria. Breastfeeding women should continue to receive CTX prophylaxis.

103. Doses of CTX among adults and adolescents. The dose of CTX among adults and adolescents living with HIV is one double-strength tablet or two single-strength tablets once daily: the total daily dose is 960 mg (800 mg sulfamethoxazole + 160 mg trimethoprim)[12].

104. Secondary CTX prophylaxis among adults and adolescents. Adults and adolescents with a history of treated PCP should be administered secondary CTX prophylaxis with the same regimen recommended for primary prophylaxis.

105. Discontinuing CTX prophylaxis among adults and adolescents. The discontinuation of CTX prophylaxis among individuals living with HIV may be considered in the context of drug toxicity and immune recovery in response to antiretroviral therapy. Discontinuation should be based on clinical judgement, including both clinical and laboratory parameters.

106. Discontinuation based on antiretroviral therapy–related immune recovery. Studies in well-resourced settings have demonstrated the safety of discontinuing CTX as prophylaxis against PCP and toxoplasmosis among people with immune recovery (CD4>200 cells per mm3) in response to antiretroviral therapy. Emerging data in resource-limited settings have demonstrated similar findings. However, no randomized clinical trials have assessed the safety and timing of the discontinuation of CTX prophylaxis following immune recovery in response to antiretroviral therapy in resource-limited settings. The general recommendation is to continue CTX prophylaxis among adults living with HIV indefinitely.

107. Some countries may consider adopting a CD4 count–guided discontinuation of CTX as prophylaxis against PCP and toxoplasmosis among people with immune recovery and CD4 >200 cells per mm3 in response to antiretroviral therapy for at least six months. In other situations (in which CTX prophylaxis was initiated based on its effect in reducing morbidity and mortality and the incidence of malaria and bacterial infections), discontinuation based on CD4 count can be considered among people with immune recovery and CD4 >350 cells per mm3 after at least six months of antiretroviral therapy.

108. The same discontinuation rules apply to people who have been prescribed dapsone prophylaxis. No consensus was reached on recommendations for discontinuing CTX prophylaxis in the absence of CD4 count monitoring in response to antiretroviral therapy. However, discontinuation could be considered among people who have received antiretroviral therapy for one year without WHO clinical stage 2, 3 or 4 events, good adherence and secure access to antiretroviral therapy. CTX prophylaxis (or dapsone if the person cannot tolerate CTX) should be recommenced if the CD4 cell count falls below the initiation threshold or if new or recurrentWHO clinical stage 2, 3 or 4 conditions occur.

[12] There is an option to give one single-strength tablets (480 mg per dose or 400 mg sulfamethoxazole + 80 mg trimethoprim) taken twice daily, as this may assist in preparing individuals for initiating the twice-daily antiretroviral therapy regimens that are commonly available in resource-limited settings.

Figure 36. Summary of recommendations for discontinuing primary CTX among adults and adolescents

Target population	Recommendations	
Adults and adolescents living with HIV	CD4 testing not available (clinical assessment only)	Do not discontinue CTX prophylaxis, particularly in settings where bacterial infections and malaria are common HIV-related events
		Consider discontinuing CTX prophylaxis among people with evidence of good clinical response to antiretroviral therapy (absence of clinical symptoms after at least one year of therapy), good adherence and secure access to antiretroviral therapy
	CD4 testing available (clinical and immunological assessment)	In countries where CTX prophylaxis is recommended only for preventing PCP and toxoplasmosis, it can be discontinued among those with evidence of immune recovery in response to antiretroviral therapy (CD4 >200 cells per mm3 after at least six months of antiretroviral therapy)
		In countries with a high incidence of bacterial infections and malaria, discontinue CTX prophylaxis among people with evidence of immune recovery related to antiretroviral therapy (CD4 >350 cells per mm3 after at least six months of antiretroviral therapy)

109. Discontinuation based on CTX adverse events. Severe adverse reactions to CTX are uncommon. If non-severe adverse events occur, every effort should be made to continue prophylaxis with CTX because of its superior efficacy in preventing PCP and bacterial infections compared with dapsone among adults. It also protects against toxoplasmosis, malaria and some enteric pathogens. Except in cases of severe adverse reaction, CTX should be temporarily interrupted for two weeks and then desensitization should be attempted, if indicated and feasible. If using dapsone is necessary, the dose for adults and adolescents is 100 mg per day. Some people cannot tolerate either CTX or dapsone. No alternative recommendation can be made in resource-limited settings.

110. For people in settings with limited laboratory capacity, the potential side effects associated with CTX prophylaxis (skin rash, bonemarrow toxicity and hepatotoxicity) can be monitored clinically. Everyone starting CTX should be provided with verbal or written information on potential adverse effects and advised to stop the drug and report to their nearest clinic if CTX-related adverse events are suspected.

Figure 37. CTX toxicity grading scale for adults and adolescents

Toxicity	Clinical description	Recommendation
GRADE 1	Erythema	Continue CTX prophylaxis with careful and repeated observation and followup. Provide

		symptomatic treatment, such as antihistamines, if available
GRADE 2	Diffuse maculopapular rash, dry desquamation	Continue CTX prophylaxis with careful and repeated observation and followup. Provide symptomatic treatment, such as antihistamines, if available
GRADE 3	Vesiculation, mucosal ulceration	CTX should be discontinued until the adverse effect has completely resolved (usually two weeks), and then reintroduction or desensitization can be considered
GRADE 4	Exfoliative dermatitis, Stevens-Johnson syndrome or erythema multiforme, moist desquamation	CTX should be permanently discontinued

111. CTX desensitization. Given the importance of CTX and the lack of an equally effective and widely available alternative, desensitization is an important component of managing adults and adolescents with HIV infection. It can be attempted two weeks after a non-severe (grade 3 or less) CTX reaction that has resulted in a temporary interruption of CTX. CTX desensitization has been shown be successful in most individuals with previous hypersensitivity and rarely causes serious reactions. Desensitization should not be attempted in individuals with a history of grade 4 reaction to previous CTX or other sulfa drugs. It is recommended to commence an antihistamine regimen of choice one day prior to starting the regimen and to continue daily until completing the dose escalation. On the first day of the regimen, the step 1 dose of CTX is given and subsequently increased one step each day. If a severe reaction occurs, the desensitization regimen is terminated. If a minor reaction occurs, repeat the same step for an additional day. If the reaction subsides, advance to the next step; if the reaction worsens, the desensitization regimen is terminated.

Figure 38. Protocol for CTX desensitization among adults and Adolescents

Step	Dose
DAY 1	80 mg sulfamethoxazole + 16 mg trimethoprim (2 ml of oral suspensiona)
DAY 2	160 mg sulfamethoxazole + 32 mg trimethoprim (4 ml of oral suspensiona)
DAY 3	240 mg sulfamethoxazole + 48 mg trimethoprim (6 ml of oral suspensiona
DAY 4	320 mg sulfamethoxazole + 64 mg trimethoprim (8 m of oral suspensiona)
DAY 5	One single-strength sulfamethoxazole-trimethoprim tablet (400 mg sulfamethoxazole + 80 mg trimethoprim)
DAY 6 ONWARDS	Two single-strength sulfamethoxazole-trimethoprim tablets or one double strength tablet (800 mg sulfamethoxazole + 160 mg trimethoprim)
a) CTX oral suspension is 40 mg trimethoprim + 200 mg sulfamethoxazole per 5 ml.	

112. Discontinuing secondary CTX prophylaxis among adults and adolescents. Recommendations for discontinuing and restarting secondary prophylaxis among adults and

adolescents are the same as for the recommendations for primary prophylaxis. These recommendations are supported by observational studies and from a randomized trial in a well-resourced setting as well as a combined analysis of eight European prospective cohorts.

113. Timing the initiation of CTX in relation to initiating antiretroviral therapy common to Infants, Children, Adult and Adolescents. Since the most common initial side effect of CTX and antiretroviral therapy (especially nevirapine and efavirenz) is rash, it is recommended to start CTX prophylaxis first and to initiate antiretroviral therapy two weeks later if the individual is stable on CTX and has no rash.

114. Clinical and laboratory monitoring of CTX prophylaxis. The safety of CTX in long-term use has been established. Drug-related adverse events are uncommon and typically occur within the first few weeks of starting prophylaxis. Clinical monitoring should be carried out regularly, ideally at a minimum of three monthly intervals, with individuals encouraged to report adverse symptoms as soon as they are noted. *No specific laboratory monitoring is required among children, adolescents and adults receiving CTX prophylaxis.*

115. Particular interest should be paid to skin reactions and symptoms such as nausea, vomiting or jaundice. Skin reaction is the most common CTX-related adverse event and is diagnosed clinically. Attention should be paid to other medications the person is receiving with possible overlapping toxicity (such as efavirenz, nevirapine and isoniazid). CTX and dapsone can induce haemolytic anaemia among people with glucose-6-phosphate dehydrogenase deficiency. These drugs should not be prescribed to individuals, particularly children, with known or suspected glucose-6-phosphate dehydrogenase deficiency. Routine testing for glucose-6-phosphate dehydrogenase deficiency in resource-limited settings is not recommended. If available, laboratory monitoring should be based on symptoms and signs (such as full blood counts if anaemia is suspected and liver function tests if hepatic dysfunction is suspected).

116. Six-monthly CD4 count monitoring is recommended, if available, to guide when to initiate antiretroviral therapy. Once antiretroviral therapy is initiated, monitoring should continue according to the standard of care for antiretroviral therapy management for the setting involved. In general, the impact of CTX prophylaxis on antiretroviral therapy toxicity is minimal. Among people on zidovudine-containing antiretroviral therapy regimens, the impact of overlapping blood toxicity with CTX prophylaxis is not significant (except for people with advanced HIV disease), and no additional laboratory monitoring is needed.

117. Treatment of bacterial and opportunistic infections among people taking CTX prophylaxis. Despite the lack of data, it is recommended to use an alternative antibiotic (where available) for treating breakthrough bacterial infections among individuals living with HIV receiving CTX prophylaxis, while continuing CTX. For toxoplasmosis and PCP infections, prophylaxis should be suspended and full active treatment initiated according to national guidelines. CTX prophylaxis should be recommenced after the treatment course.

118. Among children, adults and adolescents receiving CTX prophylaxis, breakthrough episodes of malaria should be treated, if possible, with antimalarial therapy that does not include sulfadoxine/pyrimethamine. There is no evidence to date on the efficacy of sulfadoxine/pyrimethamine in treating episodes of malaria among people taking CTX

prophylaxis. In malaria-endemic areas, intermittent presumptive therapy for malaria is recommended for pregnant women. Given the benefits of CTX in preventing and treating malaria, intermittent presumptive therapy is not recommended for pregnant women receiving CTX prophylaxis. Similarly, sulfadoxine/pyrimethamine–based intermittent presumptive therapy for malaria is not necessary for infants or children on CTX prophylaxis.

Annex 1. List of References

1. AIDS in South Asia: Understanding and Responding to a Heterogeneous Epidemic, The World Bank, 2006; UNAIDS, 2006

2. Afghanistan Epidemiological Fact Sheets on HIV/AIDS and STIs, UNAIDS, 2006

3. UNAIDS, 2006, UNODC, 2005, ORA International, 2006, Action Aid, 2006

4. Antiretroviral treatment of HIV infection in infants and children in resource-limited settings, towards universal access: Recommendations for a public health approach, WHO, 2003

5. National HIV Rapid Test Protocol, MOPH, Afghanistan, 2008.

6. Policy Statement on HIV testing UNAIDS and WHO, 2004.