Ministry of Public Health

G.D of Preventive Medicine

Directorate of Communicable Disease Control

National AIDS Control Program

Guideline on Antiretroviral Treatment

2011

Acronyms/Abbreviations

[…]	In squared brackets: fixe dose combination of…
3TC	Lamivudine
ACEI	Angiotensine converting enzyme inhibitor
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine-aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral drug
AZT	Zidovudine
bid	twice daily
BMI	Body-mass-index
bPI	boosted proteinase inhibitor
CI	Confidence interval
CKD	Chronic kidney disease
CMV	Cytomegalovirus
CNS	Central nervous system
CPT	Co-trimoxazole prophylactic treatment
DAART	Directly administered antiretroviral therapy
DBS	Dried blood spot
DNA	Deoxyribonucleic acid
DOTS	Directly observed treatment - short course
DRV	Darunavir
DRV/r	Ritonavir-boosted Darunavir
EFV	Efavirenz
ETV	Etravirine
FBC	Full blood count
FDC	Fixed-dose combination
FTC	Emtricitabine
GFR	Glomerular filtration rate
Hb	Hemoglobin
HBs	Hepatitis B surface antigen
HBsAG	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Hunan immunodeficiency virus
HIVAN	HIV-associated nephropathy
HR	Hazard ratio

HSV	Herpes simplex virus
ICESCR	International Covenant of Economic, Social and Cultural Rights
IPT	Isoniazide preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
LPV/r	Ritonavir-boosted Lopinavir
MOTT/MAC	Mycobacteria other than tuberculosis/mycobacterium avium complex
MTCT	Mother to child transmission
NACP	National AIDS control program
NNRTI	Non-nucleoside reverse transcriptiase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor (incl nucleotide reverse transcriptase Inhibitor
NVP	Nevirapine
OST	Opioid substitution therapy
PCP	Pneumocystis jiroveci pneumonia
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PITC	Provider initiated testing and counseling for HIV
PMTCT	Prevention of mother to child transmission
qd	daily
RAL	Raltegravir
RCT	Randomized controlled trial
RDA	Recommended daily allowance
RNA	Ribonucleic acid
RR	Relative risk
RTV	Ritonavir
sd-NVP	Single dose Nevirapine
TB	Tuberculosis
TB-IRIS	Tuberculosis - immune reconstitution inflammatory syndrome
TCR	Triple class resistance
TDF	Tenofovir
THC	Tetrahydrocannabiol
ULN	Upper limit of normal
VCT	Voluntary counseling and testing
VL	Viral load
VZV	Varicella zoster virus
WHO	World Health Organization

Acknowledgments

NACP decide to have specific guideline and documents to guide the relevant staff to do actual performance based on standard document and guideline and provide the qualitative HIV and AIDS service to target people. In fact the response to HIV in Afghanistan, essential information is provided in the ANASF 2006 and POP 2007.

Two Anti Retroviral Therapy centers (ART) were established in 2009 in Afghanistan (Kabul and Herat cities) also ART guideline had been developed.

In 2010, WHO had new recommendations for effective treatment of HIV and AIDS Therefore, NACP previous Anti Retroviral Therapy (ART) guideline which was developed in (July 2008 by Dr. Veronique Bortolotti, EMRO WHO and Dr. Zubair ART center responsible) revised in light of new recommendations of WHO 2010.

This ART updated guideline will offer important knowledge on Anti Retroviral Therapy (ART) for HIV service providers, program managers, trainers, and persons living with HIV and particularly ART center implementers.

Purposes of this guideline are to have standard document for Anti Retroviral Therapy & ART training, to guide the Medical and Sub-medical staff to do correct and early diagnosis of HIV and AIDS patients according to WHO clinical criteria, effective treatment of AIDS patients, PMTCT prophylaxis and treatment, TB/HIV treatment, adherence to ART and guidance for Anti Retro Viral (ARV) procurement. The guideline will lead the Medical doctors and sub medical staff when to start? And what to start? For the treatment of HIV and AIDS patient and reduce the mortality associated with HIV and AIDS in Afghanistan. The guideline will also be a useful source for organizing ART training courses for staff in the country.

The NACP/MOPH is thankful to WHO for providing support for the development of ART guideline and our deep appreciation goes to Dr. Till Kinkel WHO consultant for his efforts and technical input for enrichment of ART guideline.

The cooperation received the ART working group members were instrumental for the development of this guideline, we, therefore, would like to appreciate the inputs provided by the working group members during the guideline development process.

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Background

The Afghanistan National HIV and AIDS Strategic Framework (ANASF: 2006 -2010) sets the policy and guides the responses. It was developed through consultative and iterative processes involving the government, non-governmental stakeholders and development partners. The ANASF is designed to guide Afghanistan's response to HIV/AIDS and to assist stakeholders to develop their own strategic plans so that all initiatives in the country can be harmonized.

The Framework comprehensively provides six objectives, key strategies and 34 outcomes, that include components for HIV surveillance; VCT and HIV treatment, care and support; targeted interventions for most at risk populations and other vulnerable groups, including harm reduction for IDUs and prisoners, outreach for sex workers and their clients; joint HIV and TB services, and advocacy and communication for community leaders and the general population.

In line with strategic frame of HIV and AIDS, treatment of HIV clients and AIDS patients are an important part of the main objectives, in fact Anti Retroviral therapy (ART) is the vital need of the National AIDS Program and people living with HIV and AIDS in country, therefore NACP/MOPH established two ART centers in Afghanistan in 2009 (Kabul and Herat provinces).

At the commencement WHO has provided the ARVs to the centers and Global Fund continuously has been providing the ARVs, CD4 count machines (for absolute and percentage count), staff financial support, maintenance and other to ART center, through GTZ.

USA/CDC Atlanta also has provided two CD4 machine for Kabul and Herat for correct counting of CD4, clinical stages and early treatments of HIV and AIDS patients.

All over in Afghanistan where 57 people are under ART (ART centers/NACP 2011 January) and treatment is well accepted by patients.

Also there are challenges such as limited numbers of ART centers in the country, communication and networking among health providers from different provinces including referral of patients, adherence of people living with HIV to life-long ART and stigma and discrimination against people living with HIV.

Chapter One: General Information

Guiding Principles

- First guiding principle is "the right of *everyone* to the enjoyment of the *highest attainable standard* of physical and mental health" as defined in Article 12 of the International Covenant of Economic, Social and Cultural Rights (ICESCR) as Part of the International Bill of Human Rights, ratified by Afghanistan in 1983 as binding law since then.
- Second guiding principle is to provide recommendations based on best available evidence to date.
- Third guiding principle is to prioritize strategies which are supporting the patient to adhere to the recommended therapies to enjoy the most benefit of treatment by recommending treatments which are highly effective, well-tolerated and easy to adhere.
- Forth guiding principle is to keep procurement simple and affordable for the responsible governmental bodies to allow for equal access to therapy for all people who will benefit from treatment.

Objectives

- To bundle the tremendous knowledge into clear and easy recommendations and to guide clinicians' decision in regard to initiating, changing, stopping, modifying and monitoring of anti-retroviral therapy, prophylactic treatments and treatment of opportunistic infections.
- To provide up-to-date evidence for best clinical care.
- To guide procurement processes on national levels.
- Medical doctors working in Afghanistan should *usually* follow the recommendations of the guideline. This guideline is ***not*** a law and there is an endless variety of different cases, all of which need also individualized assessment and decisions, which might lead to physician's decision to vary therapy according to individual needs or new scientific developments.

- Nevertheless, most patients can be treated according to this guideline and a prescribing medical doctor should have good and well documented reasons in case of deviation from the recommendations before considering prescription of differing regimens.

Recommendation at a glance

Adherence	Every patient should be supported *individually* to adhere to ART before and during ART to avoid emergence of resistant virus strains, to increase therapeutic success, to improve overall tolerance and to decrease morbidity and mortality.
When to start ART	All adolescents and adults including pregnant women with HIV infection and CD4 counts of ≤350 cells/mm3, should start ART, regardless of the presence or absence of clinical symptoms. Those with severe or advanced clinical disease (WHO clinical stage 3 or 4) should start ART irrespective of their CD4 cell count.
What to use in first line ART	As first line ART should always be used a triple combination of two NRTI plus one NNRTI.
What to use in second line ART	As second line ART should always be used a triple combination of two NRTI plus LPV/r
Laboratory monitoring	All patients should have access to CD4 cell–count testing to optimize pre-ART care and ART management. HIVRNA (viral-load) testing is recommended to confirm suspected treatment failure. Drug toxicity monitoring should be symptom-directed.
HIV/TB coinfection	Irrespective of CD4 cell counts, patients coinfected with HIV and TB should be started on ART as soon as possible after starting TB treatment.
HIV/HBV coinfection	Irrespective of CD4 cell counts or WHO clinical stage, patients who require treatment for HBV infection should start complete ART as triple combination containing two NRTI active against HIV and HBV plus either one NNRTI or LPV/r.
Registration and documentation	Every patient receiving ART has to be registered with NACP and documentation reports have to be posted six-monthly to Kabul-ART-center for central collection of medical data (contact see chapter ”Important Contact Numbers/addresses” of the guideline)

When to start antiretroviral therapy	
Target group	
HIV+ asymptomatic ARV-naive individuals	CD4 ≤350 cells/mm3
HIV+ symptomatic ARV-naive individuals	WHO clinical stage 3 or 4 irrespective of CD4 cell count
HIV+ pregnant women	CD4 ≤350 cells/mm3 irrespective of clinical symptoms OR WHO clinical stage 3 or 4 irrespective of CD4 cell count

HIV/TB coinfection in ARV-naive individuals	Presence of active TB disease, irrespective of CD4 cell count
HIV/HBV coinfection in ARV-naive individuals	Individuals who require treatment for their HBV infection, irrespective of CD4 cell count

What to start	
Target group	
HIV+ ARV-naïve adults and adolescents	[TDF+FTC+EFV]
If [TDF+FTC+EFV] not feasible	[AZT+3TC+NVP]
HIV+ pregnant women	After 14th week of gestation: [TDF+FTC+EFV] Before 14th week of gestation: [AZT+3TC+NVP] or [TDF+FTC]+NVP
PMTCT **(for women not eligible for ART for their own health)**	Mother: After 14th week of gestation [TDF+FTC+EFV] until one week after definite end of breastfeeding Infant: NVP or AZT-monoprophylaxis from birth to 6 weeks of age independent of mode of breastfeeding
Infants and children	AZT+3TC+NVP (or AZT+3TC+LPV/r) For children older than 3 years EFV is possible NNRTI
HIV/TB coinfection	[TDF+FTC+EFV]
HIV/HBV coinfection	[TDF+FTC+EFV]
HIV/HCV coinfection	[TDF+FTC+EFV]

Second Line ART		
Target group	**If first line…**	**…then second line**
HIV+ adults and adolescents including pregnant women	[TDF+FTC+EFV]	[AZT+3TC]+LPV/r
	[AZT+3TC+NVP]	[TDF+FTC]+LPV/r
HIV/TB coinfection during treatment with Rifampicin	[TDF+FTC+EFV]	[AZT+3TC]+LPV/r (superboosted)
	[AZT+3TC+NVP]	[TDF+FTC]+LPV/r (superboosted)
HIV/HBV coinfection	[TDF+FTC+EFV]	[TDF+FTC]+AZT+LPV/r
HIV/HCV coinfection	[TDF+FTC+EFV]	[AZT+3TC]+LPV/r

Prophylaxis of opportunistic infections	
Cotrimoxazole Prophylactic Therapy (CPT)	All people living with HIV including pregnant women and children independent of CD4 count or clinical stage ("universal option")
Isoniazide Preventive Treatment (IPT)	Adults, adolescents and children older than 12 months living with HIV should be screened for TB with a clinical algorithm and those who are unlikely to have active TB should be offered ITP for 6 months. People living with HIV unlikely to have active TB but living in congregate settings, including prisons, should receive IPT for 6-36 months Children living with HIV should receive additional 6 months of IPT after successful completion of treatment for active TB to prevent relapse. People suffering active TB should not receive IPT
Multivitamins & Micronutrients	Pregnant women, infants and children living with HIV should receive supplementation of multivitamins&micronutrient Supplementation of multivitamins&micronutrients might be considered in all people livening with HIV in Afghanistan Infants and Children living with HIV should receive additional energy and protein supplementation

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 will have the same right to health as all other citizens, and will not be discriminated or stigmatized on the basis of their HIV status, gender, socioeconomic status, religion, ethnicity, nationality, political affiliation, law-abidance, sexual orientation or concomitant diseases (including drug dependency or psychiatric comorbidities).

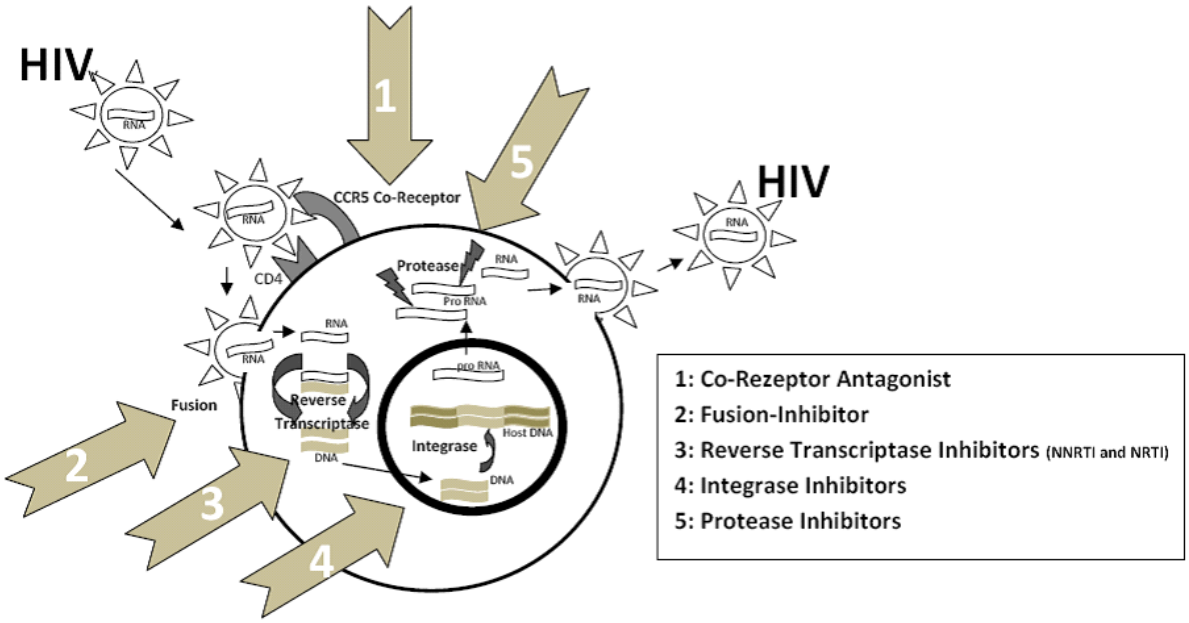
It is critical to ensure that women and children have equitable access to treatment and care services, particularly those individuals in marginalized and at risk populations.

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

Classification of ART

First drug with explicit antiviral activity was Zidovudin, discovered in 1985 and introduced as therapeutic agent in humans in 1987, only three years after discovery of HIV. Since then 28 different antiretroviral drugs reached approval of according authorities to be used in the treatment of HIV-infection. All currently marketed and approved ARV belong to one of the five following classes:

- Entry-Inhibitors:
    - Co-Receptor-Antagonists (CCR5-Antagonist)
    - Fusion Inhibitors (FI)
- Nucleosid(t)e Reverse Transcriptase Inhibitors (NRTI)
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
- Protease Inhibitors (PI)
- Integrase Inhibitors (II)



In addition several fixed dose combinations (FDC) have been produced. In the following table the globally approved ARV as generics, their class, the initial brand-name which is often used instead of the generic name and some remarks are listed to give a brief overview.

In resource-limited countries cost of the ARV plays a major role. Therefore usually not all ARVs are procured by the public health sector. In harmony with the recommendations of the evidence based guidelines developed by the partners of WHO, the Ministry of Public Health of the Islamic Republic of Afghanistan has decided to procure the marked selection of ARVs for treatment of HIV-infection in adults, adolescents, children and infants including patients with concomitant diseases or pregnancy to be used according to this guideline. As medical science and the Islamic Republic of Afghanistan are progressing rapidly, new ARVs, including possible third-line options, might become available during the period of validity of this guideline. Therefore medical doctors need to follow the developments in medical science and the Islamic Republic of Afghanistan to the best benefit of their patients.

	NRTI					
*	Zidovudine	AZT	Retrovir®	Thymidine-analog	Widely used, also in FDC: Combivir®,Trizivir®	Not to combine with d4T
*	Lamivudine	3TC	Epivir®	Cytidine-analog	Widely used, also in FDC: Combivir®, Kivexa®, Trizivir®	Active against HBV. Not to combine with FTC
*	Emtricitabine	FTC	Emtriva®	Cytidine-analog	Widely used, also in FDC: Truvada®, Atripla®	Active against HBV. Not to combine with 3TC
*	Tenofovir	TDF	Viread®	Nuleotid-RTI	Widely used, also in FDC: Truvada®, Atripla®	Active against HBV
	Abacavir	ABC	Ziagen®	Guanosine-analog	Also in FDC: Kivexa®, Trizivir®	
	Didanosin	ddI	Videx®	Adenosine-analog	Almost phased out due to severe side-effects	
	Stavudine	D4T	Zerit®	Thymidine-analog	Should be phased out due to side-effects	No to combine with AZT.
x	Zalcitabine	ddC	HIVID®	Cytidine-analog	Withdrawn from the market in 2006	
	NNRTI					
*	Efavirenz	EFV	Sustiva®, Stocrin®		Widely used, also in FDC: Atripla®	
*	Nevirapine	NVP	Viramune®		Widely used, also in FDC: [AZT+3TC+NVP]	
x	Etravirine	ETV	Intelence®	Second generation NNRTI	Active also against EFV- or NVP-resistant stains	Always in combination with a bPI (usually DRV/r)

x	Delavirdine	DLV	Rescriptor®		Not widely used	
	Protease-Inhibitors					
*	Lopinavir/r	LPV/r	Kaletra®	Only fixed-boosted PI	Most used PI	Only PI not requiring cold storage
	Ritonavir	RTV	Norvir®	Only used to boost	In combination with most PI	
x	Darunavir	DRV	Prezista®	Always to boost with Ritonavir	Increasingly important, well tolerated, very high resistance-barrier	Third line!
	Indinavir	IDV	Crixivan®	Always to boost with Ritonavir	Rarely used	
x	Tipranavir	TPV	Aptivus®	Always to boost with Ritonavir	Also active against many PI-resistant HIV-strains	Third line!
	Saquinavir	SQV	Invirase®	Always to boost with (high-dose) Ritonavir		
	Atazanavir	ATV	Reyataz®	In case of RTV-intolerance ATV can be used without booster	Frequently used PI	
x	Amprenavir	APV	Agenerase®		Replaced by FPV	
x	Fosamprenavir	FPV	Telzir®, Lexiva®	Always to boost with Ritonavir	Rarely used	
	Nelfinavir	NFV	Viracept®	Boosting with RTV is useless	Rarely used	Less potent than other PI
	Co-receptor-Antagonists					
x	Maraviroc	MVC	Celsentri® Selzentry®	CCR5-Antagonist	Only against CCR5-tropic-HIV.	Needs tropism-testing before use
	Entry-Inhibitor					
x	Enfurvitide	T-20	Fuzeon®	Entry-Inhibitor	Only for subcutaneous injection	
	Integrase-Inhibitor					
x	Raltegravir	RAL	Isentress®		Widely used	

* these drugs are available drugs for first- and second-line ART in Afghanistan procured by NACP in 2011.

X these drugs are not listed in the Essential/Licensed drug list of the Islamic Republic of Afghanistan 2007

Detailed information about the ARV and FDC recommended for use in Afghanistan are to be found in chapter "Antiretrovirals (ARV) and Formulations" of this guideline (chapter 7)

Adherence

Recommendation:

- Every patient should be supported *individually* to adhere to ART before and during ART to avoid emergence of resistant virus strains, to increase therapeutic success, to improve overall tolerance (inadequate adherence can lead to more severe side-effects) and to decrease morbidity and mortality.

Specification:

Adherence to ART is crucial for treatment success. Non-adherence is *the* leading cause of resistance. Sethi found in a prospective study that patients who reported levels of adherence of 70-79% and 80-89% had 5.01 and 3.14 times higher rates of resistant virus strains after 1 year than participants who reported adherence to > 90 % or < 60% of prescribed doses. Another study found in patients with electronically measured adherence rates of >95%, 90-94.9%, 80-89.9%, 70-79.9% and <70% rates of virologic failure in 21.7%, 54.6%, 66.7%, 71.4% and 82.1%, respectively. Studies comparing directly administered ART (DAART) in analogy with DOTS for TB-treatment found also significant and relevant differences between groups of DAART and self-administered ART: one study focusing on people who use drugs found 70.5% vs. 54.5% of virological success of ART and mean changes in CD4 count of +58.8 vs. -24 cells/µl after 6 months of therapy. Another study comparing DAART with self-administered ART found virological suppression after 24, 48 and 80 weeks of therapy significantly and relevantly different at 100% vs. 76%, 100% vs. 81% and 95% vs. 75%.

Clinical and immunological outcome of patient with lower rates of adherence has been studied in several studies in different settings. In Canada among patients with baseline CD4 counts < 200 cells/µl, adherence was the strongest independent predictor of the time to a CD4 count > 200 cells/µl (RH = 4.85, 95% CI: 3.15-7.47). In Spain one study revealed an adjusted relative hazard of death for non-adherent patients (<90% of prescribed tablets taken) of 3.78 compared with adherent patients.

“Pre-ART-counseling” before starting ART and “adherence interventions” during therapy should be individualized to the patient’s challenges and needs.

As adherence to ART is of utmost importance for the course of disease in the individual patient *and* on a public health level (resistant virus can be transmitted and the overall risk of transmission is increased), **supporting adherence is an important responsibility of the prescribing medical doctor.**

The following list gives brief advice on possible ways to increase adherence of the patient:

Information:

- The patient needs to understand the importance of therapy and adherence.
- The patient needs to understand the modalities of intake (with meal/on empty stomach, morning/ evening, once daily/twice daily, most relevant side effects and drug interactions, dose-replacement in case of vomitus, etc.)
- The patient should know which side effects may occur and should be able to judge their importance.
- The patient needs to know when to come back to the medical doctor/dispensary for routine check-ups, receipt of follow-up medication or in case of side-effects.

Motivation:

- Non-confrontational, motivational interviewing to increase the resources of the patient to adhere to the treatment has been proven to increase adherence.
- Comfortable and trustful atmosphere at the ART-center facilitate the patients visits.
- Unpleasant clinic experiences in terms of length of time spent waiting, overcrowding, lack of privacy, and unfriendly or rude interactions with clinic staff jeopardize adherence and should therefore be avoided.

Comfortable therapy:

- Selection of fixed-dose-combinations with low pill burden with simple dosing. E.g. once-daily one tablet of [TDF+FTC+EFV] is much easier than [AZT+3TC+NVP] which is twice daily and needs phasing in with [AZT+3TC] + NVP in the morning and [AZT+3TC] in the evening for two weeks.
- Selection of well-tolerated therapy. E.g. [TDF+FTC+EFV] is usually better tolerated than LPV/r-containing regimens which often cause diarrhea and are at least 5 tablets per day (4 tablets LPV/r plus NRTI-backbone)
- Side-effects need to be monitored and managed - including the patient's easy access to medical staff in case of side effects.
- Perceived importance of a side-effect might be individually different. Concerns of a patient regarding a side-effect might lead to non-adherence and should therefore always be taken seriously by the medical staff, even if objectively importance might be relatively low.
- Treatment of co-morbidities is important (e.g. depression, opportunistic infections, addiction).

Direct interventions:

- Tracing the patient in case of a missed appointment by SMS or phone-call.

Social network:

- Defining together with the patient a person who is able to support adherence and to motivate in times of crises.

Organizational tasks:

- Assuring the patient's daily access to the medication. E.g. homeless persons need a safe and hygienically acceptable and daily accessible place to store the medication if not directly administered therapy is chosen. E.g. homeless people might choose a NGO, working place, shop or doctor to store medication if directly administered therapy is not an option.

- Where feasible implementation of directly administered therapy should be considered, e.g. in combination with methadone- or TB-therapy, which are usually directly observed.

- Functioning structures can be tested by prescribing CPT, micronutrient and IPT first to detect eventual obstacles in the everyday life of the patient to store, access and take medication.

- Necessary precaution and planning in case the patient considers travelling or moving elsewhere.

Identification of adherence risk:

- Evaluation - together with the patient - of the possible risks for non-adherence and development of coping-strategies.

It is recommended to discuss adherence with every patient before starting ART and at every visit. A written adherence plan, identifying risks and possible strategies to overcome risks can be useful.

Chapter Two: Antiretroviral Therapy (ART)

When to Start Antiretroviral Therapy.

Recommendations:

- All people tested positive for HIV and confirmed according to the Afghan guideline for HIV-counseling and testing should have access to CD4 count at diagnosis and every 6 months thereafter.
- All people living with HIV in Afghanistan in WHO clinical condition 3 and 4 should be treated with ART irrespective of CD4 count.
- All people living with HIV in Afghanistan with CD4 count ≤350 cells/µl should be treated with ART irrespective of WHO clinical condition.
- All people living with HIV in Afghanistan should be supported by health professionals to enable adherence to ART by implementation of focused counseling and adherence interventions before starting ART.

WHO Clinical stages of HIV/AIDS for adolescents and adults:

CLINICAL STAGE 1	Asymptomatic Persistent generalized lymphadenopathy
CLINICAL STAGE 2	Unexplained moderate weight loss (under 10% of presumed or measured body weight) 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 Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, 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 jiroveci pneumonia (PCP) Recurrent severe 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 excluding liver, spleen or lymph nodes) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated nontuberculous mycobacteria infection Progressive multifocal leukoencephalopathy (PML) Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (coccidiomycosis or histoplasmosis) Recurrent septicaemia (including nontyphoidal Salmonella) Lymphoma (cerebral or B cell non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Evidence:

This recommendation is based on the Cochrane review "Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults" by Siegfried et al. published in 2010.

The Cochrane review and the recommendation are based above all on the CIPRA HT-001 (2009) study, a single-centre trial in Haiti, which randomized 816 ART-naive participants with a CD4 count of 200350 cells/mm3, to receive early versus standard -of-care treatment (start ART when the CD4 count is <200 cells/mm3 or following the development of an AIDS-defining illness). During the median follow-up of 21 months there were 23 deaths in the standard-treatment group (408 patients), as compared with 6 in the early-treatment group (408 patients) (HR with standard treatment, 4.0; 95% CI, 1.6 to 9.8; p=0.001) and 36 incident cases of tuberculosis in the standard-treatment group, as compared with 18 in the early-treatment group (HR 2.0; 95% CI 1.2 to 3.6; p=0.01). Applicability of this trial to the setting in Afghanistan is especially high since it was conducted in a very resource-limited setting.

A subset-analysis of the multicenter SMART-trial found similar results in high/middle/low-income setting in favor of early initiation of ART.

Observational data suggest benefit of initiating ART even at higher CD4-cell counts . WHO recommends using a 350 CD4-cells/µl threshold to initiate ART based on the following considerations:

- Studies provide evidence that stating ART at CD4 levels higher than 200-250 cells/µl reduces mortality rates in asymptomatic, ARV-naïve, HIV-infected people. The number of adverse events was also small.
- There are also studies that looked at TB incidence and results show that there is a 54% to 92% reduction in TB in individuals receiving early ART.
- An additional consideration is the HIV transmission. Early initiation of ART reduces both sexual transmission and mother-to-child transmission (MTCT) of HIV providing that there is high treatment coverage and high adherence.

Further increasing the threshold for ART initiation will increase cost for national health systems jeopardizing access to therapy for the people most in need of treatment being displaced by persons for whom treatment would be beneficial but not as urgent. Guiding principle remains that those most in need of treatment should retain priority access. Earlier initiation will mean longer exposure to ART and the possibility of more ART-related side-effects and ARV resistance. The impact of earlier initiation on adherence the potential risk of accelerating resistance is

uncertain. In Afghanistan as resource-limited country options for second- and third line therapies are limited. Therefore initiation of ART at a higher CD4 count threshold is not generally recommended at present.

The recommendation to initiate ART on the basis of clinical stage 3 or 4 is based on the evidence that clinical stage 3 or 4 conditions are independently associated with HIV-related mortality. However: CD4 count is highly recommended as many patients who present in clinical stage 2 already have fallen below 350 cells/µl.

Total lymphocyte count is not any longer recommended to trigger initiation of ART.

ART in case of acute serious opportunistic infection:

Early initiation of ART 0-2 weeks after initiation of treatment for serious opportunistic infections (dependent on the seriousness of the OI), including non-meningitic TB, has been shown to be associated with improved survival with the exception of patients with tuberculous meningitis and cryptococcal meningitis.

What to Start

Recommendation:

- Every patient eligible for ART in Afghanistan should receive a triple-combination of two NRTI plus one NNRTI as first line treatment.

First line regimen for people eligible for antiretroviral therapy is a fixed-dose combination (FDC) of:

[TDF+FTC+EFV]

TDF: Tenofovir (NRTI), 300 mg once daily

FTC: Entricitabine (NRTI), 200 mg once daily

EFV: Efavirenz (NNRTI), 600 mg once daily

This regimen is available as fixed-dose combination in one single tablet, once daily. The patient should be advised to take the pill at bedtime, unchewed on empty stomach (2 hours after dinner). If well tolerated or closely monitored for side effects - for example when part of a directly-administered ART (DAART) - drug-intake at the morning (also on empty stomach with two hours spacing from intake of fat containing food) might be considered.

This regimen is also recommended first line regimen for people co-infected with active TB, people co-infected with HBV or HCV, people with mild/moderate liver-insufficiency, people with underlying anaemia, people under methadone-based OST, pregnant women (after 14th week of gestation) and as maternal component of PMTCT.

The regimen *can* be used in people with mild and moderate renal insufficiency (Creatinine-Clearance > 30 ml/min), but an alternative might be preferred by the prescribing medical doctor.

The regimen should **not** be considered first choice in people with underlying severe depression, schizophrenic psychosis or suicidal tendencies, as those might be exacerbated by EFV-use.

Starting EFV during the first trimester of pregnancy is **contraindicated.** Teratogenicity is not proven, but EFV was possibly linked to a slightly increased risk of neural tube defects. However, for treatment after 14th week of gestation, including PMTCT, the regimen *is* recommended.

For recommendations for women living with HIV who are planning pregnancy or are pregnant see chapter "HIV, ART and pregnancy" of this guideline.

Evidence:

WHO recommends in 2010 six different optional first line regimens:

AZT+3TC+EFV; AZT+3TC+NVP; TDF+3TC+EFV; TDF+FTC+EFV; TDF+3TC+NVP or TDF+FTC+NVP.

The recommendation to use [TDF+FTC+EFV] as first line regimen in Afghanistan is based on the following reasoning:

The combination is available as once-daily fixed-dose combination (FDC) and is usually better tolerated than AZT+3TC+EFV. This offers benefits in regards to better adherence and therefore higher proportions of sustained virological suppression and greater increase in CD4 and lower risk of development of resistant viral strains.

Both NRTIs, TDF and FTC, are active against HBV, with better effectivity and lower rates of HBV-resistance than either 3TC or TDF alone.

EVF and NVP seem to have an overall similar efficacy with possible small benefits in favor of EFV. EFV is superior to NVP in regards to tolerability (especially lower rates of hepatitis and lower rates of rash and neutropenia) and requires no lead-in-dosing and less monitoring. In women with CD4 > 250 cells/µl and men with CD > 400 cells/µl NVP should not be used due to a 12-fold (women) and 5-fold (men) increased risk of hepatotoxicity. On the other hand: CNS-side-effects and negative effects on plasma–lipid-levels are more frequently seen with EFV.

EFV and EFV-containing FDC are usually recommended to be taken at bedtime due to CNS-effects. However, possible benefits of morning doses in regard to convenience or for the purpose of directly-administered therapy (DAART; e.g. within the framework of a directly-observed tuberculosis therapy or methadone-based OST) should be balanced with the benefits

of bedtime dosing. It might lead to morning dosing in patients who show good tolerance to EFV but need intensified support to adhere to ART. Especially in settings of DAART eventual CNS-side-effects can be monitored closely if EFV is dispensed in the morning.

Tenofovir can cause renal failure. Nevertheless, frequency of severe impairment of kidney function or kidney-related treatment interruption is low. Frequency of a 25% decline in GFR was observed to increase from 0.7/100 person-years of follow-up (95% CI 0.5 to 0.8) in persons never exposed to tenofovir (TDF) to 2.4/100 person-years (95% CI 1.7 to 3.0) with 4 years exposure in an observational study including 21,482 person-years of follow up. Other studies conducted before had described similar effects. Laboratory monitoring of the kidney-function is not a prerequisite to initiate TDF-containing ART but – if affordable – reasonable according to the recommendations given in chapter "*Monitoring f ART*" of this guideline.

Recommendation:

- alternative first line regimen in case of intolerance to the recommended [TDF+FTC+EFV] is:

[AZT+3TC+NVP]

AZT: Zidovudine 300 mg twice daily

3TC: Lamivudine 150 mg twice daily

NVP: Nevirapine 200 mg twice daily

Specification:

This regimen is available as fixed-dose combination in one single tablet, twice daily. The patient can take the pill independently of food-intake on empty stomach or together with a meal.

This combination has to be phased in to decrease risk of rash and hepatitis. During the first two weeks [AZT+3TC] twice daily plus NVP 200 mg once daily are prescribed separately, before escalating the NVP dose to the standard FDC [AZT+3TC+NVP] twice daily. There is no need to phase in NVP in case of concomitant treatment with Rifampicin or if switched to NVP from another suppressive regimen.

The combination is **not** recommended for people with underlying severe anaemia (HB<7 g/dl) due to risk of myelosuppression due to AZT.

The combination is **not** recommended for people with underlying active hepatitis and for initiating ART in women with CD4 count > 250 cells/µl and men with CD4 count >400 cells/µl due to increased risk of NVP-hepatotoxicity.

For people with severely impaired renal function (GFR < 30 ml/min) the regimen should be given as separated drugs and adjusted according to the recommendations in the chapter "Patients with Renal Failure"

Well justified deviations from these recommendations are possible according to patients needs.

Example 1: The ART-regimen [FTC+TDF]+NVP for people intolerant to EFV but anemic is possible and this combination is a well tolerated and effective combination, too.

Example 2: Women with the intention to get pregnant who are receiving a well tolerated [TDF+FTC+EFV]-first line regimen can be switched to [FTC+TDF]+NVP (and later back).

Second Line ART

Criteria to switch to second line ART

Recommendation:

- Viral load should be used to monitor and confirm immunological and/or clinical failure when available.
- It is recommended to switch ART in case of persistent viral load of > 5,000 copies/ml after adherence intervention.
- When viral load is not available immunological *and* clinical criteria should be used to decide about the indication to switch ART.
- It is recommended to switch ART in case of immunological failure:
    - Fall of CD4 count below baseline
    - 50% fall from on-treatment peak
    - Persistence ≤ 100 cells/µl
- It is recommended to consider switching ART in case of clinical failure:
    - new or recurrent WHO stage 4 clinical condition (if not IRIS)

Specification:

CD4 count is influenced by several factors other than ART-failure like intercurrent infections, heroine-use or daytime. It is recommended to use a targeted strategy of viral load measurement with the objective to confirm clinical or immunological failure to maximize benefits of first line ART and to avoid unnecessary switching to second line ART in a setting with limited options for second- and third line therapies.

“Targeted VL monitoring” stands for measurement of VL only in case of clinical or immunological criteria have been met to diagnose “treatment failure”. One systematic study on the accuracy of WHO immunological criteria revealed that immunological criteria do have a high negative predictive value but low positive predictive value for viral failure. Therefore, clinical/immunological failure should be confirmed by viral load measurement to avoid unnecessary switches, while not meeting immunological criteria usually is a sufficiently safe predictor of successful therapy. However, exclusive immunological monitoring will lead to an increased number of unnecessary switches to second line ART, which is of importance in a setting of limited available second and third line options.

“Targeted VL monitoring” allows also assessment of adherence and can lead to increased efforts to support the adherence of the patient.

Scaling up to routine viral load measurement is recommended as soon as resources allow. Viral load is a more sensitive indicator of treatment failure compared to immunological or clinical indicators.

Generally evidence for use of routine viral load testing as indicator for switching strategies to second line ART in resource limited settings is weak. A systematic Cochrane review could not find a benefit of routine VL-monitoring in regards to clinical course of disease, virus suppression and mortality. While clinical monitoring alone resulted in clearly inferior outcomes of patients included in the DART trial, combined immunological and clinical monitoring turned out to be equally effective as the combined virological/immunological and clinical monitoring approach in terms of virological failure, mortality and new WHO clinical stage 4 conditions during the first 36 months of ART.

The strategy of routine viral load testing allows nevertheless focusing and tailoring adherence interventions to increase success of first line ART.

Recent data show also superiority of routine viral load monitoring over clinical/immunological monitoring in regards to avoiding accumulation of resistance and thereby protecting effectivity of second line ART.

Selection of Second Line ART

Recommendation:

- Second line ART regimen should contain the Ritonavir-boosted Proteinase-Inhibitor Lopinavir (LPV/r).
- Second line ART regimen should contain two NRTIs different to the NRTIs of the first line regimen.

Specification:

If used as first line regimen…	… select as second line regimen
[TDF+FTC+EFV]	[AZT+3TC]+LPV/r
[AZT+3TC+NVP]	[TDF+FTC]+LPV/r

In case of concomitant use of Rifampicin, LPV/r should be used in a "superboosted" dosage of LPV/r 800 mg / 200 mg twice daily (i.e. twice daily 4 tablets of LPV/r 100/50)

In case of Hepatitis B co-infection, second line after [TDF+FTC+EFV] should continue [TDF+FTC] and add AZT + LPV/r to form a quadruple ART: [TDF+FTC]+AZT+LPV/r.

Third Line ART

- Third line ART should be procured on an individualized basis.
- In the absence of a third line ART, patients failing a second line ART should continue with this regimen if well tolerated.

Specification:

During the validity period of this guideline occurrence of triple class resistance (TCR) against NRTI, NNRTI and LPV/r is not expected to occur frequently. Failing a second line ART including a boosted PI in the first few years of therapy should always lead to increased efforts to support patient's adherence, as occurrence of TCR is rare in adherent patients during the first few years of therapy.

Patients who experience failure of a second line regimen despite good adherence should receive a third line ART which might include use of RTV-boosted Darunavir (DRV/r), Raltegravir (RAL) and/or Etravirine (ETV) optionally complemented by 2 NRTIs (e.g. AZT+TDF) dependent on the ART-history of the patient.

Acute HIV-infection

Recommendation:

- At present, ART for acute HIV-infection is *not* recommended.
- Patients with diagnosed or suspected acute HIV-infection need intensified counseling to avoid early transmission.

Specification:

Acute HIV-infection presents clinically as heterogenous, often flu-like syndrome with fever, maculopapular rash, arthralgia/myalgia and sometimes oral ulcerations.

During acute HIV-infection the patient has very high viral load and a rapid (but partially reversible) decline in CD4 count. Probably this early phase of HIV infection accounts for a high percentage of transmissions, as viral load is very high and usually HIV-positive status of the person is unknown; therefore risk-behavior is continued. In one study from Canada early transmission accounted for 49.4% of all transmissions.

Diagnosis of acute HIV-infection is difficult in the setting of Afghanistan, as antibody tests of 2nd and 3rd generation will give negative results during the acute episode, and p24/anti-p24-tests or RNA/DNA-PCR are not routinely available.

Even if treatment of acute HIV-infection is possibly beneficial, pilot studies, retrospective cohort studies and observational studies show mixed results regarding treatment effectiveness of acute HIV-infection. RCT are not available.

Treatment Interruption

Recommendation:

- Antiretroviral Treatment once initiated because the patient met clinical or immunological criteria for initiation should not be stopped.

- In case antiretroviral has to be stopped for whatever reason a structured procedure to avoid creation of resistance should be used.
- Special attention needs to be paid to patients co-infected with HBV as interruption of an HBV-suppressive ART regimen (containing TDF, FTC or 3TC) can result in rebound of active Hepatitis B.

Specification:

Treatment-interruption causes early rebound of HIV viral load with consecutive higher risk of transmission , rapid decrease of CD4 count, rapid clinical deterioration and causes drug-resistance (especially after repeated treatment-interruption).

Patients who wish to interrupt or reject to continue ART should be informed about the risks. It is recommended to phase out NNRTI-containing regimens by adding 7-14 days of a dual NRTI-regimen ("tail") after NNRTI was phased out. This recommendation is based on the evidence which comes from studies on NNRTI-resistance in settings using sd-NVP for PMTCT.

There is no evidence on best procedures to follow in case of an ongoing ART is out of stocks temporarily. Based on theoretical considerations it is recommended to substitute ongoing ART by another triple-ART if the original regimen is out of stock and a potent alternative is available. If impossible it's recommended to follow the procedures described above. Reduction to a mono- or dual therapy should be avoided as evidence shows insufficient viral suppression in case of reduction of a triple ART to AZT+3TC. If there is no other option is available to continue triple-ART, it is recommended to switch to LPV/r-monotherapy until the initial becomes available again. LPV/r-monotherapy in the maintenance of a suppressive regimen has been found only slightly less successful than triple-combinations in several studies.

Patients who are co-infected with HBV and receive ART should always receive a regimen which is active against both viral infections, HIV and HBV. Effective NRTIs are used in both, the standard first line regimen [TDF+FTC+EFV] and the alternative [AZT+3TC+NVP]. As in Afghanistan routinely available are only the NRTIs TDF, FTC, AZT and 3TC a double NRTI-backbone always contains at least one NRTI active against HBV, too. Interruption of ART in those patients always carries the special risk of sometimes fulminant or fatal hepatitis B. Risk of any kind of hepatitis B-flare was found to happen in 31%-33% of treatment-interruptions in one study, fulminant or fatal flares are rare but well documented.

Chapter Three: Couples, Pregnancy, Infants and Children

Serodiscordant Couples

Recommendation:

- For all people living with HIV in Afghanistan who are living in a serodiscordant relationship with an HIV-negative partner the medical doctor can consider ART irrespective of WHO clinical stage or CD4 count.

Specification:

Infectivity depends on HIV-viral load.

A prospective study of HIV-transmission among serodiscordant couples published in 2010 affirmed findings from retrospective studies, that by initiation of ART in the infected partner the transmission rate is reduced by 95% (95% CI 0.00-0.57, p=0.004).

Transmission is not completely abolished and patients need to be advised to use safe sex practices in addition to ART .

Randomized controlled trials are not published and therefore level of evidence is formally low. Proof of viral suppression is not routinely available in Afghanistan and, due to the same concerns regarding adherence and resistance as outlined in chapter "When to Start Antiretroviral Therapy" in regard to very early initiation of ART there is no general recommendation in favor of treatment of people living with HIV in serodiscordant couples yet. Nevertheless, an accurate and thorough assessment of risks and benefits of early initiation of ART in serodiscordant couples will be beneficial in certain cases and should lead to initiation where appropriate.

HIV, ART, Pregnancy and PMTCT

Recommendation:

- Pregnant women living with HIV who are *already receiving* ART for their own health should continue ART.

- If pregnancy is planned or diagnosed before 6 weeks of gestation and the mother is taking an EFV-containing ART-regimen, EVF should be replaced by NVP until 14th week of gestation. No lead in dosing for NVP is necessary if switched from EFV.

- Pregnant women living with HIV who are *eligible* for ART for their own health should receive [TDF+FTC+EFV] as first line therapy after 14th week of gestation or as soon as possible thereafter and continue ART life-long.

- Pregnant women living with HIV who are *eligible* for ART for their own health should receive [TDF+FTC] + NVP as first line therapy before 14th week of gestation and either continue [TDF+FTC] + NVP or switch to [TDF+FTC+EFV] after 14th week of gestation.

- **Pregnant women living with HIV who are *not eligible* for ART for their own health should receive [TDF+FTC+EFV] from 14th week after gestation or as soon as possible thereafter and continue ART until one week of definite end of breastfeeding. ("PMTCT")**

- Pregnant women living with HIV who are *not eligible* for ART for their own health should receive 10 days of [TDF+FTC] after completing [TDF+FTC+EFV]-treatment. ("NRTI-tail")

- Infants born to mothers living with HIV who received triple-PMTCT should receive NVP-prophylaxis or AZT-prophylaxis from birth to 4-6 weeks of age independent of mode of breastfeeding.

*Comment: The alternative PMTCT-regimen for women living with HIV and not eligible for ART for their own health (so called WHO "Option A") is equally effective, but for logistical reasons not recommended first line PMTCT in Afghanistan: using twice daily 250 mg AZT monoprophylaxis from 14th week of gestation until delivery **plus** a single dose of 200 mg NVP at onset of labor **plus** 7 days of [AZT+3TC] ("NRTI-tail"] thereafter. Infants need to be treated with NVP or AZT daily until 4-6 weeks of age (if receiving exclusively replacement feeding) or until one week after definite end of exposure to breast milk (in case of breastfeeding).*

Specification:

In making these specific recommendations major importance is attached to:

- Efficacy of the regimen in protecting the child from infection.

One randomized trial compared different regimens of ART for mothers from 18th week of gestation until end of breastfeeding. In conclusion, 2NRTI+NNRTI, 3NRTI and 2NRTI+bPI have been effective with MTCT rates of only 1% and 6-month infant mortality rates of 2-4%.

The alternative regimen of AZT-monotherapy for the mother **plus** a single dose of 200 mg NVP at onset of labor **plus** 7 days of [AZT+3TC] ("NRTI-tail"] thereafter resulted in similar rates of

infection of the infant (1.8% vs. 2%) at birth , but children need to receive NVP (once daily) or AZT (twice daily) in weight- or age-adopted dosing during the entire time of breastfeeding.

- Safety for mother and child.

Early studies in monkeys, case-reports from humans and a larger retrospective cohort analysis have raised the suspicion that use of **EFV** during pregnancy might increase risk of neural tube defects in the unborn. Other observational studies on this issue and a recently published comprehensive review did not confirm increased risk of birth defects linked to EFV-use in pregnancy. As the data are still inconclusive and prospective randomized trials won't be launched, it is recommended to avoid EVF in the first trimester of pregnancy if alternatives (NVP, LPV/r) are available. The neural tube closes at 28th day of embryonic period.

Studies on the safety of **AZT** in the context of high rates of underlying anaemia produced conflicting results. A case-report of a woman suffering severe macrocytic anaemia due to AZT-exposure during pregnancy however raised concerns. In the French ANRS 075 study, 15 of 445 (3.4%) of pregnant women receiving AZT/3TC developed relevant anaemia not explained otherwise. The PACTG 076 study found the risk of maternal anaemia not increased by AZT-containing PMTCT, but reported significant reductions in Hb-levels of the newborns. Prevalence of grade 3 or 4 anaemia in newborns in France before and after initiation of PMTCT containing AZT was 3% and 8% (p=0.04 for the comparison of two independent cohorts of independent studies). The most recent large observational study of 24,105 women in India found no association of AZT-use in pregnancy and maternal anaemia, even though background-prevalence of anaemia in the pregnant women was 38.7%. In conclusion, benefit of AZT-containing PMTCT clearly outweighs the risk, but women with underlying anaemia might prefer AZT-free, equally effective PMTCT-regimens.

In a macaque model, perinatal exposure to very high dose **TDF** resulted in bone toxicity in some offspring, other studies in macaques found no teratogenic or toxic effects of TDF when administered in pregnancy. Perinatal use of TDF as part of ART in women has been well tolerated in the short term by mothers and their infants and is increasingly used in this context. Experience from pregnant women treated with TDF for Hepatitis B infection suggests no risk of teratogenicity or toxicity related to pregnancy.

There was no increased incidence of malformations in mouse and rabbit embryofetal toxicology studies of **FTC.** Clinical evidence in humans did not show any increased risk of birth defects with FTC use during pregnancy.

- Protecting the mother and – if infected despite PMTCT – the child from acquiring resistant viral strains.

Apart from preventing vertical transmission and limiting fetal and maternal adverse effects, maintenance of future therapy options for the mother should be one of the main goals when giving short-term antiretroviral therapy to pregnant women. Sd-NVP as PMTCT is burdened with

high rates of subsequent NNRTI-resistance in mothers and infants infected with HIV. Women initiating NVP-containing triple-ART-regimens in the first year after sd-NVP suffer clinically poorer outcome and higher viral failure rates than women treated with LPV/r containing triple ART. sd-NVP is therefore not any longer recommended as PMTCT-option if alternatives are available.

Triple-ART is less vulnerable to emergence of resistance, even if combination therapy does not completely abolish risk of resistance.

- Comfortable dosing to support mother's efforts to complete adherence.

The recommended regimen [TDF+FTC+EFV] is the only once-daily-one-tablet regimen available at present. It therefore offers highest possible comfort if ART is necessary.

- Easy compatibility with the national procurement procedures.

[TDF+FTC+EFV] is the preferred first line regimen for almost all people eligible for ART in Afghanistan. Therefore, this regimen should be available at all ART-centers. Due to fortunately low numbers of pregnant women living with HIV in Afghanistan recommending differing regimens would either risk the aim of decentralization or accept probable expiration of ARVs limited to this specific indication.

HBV/HIV-co-infected mothers:

Vertical transmission of HBV, usually during labor, is very frequent. WHO recommends preference for the alternative PMTCT-regimen, which is basically free of HBV-active ARVs (except the 7 days of 3TC), in mothers neither in need of treatment of HIV nor HBV. This recommendation is based on the concerns regarding expectable hepatitis flares at the time of termination of ART. New data – however – show consistently reduced rates of vertical transmission of *HBV* in mothers treated with 3TC during third trimester of pregnancy and during labor. For definite recommendations for or against ART with anti-HBV-activity as preferred option data are not yet sufficient. A comprehensive presentation of data available in 01'2011 can be found at: . WHO will publish recommendations on treatment and prophylaxis of hepatitis B soon.

Consultation with Kabul ART Center is strongly recommended in case of treatment-decisions in a pregnant woman living with HIV/HBV-co-infection.

WHO has published an updated PMTCT-guideline in 2010.

Infants and Children

By end of 2010 no infants and children in the age of less than 6 years of age have been diagnosed to be HIV infected in Afghanistan. The following chapter is therefore only a general advice and reflects the most important recommendations given by WHO 2010 in the guideline "Antiretroviral therapy for HIV infection in infants and children: towards universal access." which is available online at:

http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf.

In case of an infant or child being infected with HIV, having been exposed to HIV or born to a mother living with HIV it is urgently recommended to contact Kabul ART-centre for further advise.

Diagnosis of HIV in Infants and Children

Recommendation:

- It is strongly recommended that newborns to mothers living with HIV have access to HIV-RNA/DNA-PCR at 4-6 weeks of age, irrespective of feeding option. If testing at 4-6 weeks was not done, the virologic test is recommended at the earliest opportunity thereafter.
- It is strongly recommended that newborns of mothers living with HIV have access to a second confirmatory virological test for HIV from a second, different blood sample in case the first test was found positive for HIV.
- In infants and children undergoing virological testing, the following assays (and respective specimen types) are strongly recommended for use:
    - HIV DNA on whole blood specimen or dried blood spots (DBS)
    - HIV RNA on plasma or DBS
    - ultrasensitive p24 antigen (Up24 Ag) on plasma or DBS
- It is recommended that all newborns to mothers living with HIV or with exposure to HIV have access to HIV-antibody tests (rapid-test/Western-blot) at the age of 9 months, followed by a virological in case serological test is reactive.
- For HIV-exposed children who are breastfed, it is recommended that breastfeeding is not discontinued in order to perform any kind of diagnostic HIV test. A virological test at 4-6 weeks is recommended to establish the HIV status at birth, using the regular algorithm (as mentioned above). Nonetheless, the virological test has to be repeated at 6 weeks after the complete cessation of breastfeeding.

- In Infants with symptoms of HIV infection, it is recommended virological testing for diagnosis. If virological test is not available, serological test and clinical algorithm are recommended for diagnosis. Whenever possible, HIV serological test should be performed for the mother of the respective infant/child.

- It is recommended that children with symptoms of HIV-disease or exposure to HIV in the age of 12-18 month have access to HIV-antibody tests (rapid-test/Western-blot), followed by a virological test in case serological test is reactive.

- It is recommended that children with symptoms of HIV-disease or exposure to HIV in the age of 18 months or more are diagnosed by using the same algorithm as in adult patients.

For infants and children living with HIV detailed strategies have to be developed on an individual base to avoid loss to follow-up. This might include out-reach services and close collaboration with specialized mother and children health programme providers, immunization programmes, community health workers and the family as well as inter-provincial collaboration of ART centers in case of migration or travelling.

When to Start in Infants and Children

Recommendation:

- **It is recommended to start ART in all HIV-infected infants and children < 24 months of age as soon as possible independent of CD4 count or clinical condition.**

- It is recommended to start ART in all infants and children < 24 months of age tested positive in the first virological test without waiting for the result of the second test.

- It is recommended to initiate ART for all HIV-infected children between 24 and 59 months of age with CD4 count of ≤750 cells/mm³ or %CD4+ ≤ 25 %, whichever is lower, irrespective of WHO clinical stage.

- It is recommended to initiate ART for all HIV-infected children more than 5 years of age with a CD4 count of ≤350 cells/mm³ (as in adults), irrespective of WHO clinical stage.

- It is recommended to initiate ART for all HIV-infected infants and children with WHO clinical stages 3 and 4, irrespective of CD4 count.

- In the absence of virological or serological tests, initiate ART for any child under 18 months of age who has been given any presumptive diagnosis of HIV infection. In this case, treatment should be closely monitored and confirmation of HIV infection should be obtained as soon as possible using age-appropriate testing methods.

Specification: Clinical staging for infants and children:

CLINICAL STAGE 1	Asymptomatic Persistent generalized lymphadenopathy
CLINICAL STAGE 2	Unexplained persistent hepatosplenomegaly Papular pruritic eruptions Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Unexplained persistent parotid enlargement Lineal gingival erythema Herpes zoster Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Fungal nail infection
CLINICAL STAGE 3	Unexplained moderate malnutrition 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 weeks of life) Oral hairy leukoplakia Acute necrotizing ulcerative gingivitis/periodontitis Lymph node TB Pulmonary TB Severe recurrent bacterial pneumonia Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease including bronchiectasis Unexplained anaemia (<8.0 g/dl), neutropenia (<0.5x109/L3) or chronic thrombocytopenia (<50 x 109/L3)
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 TB Kaposi sarcoma Oesophageal candidiasis (or candiadisis of trachea, bronchi or lungs) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age more than 1 month Extrapulmonary cryptococcosis including meningitis Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated non-tuberculous mycobacterial infection

	Cerebral or B cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy HIV-associated cardiomyopathy or nephropathy Generalized Penicillinosis

What to Start ART in Infants and Children

Recommendation:

- Recommended first line regimen for infants or children < 12 years of age and eligible for ART is:

  AZT+3TC+NVP

- It is recommended to use AZT+3TC+LPV/r as first line ART in infants and children < 24 months of age if previously exposed to NVP-containing PMTCT-regimens.

- It is recommended to use for infants and small children liquid formulations.

	No or unknown previous exposure to ARVs	Previous exposure to ARVs
Infants (children under 12 months)	AZT + 3TC + NVP	AZT + 3TC + LPV/r
Children aged 1-2 years	AZT + 3TC + NVP	AZT + 3TC + LPV/r
Children aged 2-3 years	AZT + 3TC + NVP	AZT + 3TC + NVP
Children older than 3 years	AZT + 3TC + NVP(or EFV)	AZT + 3TC + NVP(or EFV)

Dosage of First line ART in Infants and Children

	Body weight	3-6 kg		6-10 kg		10-14 kg		15-20 kg		20-25 kg	
Drug		**a.m.**	**p.m.**	**a.m.**	**p.m.**	**a.m.**	**p.m.**	**a.m.**	**p.m.**	**a.m.**	**p.m.**
AZT 10 mg/ml	**Syrup**	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml				
AZT 300 mg	**Tablet**							½ tbl	½ tbl	1 tbl	½ tbl
3TC 10 mg/ml	**Syrup**	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml				
3TC 150 mg	**Tablet**							½ tbl	½ tbl	1 tbl	½ tbl
NVP 10 mg/ml	**Syrup**	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml				
NVP 200 mg	**Tablet**							1 tbl	½ tbl	1 tbl	½ tbl
if LPV/r is used instead of NVP:											
LPV/r 80/20 mg/ml	**Syrup**	1 ml*	1 ml*	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml
***in infants/children 4-6 kg WHO recommens to use already 1.5 ml bid.**											

- Use of alternatives in case of HIV/HBV or HIV/TB co-infection or in case of severe anaemia or neutropenia should be decided on individual basis in close coordination with Kabul ART center.

Monitoring:

For children who are NOT yet eligible for ART

- Because of the rapid rate of disease progression in infants and young children, more frequent clinical and laboratory monitoring is indicated for them than for adults.

- *Clinical evaluation* of children who are not yet eligible for ART should be performed at every 3 to 6 months, at minimum, and should include the same parameters as are used in the baseline evaluation.

- *CD4 monitoring* should be performed every six months in order to determine whether the child has become eligible for treatment. Percent CD4 is preferred for children under 5 years old rather than absolute CD4 count.

For children on ART

- The monitoring will depend on child's response to ART. Nevertheless, at minimum, after starting ART, follow up visit should occur:

    - For infants: at weeks 2, 4, 8 and then every 4 weeks for the first year

    - For children: at weeks 2, 4, 8, 12 and then every 2-3 months once the child has stabilized on therapy.

- *Clinical monitoring* include assessment of signs of infant/child's response to ART, addressing the child's or caregiver's understanding of and adherence to therapy, as well as addressing their need to additional support.

- *CD4 monitoring* is recommended at 6 month after the initiation of ART and every 6 months thereafter.

- Though not essential in resource-limited settings, *viral load* should be used whenever possible to confirm suspected treatment failure.

- Laboratory monitoring should be symptom directed only after clinical indication with the exception of Hb levels which should be measured routinely at start, 4 weeks after initiation of AZT and quarterly thereafter.

Preventive Therapies:

- All children older than 12 months of age and unlikely to have active TB should be offered 6 months of Isoniazide Preventive Therapy (IPT) at a daily dose of 10 mg/kg bodyweight (maximum dosage 300 mg/d)

- HIV-infected children should receive one recommended daily allowance (RDA) of micronutrients/multivitamins per day.

- All infants and children living with HIV should receive Co-trimoxazole prophylactic treatment (CPT)

- All infants and children living with HIV should receive all standard vaccinations with the *exception* of BCG-vaccination and limitations for children with symptomatic or severe immunodeficiency (%CD4 cell less than 15%).

Chapter Four: ART in patients with concomitant diseases

Tuberculosis Co-infection

Recommendation:

- All people living with HIV in Afghanistan should be screened *clinically* for active tuberculosis at *every* contact with the health care provider.
- All HIV-infected patients should be counseled about the risk of acquiring TB, strategies for reducing exposure, clinical manifestations of TB disease and the risk of transmitting TB to others.
- All people living with HIV in Afghanistan with *active* tuberculosis should start ART independent of CD4 count.
- Treatment of active tuberculosis should start first, followed by *early* initiation of ART (within 2-8 weeks after TB-treatment has started)
- Preferred first line ART is [TDF+FTC+EFV] for people co-infected with TB and HIV.
- As second line ART in case of concomitant use of Rifampicin, LPV/r should be used in a "superboosted" dosage of LPV/r 800 mg / 200 mg twice daily (i.e. twice daily 4 tablets of LPV/r 100/50) plus normal doses of a 2-NRTI-backbone [AZT+3TC].

Specification:

People living with HIV are at 20-37 times higher risk of developing active TB and TB is responsible for a very high percentage of deaths among people living with HIV. Specific data from Afghanistan are lacking so far, but Afghanistan as one of the high-TB-burden countries in the world, needs to focus on HIV/TB-co-infection in *every* patient.

Clinical screening means: A patient who is reporting none of the symptoms **fever, nights-sweats, productive cough (>2 weeks) or weight-loss** has probably no active TB (negative predictive value: 97.7% in a population of 5% active TB among people living with HIV).

Patients who show one of the symptoms indicated above have to be considered TB-suspect and diagnosed accordingly, especially have to be transferred to NTP for diagnosis, registration and treatment, undergo Sputum-examination and Chest-X-ray for diagnosis of pulmonary TB.

Treatment of TB should follow the national guideline for tuberculosis treatment. TB-treatment is recommended in a daily regimen which is in HIV-co-infected individuals clearly superior to three times weekly regimens.

Although treatment of active TB has highest priority recent studies prove the concept of early initiation of ART in patients who receive TB-treatment.

Former recommendations of delayed ART-start after completion of TB-therapy were based on concerns regarding high pill burden, increased and overlapping side effects of drugs, increased number of cases of IRIS and logistical issues. In contrast to former recommendations, to date early initiation is recommended. The SAPIT-trial, an open-label, randomized, controlled trial conducted in South Africa, found a reduction of mortality of 56% (5.4 per 100 person-years in the early initiation group, as compared with a death rate of 12.1 per 100 person-years in the sequential-therapy group: hazard ratio in the integrated-therapy group, 0.44; 95% CI 0.25 to 0.79; p=0.003). The indeed increased risk of IRIS-manifestation (53/429 patients (12.4%) in the integrated-therapy group versus 8/213 patients (3.8%) in the sequential-therapy group ($p < 0.001$)) and the need for corticosteroid-therapy in 5 versus 1 patient did not change the overall picture of beneficial early initiation. No death was attributable to IRIS or drug-interaction/side-effects.

Another study from Spain assessed the effect of simultaneous start of ART and TB-therapy among 1217 patients. Simultaneous therapy was associated with improved survival (hazard ratio 0.38; 95% CI 0.20 to 0.72, $p = 0.003$).

An exception of the beneficial outcome of early initiation is TB meningitis. In case of TB meningitis, sequenced therapy (ART-initiation after completion of TB treatment) is recommended.

As Efavirenz shows fewer interactions with Rifampicin than Nevirapine and boosted Lopinavir the recommended first line ART for HIV-infected patients in need of treatment for active TB is [TDF+FTC+EFV]. In case of EFV intolerance, [AZT+3TC+NVP] or [AZT+3TC] + TDF are acceptable, but inferior options.

In combination with Rifampicin, LPV/r needs to be dosed twice as high which is usually causing substantial gastrointestinal LPV/r side-effects.

Treatment of latent TB is indicated and recommended with Isoniazide 300mg/d plus Pyridoxin (B6) 25-50 mg/d for 6-9 months.

IRIS: Immune Reconstitution Inflammatory Syndrome

Clinical failure is defined as new or recurrent Clinical Stage IV condition.

However, clinical appearance of an illness must not always indicate collapse or deterioration of the immune system but might be symptom of recovery of the immune system and therefore result of a successful therapy.

The underlying phenomenon is described as *IRIS* (immune reconstitution inflammatory syndrome), where a preexisting infection which was not symptomatic due to an anergic immune system, becomes symptomatic as soon as the restored immune system starts battling the infection. Another form of IRIS is called “paradoxical IRIS” which is characterized by worsening of an OI which was diagnosed and treated (at least partially successfully) already *before* starting ART.

Several opportunistic infections have been described in the context of IRIS. Frequency of IRIS depends on local context, preventive therapies, selection of study-population, definition of IRIS and other factors. Most common IRIS-manifestations are reported for tuberculosis, herpes zoster, herpes simplex, PCP, cryptococcosis and CMV. Generally IRIS should be suspected in patients suffering from worsening or new onset of a symptomatic opportunistic infection during the first 3(-6) months of ART especially in case of atypical presentation of the disease regarding affected organ, location or clinical appearance. Patients who started ART at very low CD4-counts (<100 cells/µl) are at higher risk to develop IRIS. Overall frequency reported in literature shows a very wide range of 5%-30% of people starting ART, depending on inclusion criteria of the study-population and on differing definitions of IRIS.

Opportunistic infections during the first months after initiation of ART can occur also due to a still very weak immune system. In neither case (IRIS or “genuine” OI), new OI-symptoms *during the first three months* should be considered ART-failure. In case of new onset of a symptomatic OI during the first 3(-6) months, ART should be continued and treatment of OI should be initiated.

New onset of symptoms of OI > 3(-6) months after ART-initiation might indicate IRIS, “genuine OI” or treatment-failure. Clinical differentiation is usually not possible. Efficacy of ART should be confirmed by immunological (CD4 count) and virological tests.

Compared with a group of patients who developed no IRIS long-term outcome of patients with IRIS is not significantly different to patients free of IRIS, if the IRIS-opportunistic infection was treated. In contrast outcome of patients who develop a ”genuine OI” after starting ART (but with insufficient rise in CD4) is significantly worse. Of special importance is mycobacterial IRIS:

Mycobacterial IRIS

Mycobacterial IRIS accounts – globally – for approximately one third of all cases of IRIS. In countries with high TB burden – such as Afghanistan – probably even more. Generally, “unmasking” and “paradoxical” IRIS should be differentiated. Meintjes and co-workers have proposed case definition for research purposes.

"ART-associated TB" refers to all TB diagnosed during ART, while the subset of patients who develop rapidly progressive signs and symptoms of TB, with exuberant inflammatory features, after initiation of ART are called "unmasking TB-associated IRIS". "Unmasking TB-associated IRIS" by definition refers to the activation of a before ART-initiation *asymptomatic* latent TB. The patients must not have been on treatment of *active* TB before ART-initiation to meet the criteria for "unmasking TB-associated IRIS". A study published in 2011 showed a 3.8% incidence of "ART-associated TB" (including "unmasking TB-associated IRIS") in a sample of patients who have been screened *intensively* before commencement of ART, including CXR and sputum-culture. Cost-efficacy of this approach is not yet established. However: Intensified case-finding seems to be an effective mechanism to detect high-risk patients for "ART-associated TB" and will lead to an earlier TB diagnosis and ultimately to reduced morbidity and mortality IRIS-TB.

Treatment of "ART-associated TB" (including "unmasking TB-associated IRIS") is initiation TB-treatment in addition to ART.

"Paradoxical TB-IRIS" by definition refers to worsening of clinical symptoms of a previously (at least partially/initially successfully) treated TB-infection with sometimes very atypical manifestations. It usually occurs during the first 1-3 months after initiation of ART. Frequency of "paradoxical TB-IRIS" in patients having an active TB disease (under treatment) is estimated to occur in 11-45% of patients. However, risk factors for paradoxical TB-IRIS are: disseminated TB infection, low body weight (BMI < 18.5 kg/m²), low CD4 count (<100 cells/µl), prompt rise of CD4 count after commencement of ART. Especially acute inflammatory reactions affecting lymph-nodes, meningeal TB, mucosal/serosal sites and also worsening of pulmonary TB are seen frequently.

Treatment of "Paradoxical TB-IRIS" includes in mild cases use of non-steroidal anti-inflammatory agents. In severe cases (high fever, increased intracranial pressure, serositis, ulcerative lymph node enlargement) use of prednisolone 1-2 mg/kg body weight/ day for 2 weeks with subsequent gradual reduction is indicated. Interruption of ART should only be considered in acutely life-threatening cases of IRIS. TB-Treatment should never be interrupted!

Definite distinction between TB-treatment failure (e.g. due to multi-resistant TB-infection) and paradoxical TB-IRIS is sometimes difficult. Thorough examination of the patient to detect possible failure of TB-treatment is essential, whenever available including drug-susceptibility-testing. Suspected exacerbation on the ground of multi-drug resistance of the mycobacterium must not be treated with corticosteroids.

The risk of TB-IRIS is not a reason to withhold ART from a patient.

Patients with Severe Anaemia

Recommendation:

- Anaemia in patients living with HIV needs to be diagnosed and treated.
- AZT should be avoided in anemic patients with a hemoglobin level <7 g/dl.
- Patients receiving AZT-containing ART with underlying risk factors for anaemia (low CD4 count, low BMI, low Hb-levels, co-medication) should have Hb-monitoring after 1 months and quarterly thereafter in addition to clinical/symptomatic screening.

Specification:

"Unexplained" anaemia is seen in patients with advanced immunosuppression and therefore graded a WHO clinical condition III. Anaemia of inflammation (or "anaemia of chronic disease") is probably the most frequent cause of HIV-related anaemia. Sometimes HIV-related anaemia may also be symptom of bone-marrow infection with Mycobacteria other than tuberculosis (MOTT/MAC) or other bone-marrow diseases.

In addition, HIV infection aggravates anaemia due to malaria.

Anaemia, which is not directly caused by HIV, is a frequent comorbidity. Common causes of anaemia are malnutrition, malaria, thalassemia and intestinal worms.

People living with HIV frequently suffer from drug-related myelosuppression, especially due to AZT, Co-trimoxazole, interferon and ribavirin and isoniazide.

Incidence of severe anaemia as adverse side effect of AZT-treatment was found in 5-10% of cases with preexisting anaemia, low CD4-cell count and low BMI as risk factors.

Anaemia is a marker for disease progression and has been associated with decreased survival.

Patients with anaemia therefore need to be examined for the cause of anaemia, which may be multifactorial. Treatment of iron- and vitamin-deficiencies, malaria and intestinal worm-infection should be prescribed if diagnosed. Additional and combined therapy with myelotoxic drugs should be monitored closely. Although not mandatory precondition, patients starting AZT-

containing ART with underlying risk factors (low CD4 count, low BMI, low Hemoglobin levels, co-medication) should have Hb-monitoring in addition to clinical/symptomatic screening. AZT must be stopped in case of severe anaemia. (Hb < 7 g/dl)

Patients with Renal Failure

Recommendation:

- It is recommended to monitor patients with chronic kidney disease (CKD) closely and to adjust dosage and/or dosage-interval accordingly.

Specification:

HIV-infection is a risk factor of renal failure. HIV associated nephropathy (HIVAN) is a form of glomerulonephritis (with nephritic sediment and nephrotic proteinuria) and is graded a WHO clinical stage 4 condition and therefore an indication to start ART. Usually HIVAN occurs when CD4 falls below 100 cells/µl, but has been reported also in patients with higher CD4 count. HIVAN is much more frequent in people of black ethnicity.

Definite diagnosis of HIVAN – especially differential diagnosis of post-infectious glomerulonephritis and HCV-associated glomerulonephritis – requires kidney-biopsy. Since a patient with nephritic/nephrotic syndrome and CD4 count < 100cells/µl is already eligible for ART on the basis of CD4-cell count only and HIVAN with CD4 count > 350 cells/µl is rare initiation of ART in patients based on kidney failure only is *not* recommended.

Arterial hypertension and diabetes mellitus (both more frequent among people living with HIV than among sero-negative) are frequent causes of chronic kidney disease and need to be treated. Anti-hypertensive (including ACEI) and anti-diabetic treatment obtain therefore priority. Nephrotoxic substances must be avoided.

Dose Adjustment for ARV

Proper selection and dose-adjustment of antiretrovirals and other commonly used drugs for patients with kidney disease are important components of care for patients with HIV infection.

Isolated case reports of nephrotoxicity have been reported with almost all agents, but renal disease has been associated with (indinavir and) tenofovir more often than with other ARVs.

In fact, tenofovir-associated renal dysfunction is a rare event in prospective clinical trials, particularly among ART-naive patients.

No significant change in GFR was demonstrated in a comparison of tenofovir/emtricitabine versus fixed-dose zidovudine/lamivudine with efavirenz in ART-naive patients during 144 weeks of treatment. A prospective observational study including 3316 patients with normal, mildly- or moderately reduced GFR found that despite screening, mild-to-moderate baseline renal impairment was relatively common, but these participants had greatest *increases* in GFR after starting ART. Severe GFR impairment was rare (1.6%) regardless of ART regimen. Higher baseline body mass index and systolic blood pressure were both associated with larger decreases in GFR at 96 weeks.

Clinical screening in all patients and laboratory screening of kidney function (serum-creatinine, proteinuria, glucosuria) in high-risk patients (elderly, low body eight, pre-existing impaired renal function, hypertension, diabetes mellitus, co-commitant use of nephrotoxic drugs) at intervals is not essential but recommended.

NNRTIs, bPIs, Raltegravir and Maraviroc are almost exclusively eliminated hepatically; therefore, dose-adjustment of ARVs in patients with underlying CKD is only necessary in NRTIs.

For necessary dose-adjustments it is recommended to *estimate* the creatinine clearance using the Cockroft-Gault-Formula:

Creatinine Clearance [ml/min] = (140-age)*body-weight/(creatinine*72)

For women: x 0.85

The following table gives recommendations for dose adjustment in patients with CKD:

Patient with Creatinine Clearance > 50 ml/min			
Recommended first line	[TDF+FTC+EFV] (standard)	[245+200+600] (standard)	Once daily (standard)
Alternative	[AZT+3TC+NVP] (standard)	[300+150+200] (standard)	Twice daily (standard)
Second line	[AZT+3TC]+LPV/r [TDF+FTC]+LPV/r	[300+150]+400/100 (standard) [245+200]+400/100 (standard)	Twice daily (standard) Once/twice daily (standard)

Patient with Creatinine Clearance 30 - 50 ml/min			
Recommended first line	[TDF+FTC+EFV] (standard) **Plus** EFV	[245+200+600] (standard) 600 mg	**Every 48 hours** **Every other day**
Alternative	AZT **Plus** 3TC **Plus** NVP	300 mg 150 mg 200 mg	Twice daily **Once daily** Twice daily
Second line	Either:[4] AZT **Plus** 3TC **Plus** LPV/r Or:[5] [TDF+FTC] **Plus** LPV/r	 300 mg 150 mg 400/100 mg [245+200] mg 400/100 mg	 Twice daily **Once daily** Twice daily **Every 48 hours** Twice daily

Patient with Creatinine Clearance 10-30 ml/min			
Recommended first line	AZT **Plus** 3TC **Plus** NVP or EFV	300 mg **100 mg** 200 mg or 600 mg	Twice daily **Once daily** Twice daily
Second line	[TDF+FTC] **Plus** LPV/r	245+200 400/100	**Twice weekly** Twice daily

Co-trimoxazole-prophylactic treatment should be used in standard dose all for patients with creatinine clearance > 30ml/h and should be reduced to 400+80 mg/d in case of creatinine clearance 15-30 ml/min. In patients with creatinine clearance < 15 ml/min co-trimoxazole should not be used.

Patients with Hepatic Disease

Liver function should be graded in patients with underlying hepatic disease by calculating the Child-Pugh-Score:

Criterion	**1 point**	**2 points**	**3 points**	**unit**
Total bilirubine	< 2	2-3	>3	*mg/dl*
Serum albumin	>3.5	2.8-3.5	<2.8	*g/dl*
International Normalized Ratio (INR)	<1.7	1.7-2.2	>2.2	

Ascites	no	mild	> mild	
Hepatic encephalopathy	no	stage I-II	stage III-IV	
Classification	**5-6 points**	**7-9 points**	**≥ 10 points**	
CHILD-PUGH-CLASS	A	B	C	

Adjustment of ARV-dose is not necessary for **3TC, FTC, TDF**.

AZT might accumulate with severely impaired liver function. A definite recommendation to adjust AZT-dose can't be given. Patients with impaired liver function who are receiving AZT as part of ART should be monitored closely for signs of AZT-toxicity (myelosuppression) and AZT should be adjusted individually.

EFV, NVP, LPV/r are contraindicated in patients with severely impaired liver function (Child-Pugh-Class C)

For people living with HIV with liver cirrhosis in Child-Pugh-Class C prescription of a Triple-NRTI regimen (e.g. [TDF+FTC]+AZT) might be considered.

Hepatotoxicity of ARVs:

The largest observational study including 8,851 participants found the overall incidence of severe hepatotoxicity among patients receiving different regimens of ART to be as high as 9.3% with risk factors like baseline elevation in serum ALT, concomitant hepatotoxic medications, thrombocytopenia, and renal insufficiency and HCV co-infection.

NVP causes elevation of liver enzymes in up to 20% of patients. Severe hepatotoxicity is rare. NVP was found in several studies to be slightly more hepatotoxic than EVF.

After initial reports of increased NVP-hepatotoxicity among patients with higher CD4-cell-count (women >250 cells/µl, men >400 cells/µl), pregnancy and underlying hepatic disease, newer studies show conflicting results and can't find any association of NVP-hepatotoxicity with CD4 count or pregnancy.

Based on the older evidence from early reports NVP-associated-liver-toxicity is considered to be linked to CD4 count and gender and is therefore still not recommended as first line regimen in women with CD4 count < 250/µl and men with CD4 count < 400 cells/µl.

Independently of CD4 count, gender and pregnancy NVP should be stopped in patients experiencing jaundice or elevated plasma lactate levels or rise of transaminases (ALT) above 5 x ULN (upper limit of normal) or in case ALT-elevation is combined with skin rash.

Hepatitis B Co-infection

Recommendation:

- For all people living with HIV in Afghanistan with a confirmed, *chronic*, *active* Hepatitis B, who have repeated proof of ALT > 2 x ULN and repeated proof of HBV-DNA > 2.000 IU/ml (≈10,000 copies/ml) ART should be initiated irrespective of WHO clinical stage or CD4 count.

- People eligible for ART and co-infected with HBV should receive standard dose of [TDF+FTC+EFV] as preferred first line ART.

- For people living with HIV with liver cirrhosis in Child-Pugh-Class C prescription of a Triple-NRTI regimen (e.g. [TDF+FTC]+AZT) might be considered.

- As second line therapy after virological, immunological or clinical failure of [TDF+FTC+EFV], [TDF+FTC]+AZT+LPV/r is recommended to avoid exacerbation of HBV.

Specification:

Acute Hepatitis B infection in HIV-negative individuals leads to chronic infection in 2-5% of patients while there is evidence from a retrospective analysis of patients' records that in HIV-co-infected individuals HBV-co-infection leads to chronification in 23%. However: *Acute* hepatitis B infection should not lead to initiation of ART in patients otherwise not eligible for initiation of ART.

Chronic HBV-infection requires by definition proof of infection (persistent HBs-sero-positivity) for more than 6 months at least.

There is no agreed definition of chronic active hepatitis in resource-limited settings yet. As long as there is no agreed definition of chronic active hepatitis in resource-limited settings patients might be evaluated by ALT and HBV-DNA where available and affordable.

Liver-related mortality was higher in men with HIV-1 and HBsAg (14.2/1000 person years) than in those with only HIV-1 infection (1.7/1000, $p<0.001$) or only HBsAg (0.8/1000, $p<0.001$)

A retrospective analysis of 2,041 patients co-infected with HBV and HIV found a significantly reduced risk of liver related death (RR 0.73, 95% CI: 0.59-0.90, $p=0.004$) among patients who received 3TC containing ART. One randomized controlled trial showed superiority of a TDF-based ART over 3TC-based regimens in respect to suppression of HBV-DNA and in early HBV-resistance development . Another cross-sectional analysis showed superiority of TDF plus either 3TC or FTC in regard to HBV-DNA suppression over TDF-monotherapy. Therefore TDF-based first line ART, combined with a second HBV-active ARV (3TC or FTC) is preferred option in therapy-naïve and 3TC-experienced HIV/HBV-co-infected individuals.

Interruption of ART in HBV/HIV-co-infected patients always carries the special risk of sometimes fulminant or fatal hepatitis B-flares. Risk of any kind of hepatitis B-flare was found to happen in

31%-33% of treatment-interruptions in one study, fulminant or fatal flares are rare but well documented.

Hepatitis C Co-infection

Recommendation:

- Eligibility for ART in HIV/HCV-co-infected individuals relies on the same criteria as for HIV-mono-infected patients.
- People eligible for ART and co-infected with HCV should receive standard dose of [TDF+FTC+EFV] as preferred first line ART.
- For people living with HIV with liver cirrhosis in Child-Pugh-Class C prescription of a Triple-NRTI regimen (e.g. [TDF+FTC]+AZT) might be considered.
- As second line therapy after virological, immunological or clinical failure of [TDF+FTC+EFV], [AZT+3TC]+LPV/r is recommended.

Specification:

HCV/HIV-co-infection is frequent in people living with HIV in Afghanistan.

HIV-related immunosuppression accelerates the course of hepatitis C with earlier incidence of liver cirrhosis and hepatocellular carcinoma. Antiretroviral therapy with immune recovery slows down the course of hepatitis C. Due to concerns regarding increased rates of hepatotoxic side-effects of ARVs and prolonged need for ART in case of earlier initiation of ART (with impact on the health system, eventual development of resistance and concerns regarding adherence), there is no clear recommendation to start ART in HCV-co-infected individuals earlier. So far criteria for eligibility of HIV/HCV-co-infected individuals for ART do not differ from HIV-mono-infected individuals.

NVP should be avoided in HCV/HIV-co-infected individuals. EFV is preferred NNRTI.

Patients receiving **EFV** and HCV-treatment (interferon/ribavirin) need to be monitored closely due to additive risk of depression. Generally patients should not start EFV and interferon/ribavirin together, but phased. It is usually recommendable to start with ART and commence HCV-therapy not before ART is well tolerated.

AZT must not be combined with HCV-treatment (Interferon/ribavirin) due to additive myelotoxicity.

In patients co-infected with HCV/HIV who do not yet receive ART and CD4 count > 350 cells/µl, HCV-treatment should be started before ART if HCV treatment is accessible and affordable for the patient. Patients with CD4 count < 350 cells/µl should start ART first.

In patients co-infected with HCV/HIV who do receive ART, ART should be adjusted to eventual HCV-treatment before initiation of HCV-treatment to avoid additive toxicities of both treatments as far as possible. Initiation of HCV-treatment must not jeopardize success of ART.

HCV-treatment with interferon/ribavirin is contraindicated with CD4 count < 200 cells/µl and should be used very carefully at CD4 counts of 200-350 cells/µl.

ART and drug-dependency

Recommendation:

- A comprehensive package of interventions to prevent the transmission of HIV must include measures to reduce unsafe injecting of opioids, including the treatment of opioid dependence and antiretroviral therapy.
- All people who use drugs should have equitable access to diagnosis and treatment for TB, hepatitis B/C, HIV and opioid dependence.
- To improve adherence, directly administered/observed therapy of HIV and TB should be integrated with opioid agonist maintenance treatment and given in the same location.
- Abstinence from drug-use must not be a precondition to initiate ART.

Specification:

Methadone appears to reduce the risk of HIV infection among people who inject drugs by approximately 50% (RR 0.45, 95%CI 0.35 to 0.59) and there is a similar reduction in HIV sero-conversion rates (RR 0.36, 95%CI 0.19 to 0.66) compared to withdrawal or no treatment.

Adherence to ART is challenging in the context of pathological substance-use and needs strengthened support from the medical care providers. Excellent results can be obtained from patients in (directly observed) opioid maintenance programs.

People who use drugs without access to treatment of drug-addiction need repeated and intensified counseling for adherence to ART as well as social support to find solutions for challenges like storage of medication, theft, confiscation etc. Directly administered therapy (DAART) might be a recommendable option to support the patient to adhere to the therapy initially.

Patients enrolled in methadone based opioid substitution programs usually need higher doses of methadone after initiation of NVP- or EFV-containing ART. NVP and EFV are lowering methadone plasma-levels which can cause opioid withdrawal in patients who have been stable before. It is important to recognize this interaction because NNRTI-induced opioid withdrawal is jeopardizing adherence to ART and OST. LPV/r might influence methadone levels, but association and clinical significance are less clear. Medical doctors initiating NNRTI or – equally important – stopping NNRTI in patients enrolled in methadone based OST-programs have to consider these interactions.

Use of cannabinoids (THC, hashish, marihuana) has no effects on success of ART. EFV can cause false positive results for THC in urine drug screening.

Patients with psychiatric illnesses

Recommendation:

- All people living with HIV should be screened clinically for symptoms of severe neuropsychiatric disorders, including major depression, before starting ART
- Persons with severe neuropsychiatric comorbidity should receive Efavirenz only if close clinical monitoring is available (e.g. as directly administered daily therapy)
- All people with severe neuropsychiatric co-morbidities deserve intensified support in regard to adherence to ART.

Specification:

Neuropsychiatric effects are the main adverse event of Efavirenz. There is a wide range of different systems used to report neuropsychiatric adverse events in HIV clinical trials. Grade 2-4 neuropsychiatric adverse events may occur in up to 20% of patients treated with Efavirenz. The large 2 NN-, ACTG 5142-, INITIO-QoL-trials did not report increases in Grade 3-4 neuropsychiatric adverse events or negative changes in mental health scores in comparison to NVP, LPV/r and NFV/r respectively.

In conclusion, EFV should be used with caution in patients with preexisting severe mental disorders or major depression and should be changed (either single replacement of EFV <> NVP, or change from [TDF+FTC+EFV] to [AZT+3TC+NVP]) in case of Grade3/4 neuropsychiatric side effects. The [TDF+FTC+EFV] – regimen is also recommended for patients who are included in directly observed forms of therapy (TB, methadone-maintenance-therapy) as close follow-up is possible. Under such circumstances deviation from the recommendation to take EFV at bedtime is possible and might be beneficial.

Chapter Five: Prophylactic Treatments

Post Exposure Prophylaxis (PEP)

Recommendation:

- First line regimen is:

AZT, Zidovudin, 300 mg twice daily
3TC, Lamivudin, 150 mg twice daily
LPV/r, boosted Lopinavir, 400/100 mg twice daily

- Duration of PEP is maximally 28 days or whenever earlier HIV-risk can be excluded.

Specification:

Post-exposure prophylaxis should only be offered for exposure that has the potential for HIV transmission.

Wound and skin sites should be cleansed with soap and water immediately. The wound should not be squeezed. Exposed mucous membranes should be flushed with water.

When there is a risk of HIV transmission, post-exposure prophylaxis should be initiated as soon as possible, within hours and no later than 72 hours following the potential exposure.

Post-exposure prophylaxis **is indicated**:

- Percutaneous needle stick injury with hollow needle.
- Deep injury (e.g., cuts), apparently blood-stained.
- Intravenous injection with a previously used needle.
- Transfusion of HIV-containing blood products (or if HIV contamination is highly probable).
- Unprotected receptive sex with an HIV-infected person.
- Sharing contaminated needle or equipment with people who use drugs.

Post-exposure prophylaxis **might be considered**:

- Superficial injury (e.g., with surgical needle).
- Contact of mucosal membrane or damaged skin with fluids with high viral load.
- Unprotected receptive oral sex with ejaculation with an HIV-infected person.
- Unprotected receptive sex with a person whose HIV status is unknown but with documented HIV-risk behaviors e.g. intravenous drug use.
- A victim of rape when the offender's HIV-status is unknown.

Post-exposure prophylaxis **is not indicated**:

- if the exposed person is HIV-positive from a previous exposure.
- if the exposure does not pose a risk of transmission, that is, after:
    - exposure of intact skin to potentially infectious body fluids.
    - sexual intercourse using a condom that remains intact.
    - any exposure to non-infectious body fluids (such as faeces, saliva, urine and sweat).
    - exposure to body fluids from a person known to be HIV-negative, unless this person is identified as being at high risk for recent infection and thus likely to be within the window period.
- if the exposure occurred more than 72 hours previously.

When offering PEP HIV-PITC should be offered according to the national guideline although not a prerequisite to start PEP.

If HIV-status of a potential source of infection is unknown *voluntary* HIV testing of the source should be sought. However, this should not lead to delay in starting PEP nor should an unknown status of a potential source of infection give reason to withhold PEP. In case the alleged source turns out to be HIV negative with very low probability of being in the antibody-negative window-period, PEP can be stopped.

Systematic studies on PEP are lacking. There is no direct evidence to support the use of multi-drug antiretroviral regimens following occupational exposure to HIV. However, due to the success of combination therapies in treating HIV-infected individuals, a combination of antiretroviral drugs should be used for PEP.

In case the drugs listed as first line option are not available as soon as possible, almost any other regimen might be used, including [TDF+FTC+EFV] or other combinations. Guidelines, other than the WHO-guideline, recommend also AZT+3TC+TDF or AZT+TDF+FTC, dual regimens (e.g. AZT+3TC only or TDF+FTC only) , TDF+FTC+LPV/r .

NVP should generally not be used for PEP due to documented severe hypersensitivity reactions with hepatic failure.

Duration:

Recommendation:

- Continue PEP for 28 days.
- Stop PEP as soon as alleged source turns out to be HIV-negative.

Opportunistic Infections Prophylactic Treatments

Co-trimoxazole Prophylactic Therapy (CPT)

Recommendation:

- All people living with HIV in Afghanistan (including pregnant women) should receive Co-trimoxazole 960 mg once daily as primary and/or secondary prophylactic treatment independent of clinical stage or CD4 count. ("universal option")
- Patients with a creatinine clearance of 15-50 ml/min should receive Co-trimoxazole 480 mg once daily as primary and/or secondary prophylactic treatment independent of clinical stage or CD4 count.
- Patients with a creatinine clearance < 15 ml/min should not receive CPT.
- Infants and children exposed to HIV or living with HIV in Afghanistan should receive CPT starting at 6 weeks after birth and continue CPT life-long or until HIV-infection is excluded.

Conditional recommendation:

- Infants born to mothers living with HIV who have received comprehensive PMTCT-triple ART including infant prophylaxis might receive CPT.

Specification:

Studies from several parts of the world showed benefit of CPT among adults with low CD4 count, independent of CD4 count, children and pregnant women in regard to morbidity and mortality .

CPT showed effectivity in prevention of cerebral toxoplasmosis, pneumocystis jiroveci pneumonia (PCP), malaria, skin-infections, enteritis and other bacterial diseases, including amnionitis during pregnancy. .

In a country with limited human, technical and financial resources to diagnose and treat PCP, Toxoplasmosis, malaria and other infections, prevention gains special importance. People living with HIV in Afghanistan are exposed to a multitude of potential infection risks. Therefore, a "universal approach" to CPT is chosen in Afghanistan.

Infants and Children living with HIV should receive the following simplified dosages:

Age	Co-trimoxazole dosage
6 weeks-6 months	120 mg once daily (syrup)
6 months-6 years	240 mg once daily (syrup or crushed tablet)
6 years-12 years	480 mg once daily (tablet or crushed tablet)
>12 years	960 mg once daily (tablet)

Infants born to mothers who received comprehensive triple ART as PMTCT regimen including infant prophylaxis might receive CPT. The prescribing medical doctor has to weigh up possible CPT side-effects with possible benefits and probability of HIV-infection of the infant. While benefits of CPT for infants infected with HIV are highly evident, there is no evidence of HIV-negative children profiting from CPT – by contrast one study from South Africa reported no benefit but a trend to increased rates of diarrhea among HIV-negative infants treated routinely with CPT. Treatment of infants with CPT is usually well tolerated but side effects – including serious conditions like Stevens-Johnson-Syndrome, , severe anaemia or pancytopenia – are reported. As infection of an infant born to a mother who received comprehensive triple ART as PMTCT regimen including infant prophylaxis is expected to be very low (1-3%), cost-benefit-analysis probably will turn out to be negative, including a very high number needed to treat. Recommendation for CPT regarding this target group is therefore only conditional and depends on characteristics of the individual case.

Discontinuation in a country which chooses "universal approach" (CPT for all people living with HIV) is not recommended except for discontinuation on the basis of Co-trimoxazole-side effects. Patients and caregivers of infant or children living with HIV should be provided with verbal or written information on the potential adverse effects, and advised to report to their nearest health facility if co-trimoxazole-related adverse events are suspected.

Grading of side effects:

Toxicity	Clinical description	Recommendation
Grade 1	Erythema	Continue CPT Monitor closely Consider antihistaminics
Grade 2	Maculopapular rash Dry desquamation	
Grade 3	Vesiculation Ulceration	Stop CPT Try desensitization after restitution
Grade 4	Exfoliative dermatitis Stevens-Johnson-Syndrome Erythema multiforma Moist desquamation	Stop CPT permanently Document

In Afghanistan, an alternative to Co-trimoxazole for prevention (e.g. Dapsone) is not routinely available. In cases of treatment-interruption due to Grade (1-)3 side-effects, it is recommended to restart CPT after complete recovery according to the following "desensitization-scheme". It is recommended to combine the period of desensitization with an anti-allergic anti-histaminic.

For desensitization liquid formulations should be used if available.

Desensitization-scheme for Co-trimoxazole (adults)	
Day 1	1/10 = 96 mg (80+16mg)
Day 2	2/10 = 192 mg (160+32mg)
Day 3	3/10 = 288 mg (240+48 mg)
Day 4	4/10 = 384 mg (320+64 mg)
Day 5	5/10 = 480 mg (400+80 mg)
Day 6 onwards	10/10= 960 mg (800+160 mg)

Initiation of ART should be preceded by pre-ART-counseling including an adherence intervention. CPT (and IPT and micronutrients) can be started first, followed by ART two weeks later if clinically and logistically appropriate. Phased initiation of medication (CPT/ITP/micronutrients/OI-therapy first, followed early by ART) is often beneficial because it allows diagnosis and correlation of eventual side-effects to specific drugs.

In case of Grade 4 adverse events, CPT has to be stopped definitely. Desensitization should not be tried.

Isoniazide Preventive Treatment (IPT)

Recommendation:

- Adults, adolescents and children (older than 12 months) living with HIV should be screened for TB with a clinical algorithm and those who are unlikely to have active TB should be *offered* IPT.
- People living with HIV unlikely to have active TB but living in congregate settings, including prisons should *receive* IPT.
- People suffering active hepatitis should *not* receive IPT.
- **Dosage for adults and adolescents** : Isoniazide 300 mg/d once daily for 6 months.
- **Dosage for people living in congregate setting (e**.g. prison): Isoniazide 300 mg/d once daily for 6-36 months.
- **Dosage for children**: Isoniazide 10 mg/kg bodyweight once daily (maximum daily dose of 300 mg) for 6 months.
- Children living with HIV should receive additional 6 months of IPT after successful completion of treatment for active TB to prevent relapse.
- Addition of 25-40 mg/d Pyridoxine (Vitamin B6) is recommended, especially in children. Use of fixed-dose combination is recommended.

Evidence:

Isoniazide Preventive Therapy (IPT) refers to the treatment of latent tuberculosis to avoid activation to active TB as well as reactivation and prophylaxis against new infections.

Isoniazide is highly effective in the treatment of latent TB. . Diagnosis of latent tuberculosis is not routinely possible in Afghanistan, Tuberculin skin test (TST) requires cold chain and is not widely available. Nevertheless latent tuberculosis is probably highly prevalent in Afghanistan especially among people living with HIV as prevalence of TB is high in the general population and risk factors for HIV-infection (like injecting-drug use, imprisonment, etc.) overlap with risk factors for tuberculosis. Therefore WHO recommends in countries with high prevalence of tuberculosis and limited resources IPT for all people living with HIV, including children and pregnant women and without requiring TST. Only precondition is the clinical exclusion of active TB-disease and active hepatitis.

While IPT is effective in people with latent TB (TST positive) a review of studies investigating effect of IPT in people with negative TST failed to show any significant effect on incidence of active TB. Significant effect on mortality was not found in either group which might be due to the very low overall mortality rates in the included studies.

Risk of hepatitis due to Isoniazide therapy is estimated to be 0.5-2%. Therefore IPT in people with pre-existing active hepatitis is not recommended. Peripheral neuropathy is a rare side effect of Isoniazide therapy but prescribers should screen patients clinically for eventual symptoms of peripheral neuropathy.

IPT and the risk for Isoniazide-resistance: several small studies have been published in the recent 60 years investigating the effect of IPT on the emergence of INH-resistance. Definition of INH-resistance is sometimes differing from study to study and the results are difficult to compare. A meta-analysis and the GRADE assessment of evidence included in the WHO guideline have been published recently. Both have found a relative risk of INH-resistance among cases of active tuberculosis among people who had received ITP before of 1.45 and 1.87, respectively, with neither of them being statistically significant. Thus these results do not proof increased risk of INH-resistance by IPT, nor are these results proof of the opposite. Based on the published evidence a definite statement on increased risk of INH-resistance induced by IPT is not possible.

In conclusion:

IPT is recommended for all people living with HIV in Afghanistan after definite exclusion of active TB. People suffering active hepatitis should not receive IPT. Priority-treatment in people living with HIV in Afghanistan should always be ART if eligible for ART as well as CPT for all (universal option). If additional pills are accepted by the patient and adherence to medical treatment is expected to be high IPT should be offered and should always be followed by close documentation. Data should be made comprehensively available to country-specific evaluation.

Multivitamin and Micronutrient Supplementation

Recommendation:

- Pregnant women, infants and children living with HIV in Afghanistan should receive supplementation of micronutrients.
- Supplementation of micronutrients might be considered in all people living with HIV in Afghanistan.

Specification:

According to estimations of UNICEF, in Afghanistan, iron deficiency (65%) and Iodine deficiency (45%) are highly prevalent and 53% of children suffering Vitamin A deficiency. Several studies have shown positive effects of supplementation of micronutrients on morbidity and mortality of people living with HIV in different settings. More specifically zinc, vitamin A, selenium, iron and multi-micronutrient interventions have shown beneficial effects.

Other studies did not find effects of micronutrient-supplementation on mortality of HIV-positive adults .

Nutrition for HIV-Infected Children (1 to 10 years)

Requirements:

- **Energy**
    - Asymptomatic: Require 10% more energy to maintain growth than healthy children.
    - Symptomatic with no weight loss: Require 20 - 30% more energy than healthy children.
    - Symptomatic with weight loss: Require about 50 - 100% more energy than healthy children.
- **Protein:** Protein requirements are the same as those for an uninfected child. It should be based on an individual's symptoms and needs.
- **Micronutrients:** Micronutrient requirements are the same as those for an uninfected child. It should consider possible deficiencies.

The following should be considered in the nutritional care and support of HIV-infected children:

- Periodic nutritional assessment and growth monitoring.
- Growth is a very sensitive indicator of HIV progression in children: Poor growth normally precedes CD4 decline and the development of OIs (especially TB).
- Weighing, charting on a health card and interpretation should be done by a trained staff member. The charting should start with the birth weight, if available. MUAC can be used where weighing tools are not available or weight measurement is not possible.

- In the first year, nutritional assessment should be done every month in keeping with recommendation for all children. Thereafter, assessment can be done every three months. If there is growth faltering or problems with feeding, however, assessment should be done monthly or more frequently depending on the health of the child.

2. Assess feeding practices and dietary intake with every contact, including dietary-related problems (e.g. poor appetite, chewing, swallowing, intolerance, food taboos and history of nutritional supplementation).

Vaccinations

Recommendation:

- All infants and children living with HIV and infants born to mothers with HIV should receive all standard vaccinations according to the national vaccination plan, except BCG-vaccination.
- Infants and children living with HIV should not receive Bacille Calmette-Guérin (BCG)-vaccination for TB.
- Infants and children living with HIV or exposed to HIV and unclear HIV-status should receive an extra dose of measles vaccine at the age of 6 months.
- Children with symptomatic or severe immunodeficiency (%CD4 cell less than 15%) should receive ART before vaccinations with attenuated alive vaccines (VZV, measles, mumps, rubella)
- All people living with HIV and negative HBs-Antigen-rapid test should be actively immunized against hepatitis B.

Specification:

After comprehensive PMTCT including infant-prophylaxis infants born to mothers living with HIV are rarely infected with HIV. Even if infected, children are usually infected during labor or shortly afterwards. Although immunodeficiency can progress rapidly, majority of children are not immune-compromised in the first few months. Non-replicating vaccines, including hepatitis A, hepatitis B, influenza, diphtheria, tetanus, pertussis are safe and immunogenic in children living with HIV, even if sometimes less immunogenic than in HIV-negative vaccinees, dependent on study-setting, age and immune status of the vaccinee.

The live attenuated Measles-, Mumps-, Rubella- and Varicella-Vaccine can be safely used in children 1-5 years of age with CD4-% >15% or CD4 count > 500 cells/µl

Measles vaccine – as live vaccine – is relevantly less immunogenic in children living with HIV, dependent on CD count. Better immunogenicity was found in one study comparing measles-vaccination before and after 12 months of age in the group of children infected with HIV who had been immunized earlier in life. Therefore earlier measles-vaccination might be considered.

Oral poliovirus vaccine (OPV) is immunogenic in HIV-infected children. Some studies report prolonged excretion of potentially neurovirulent OPV strains. Significance of these findings can't be judged yet. Polio vaccination - however – is of utmost importance for all children in Afghanistan.

Bacille Calmette-Guérin (BCG)-vaccination is not recommended in children living with HIV, because of the risk to develop disseminated BCG disease.

Hepatitis B vaccination is recommended for all people living with HIV whose HBs-Antigen-rapid-test is negative. Vaccination is less successful in vaccinees living with HIV, dependent on ART and CD4 count. Therefore in people living with HIV and low CD4 count initiation of ART is recommended first followed by HBV-vaccination after immune reconstitution (as soon as CD4 count exceeds 200/µl).

Chapter Six: Management and Documentation of ART

Monitoring of ART

General recommendations:

- Clinical check-up, including physical examination and intensified case finding for TB at every visit is strongly recommended.
- Clinical check-up with physical examination at every visit should include examination of side-effects (e.g. rashes) and also clinical diagnosis of sexually transmitted infections.
- Routine laboratory or radiologic monitoring is generally *not a precondition* to start/continue ART.

Specific recommendations:

- CD4 count is recommended at diagnosis of HIV and every 6 months thereafter.
- HBs-screening is recommended at diagnosis of HIV and should be repeated every 12 months if negative.
- FBC, creatinine and ALT are useful at diagnosis of HIV if affordable.
- Hb is recommended before starting AZT and later either symptom-directed.
- Hb is recommended before starting AZT and after 1 month and quarterly thereafter in patients with CD4 count < 200/µl and/or BMI < 18.5 kg/m² or anaemia at baseline.
- Creatinine-clearance is recommended before starting ART.
- Creatinine-clearance is recommended every 3 months in patients receiving TDF and high risk for renal adverse events.
- ALT is recommended in patients before starting NVP and at weeks 4 and 12 *or earlier* in case of NVP-related exanthema. In women with CD4 count > 250/µl at NVP-initiation, ALT is recommended also after 2 weeks.
- ALT is recommended in patients living with HBV or HCV at diagnosis, at start of ART and at weeks 4 and 12 after initiation of ART (independent of used ARVs).
- Psychiatric clinical assessment is recommended at initiation of EFV and at weeks 2 and 4 after initiation of ART.

Monitoring-Calendar for people on ART								
	HIV-diagnosis	**Start of ART**	**2 weeks**	**4 weeks**	**8 weeks**	**3 months**	**6 months**	**12 months**
Physical examination	X	X		X	X	X	X	X
Intensified TB Case finding	X	X		X	X	X	X	X
CD4	X	X					X	X
HBs	X							
Hb	(FBC)	if AZT		If AZT and high risk		If AZT and high risk	If AZT and high risk	If AZT and high risk
CreaC	(X)	if TDF				If TDF and high risk	If TDF and high risk	If TDF and high risk
ALT	(X)	If NVP	If NVP-initiation in women CD/count > 250/µl	If NVP Or HBV Or HCV		If NVP Or HBV Or HCV	If NVP	If NVP
Psychiatric clinical assessment	(X)	If EFV	If EFV	If EFV				If EFV
Adherence intervention		X	X	X	X	X	X	X

Documentation of Cases

Documentation of pre-treatment screening, therapeutic decisions and patients follow-up are most relevant sources to gain country specific data to tailor procurement, resource allocation, treatment-guidelines and national HIV-policies. Therefore documentation and collaboration with the national registry are a very important responsibility of all medical doctors treating people living with HIV. Documentation and registration are essential part of comprehensive care for people living with HIV according to the national guideline!

For clinical staging it is essential to take the *comprehensive history* of the patient including asking for symptoms of meningitis, headache, ophthalmologic symptoms, symptoms of the upper and lower digestive tract (including oral cavity), the respiratory tract, the musculoskeletal system, and TB-clinical screening (fever, night-sweats, weight-loss, and productive cough for more than 2 weeks).

Clinical examination has to be comprehensive including screening for CNS-symptoms, the oral cavity, search for enlarged lymph nodes, taking weight, inspection of the complete skin and the genitals, auscultation of the lung and heart, heart-rate, blood-pressure and body-weight.

Technical examinations – such as X-ray, lumbar puncture or other – might be indicated in a targeted way in some patients.

As Lab tests a full blood count, ALT, serum-creatinine and HBs-AG rapid test are desirable, but not essential. All investigations together allow clinical staging and should be documented according the "HIV and ART documentation form" attached as **Annex 1.**

This form should be posted to Kabul-ART-center for central collection of medical data every six months! (contact see chapter "Important Contact Numbers/addresses" of the guideline) Epidemiologic research as basis for accurate and well focused allocation of funds and resources needs participation of all stakeholders. Therefore documentation according to the form is extremely important!

Referral and Registration

All HIV +ve patients are registered at their first visit to the ART center, the registration is system is a computer based system and the below form should be copied, filled and posted to Kabul ART-center for central registration and collection of medical data: (contact see chapter "Important Contact Numbers/Addresses" in this guideline)

شماره/ID:

اسم یا تخلص/Last Name/ Name:

ولد/ FatherName:

محل تولد/Province of Birth:

تاریخ راجستر/Date of Registration:

تداوی امراض انتانی/Prophylaxis of OI:

تداوی ART:

فوت/حیات Dead/Alive:

محل تشخیص:

تاریخ تشخیص:

جنس:

آدرس فعلی:

مرجع مرسله/Ref by:

طرق انتقال/Route of Trans

تداوی امراض انتانی/Prophylaxis of OI

تداوی ART:

تصویر/Photo:

سن:

حالت مدنی:

شماره مبایل:

0

معتاد زرقی:

وزن:

مشاوره قبل و بعد از تست

After registration is complete, blood test for CD4 count is done by PIMA BEEDS CD4 count machine which is portable and performs only absolute count not percentage. In near future new CD4 count machines may allow also measurement of CD4%.

If the patient is eligible for treatment the form below is filled and **contains the patient ID:**

HIV Care/ART Card - ART کارت تداوی

شماره:ID

تاریخ شروع ART:

وزن:

همکار/همراه:

مشاوره قبل از ART ☐

طبقه کلینیکی:

معاینات لابراتواری ☐

نتیجه معاینات:

ایجاب تداوی به اساس:

☐ Clinically

CD4 count:

TLC:

شکایت فعلی:

قبلاً ART اخذ نموده ☐

کدام رژیم:

تاریخ شروع ART:

علت توقف:

تداوی:

خط اول:

علت تبدیل یا تعویض:

خط دوم:

مشکل OI:

تداوی برای OI:

Chapter Seven: Specification of Antiretroviral Drugs

Antiretrovirals (ARV) and Formulations

In sqared brackets […] fixed dose combinations (FDC)

ARV	Standard-Dosage	Indication	Side-effects	comments	Interactions
[TDF+FTC+EFV] 300+200+600 mg	Once daily, one tablet empty stomach. Start with intake at bedtime. If well tolerated time of intake might be moved to the morning, e.g. if DAART or in combination with TB-medication/ methadone offers striking benefits of morning-intake.	**first line** including patients with anaemia, HBV-, HCV-, TB-co-infection, PMTCT (after 14th week of gestation), CKD (Creatinine-Clearance >30 ml/min), methadone-co-medication	**TDF:** rarely (2-5%) renal side effects, osteomalacia, rises of Plasma-CreatinKinase (CK) (probably without significance) **FTC:** rarely headache, rash, nausea, diarrhea **EFV:** frequently during the first weeks CNS-symptoms (dizziness, night-mares, depression, confusion), 15% mild rash, ALT-elevations, hyperbilirubinaemia (less frequent in comparison to NVP)	**TDF and FTC** are highly active against HBV. TDF: do not use routinely if Crea-Clear <30. **TDF:** To monitor renal side effects: urine-glucose, serum-creatinine and potassium. **EFV** is contraindicated in first trimester of pregnancy.	**TDF:** careful with Aciclovir (renal side-effects) **EFV:** Methadone dosage usually needs to be adjused (increased)
[AZT+3TC+NVP] 300+150+200 mg	Twice daily one tablet With or without meal As NVP requires phasing-in, initiation of [AZT+3TC+NVP] two weeks of [AZT+3TC] (bid) + NVP (qd) should precede No phasing-in when switched from EFV or in combination with Rifampicin	**alternative first line** if [TDF+FTC+EFV] is contraindicated or not well tolerated (severe CKD, severe psychiatric disorder)	**AZT:** myelotoxicity: macrocytic anaemia, neutropenia, gastrointestinal side-effects, headache **3TC:** rare. **NVP:** hepatotoxicity, especially if CD4 count is > 250/µl (women) or 400/µl (men) in ART-naïve patients. Monitor ALT! **NVP:** Exanthema.	Do not use FDC if creatinine-clearance is < 50 ml/min (use separated ARVs) **NVP:** If rash during phasing-in, prolong phasing-in. With only mild exanthema try antihistaminic. In case of severe exanthema, stop NVP, try steroids (1 mg/kg Prednisolon). In case of Exanthema and elevation of ALT > 2* ULN stop NVP.	**AZT:** increased myelotoxicity in combination with Cotrimoxazole, Ribavirin, Interferon, Amphotheric. B **NVP:** do not combine with Ketoconazole, Rifampicin. Fluconazole increases NVP-plasmalevels without affecting hepatotoxicity **NVP:** Methadone dosage usually needs to be adjused (increased)
[TDF+FTC] 300+200 mg	Once daily, one pill	For combination with LPV/r in second line after failure of [AZT+3TC+NVP] To combine with NVP in case of EFV-intolerance/ contraindication (planned pregnancy, 1st trimester of pregnancy, severe	**TDF:** rarely (2-5%) renal side effects, osteomalacia, rises of Plasma-CreatinKinase (CK) (probably without consequence) **FTC:** rarely headache, rash, nausea, diarrhea	**TDF and FTC** are highly active against HBV. TDF: do not use routinely if Crea-Clear <30. **TDF:** To monitor renal side effects: urine-glucose, serum-creatinine and	**TDF:** careful with Aciclovir (renal side-effects)

		psychiatric disorder) In rare cases to combine with AZT as "triple-nuke" (e.g. severe psychiatric disorder + CHILD C liver cirrhosis) "NRTI-tail" when [TDF+FTC+EFV] is stopped (for whatever reason)		potassium. EFV is contraindicated in first trimester of pregnancy.	
[AZT+3TC] 300+150 mg	Twice daily one tablet With or without meal	For combination with LPV/r in second line after failure of [TDF+FTC+EFV] To combine with EFV in case of NVP-contraindication/ intolerance. (hepatotoxicity, severe rash) During lead-in-phase of NVP "NRTI-tail" when [AZT+3TC+NVP] is stopped (for whatever reason)	**AZT:** myelotoxicity: macrocytic anaemia, neutropenia, gastrointestinal side-effects, headache **NVP:** hepatotoxicity, especially if CD4 count is > 250/µl (women) or 400/µl (men) in ART-naïve patients. Monitor ALT! **NVP:** Exanthema.	Do not use FDC if creatinine-clearance is < 50 ml/min (use separated ARVs)	**AZT:** increased myelotoxicity in combination with Cotrimoxazole, Ribavirin, Interferon, Amphotheric. B
AZT 300 mg	Twice daily one tablet (adjustment for severe CKD: see chapter "patients with renal failure"	**Severe CKD** In rare cases to combine with AZT as "triple-nuke" (e.g. severe psychiatric disorder + CHILD C liver cirrhosis)	**AZT:** myelotoxicity: macrocytic anaemia, neutropenia, gastrointestinal side-effects, headache		**AZT:** increased myelotoxicity in combination with Cotrimoxazole, Ribavirin, Interferon, Amphotheric. B
AZT liquid 10 mg/ml	Dosing see chapter "Infants and Children" and "HIV, ART and Pregnancy"	Small children, PMTCT (infant prophylaxis)	**AZT:** myelotoxicity: macrocytic anaemia, neutropenia, gastrointestinal side-effects, headache		**AZT:** increased myelotoxicity in combination with Cotrimoxazole, Ribavirin, Interferon, Amphotheric. B
3TC 150 mg	Dosing in severe CKD see chapter "patients with renal failure"	**Severe CKD**	rare.	No combination with FTC	
3TC liquid 10 mg/ml	Dosing see chapter "Infants and Children" and "patients with renal failure"	**Small children, Severe CKD**	rare.	No combination with FTC	
EVF 600 mg	empty stomach. Start with intake at bedtime. If well tolerated time of intake might be moved to the morning, e.g. if DAART or in combination with TB-medication/ methadone offers striking benefits of morning-intake.	Severe CKD, to combine with [AZT+3TC] in case of NVP-contraindication/ intolerance. (hepatotoxicity, severe rash)	**EFV:** frequently during the first weeks CNS-symptoms (dizziness, night-mares, depression, confusion), 15% mild rash, ALT-elevations, hyperbilirubinaemia (less frequent in comparison to NVP)	**EFV:** is contraindicated in first trimester of pregnancy. No combination with NVP!	**EFV:** Methadone dosage usually needs to be adjused (increased)
NVP 200 mg	Twice daily one pill NVP requires	To combine with [TDF+FTC] in case	**NVP:** hepatotoxicity, especially if CD4	**NVP:** If rash during phasing-	**NVP:** do not combine with

	phasing-in: initiation NVP once daily 200 mg for two weeks before increasing to twice daily. No phasing-in when switched from EFV or in combination with Rifampicin	of EFV-intolerance/contrain dication (planned pregnancy, 1st trimester of pregnancy, severe psychiatric disorder)	count is > 250/µl (women) or 400/µl (men) in ART-naïve patients. Monitor ALT! **NVP:** Exanthema.	in, prolong phasing-in. With only mild exanthema try antihistaminic. In case of severe exanthema, stop NVP, try steroids (1 mg/kg Prednisolon). In case of Exanthema and elevation of ALT > 2* ULN stop NVP. No combination with EFV!	Ketoconazole, Rifampicin. Fluconazole increases NVP-plasmalevels without affecting hepatotoxicity **NVP:** Methadone dosage usually needs to be adjused (increased)
LPV/r 200/50 mg	Twice daily two tablets Intake together with meal	Second line	Diarrhea (!) Nausea		Several interactions! Avoid combination with Simvastatin, Antiepileptic drugs, tricyclic antidepressants. Combination with Rifampicin needs superboosted dose of twice daily 4 tablets which is hardly tolerated.
NVP liquid 10 mg/ml	Dosing see chapter "Infants and Children" and "HIV, ART and Pregnancy"	Small children PMTCT(infant prophylaxis)	NVP: hepatotoxicity, especially if CD4 count is > 250/µl (women) or 400/µl (men) in ART-naïve patients. Monitor ALT! NVP: Exanthema.	NVP: If rash during phasing-in, prolong phasing-in. With only mild exanthema try antihistaminic. In case of severe exanthema, stop NVP, try steroids (1 mg/kg Prednisolon). In case of Exanthema and elevation of ALT > 2* ULN stop NVP.	NVP: do not combine with Ketoconazole, Rifampicin. Fluconazole increases NVP-plasmalevels without affecting hepatotoxicity NVP: Methadone dosage usually needs to be adjused (increased)
DRV (Darunavir) 300 mg + RTV (Ritonavir) 100 mg	twice daily two tablets DRV plus twice daily 100 mg RTV (separately) take with meal	Third line	Moderate. gastrointestinal side effects 7% reversible exanthema during the first weeks of therapy	**PROTEINASE -INHIBITOR** Not yet routinely available in Afghanistan	Several interactions! Avoid combination with Simvastatin, Antiepileptic drugs, tricyclic antidepressants. Decreases methadone-plasmalevels Increases calcium-antagonist-serum-levels Increases PDE5-

					Inhibitor-plasma-levels (Sildenafil)
RAL (Raltegravir) 400 mg	Twice daily one tablet With or without meal	Third line	Rare. Gastrointestinal side effects and vertigo	**INTEGRASE-INHIBITOR** Not yet routinely available in Afghanistan	Rifampicine decreases RAL-plasmalevels by 50%, RAL-dose has to be doubled.
ETV (Etravirine) 100 mg	Twice daily two tablets After meal	Eventual third line	Frequent. Rash Nausea Stevens-Johnson syndrome Ischämic heart attack Gastrointestinal side effects CNS-side effects	**NNRTI (2nd generation)** Not yet routinely available in Afghanistan Usually effective even in virus with NNRTI-resistance-mutation (K103N).	Multiple interactions! (methadone, anti-fungals, anti-arrhthmics, macrolids, sildenafil, and many more) No combination with anticonvulsants, Rifampicine.

Management of ART Side-effects

With the development of new ARVs side-effects of ARVs have become less frequent and less severe than in the early years of ART. Still, side-effects are not rare and need to be diagnosed, documented, reported and treated.

The following tables list the grading of severity of common side effects and their proposed treatment. However: Treatment of side-effects needs to be adjusted to the patient's individual conditions. The listed possible interventions are only suggestions and do not relieve the medical doctor of the duty to adjust eventual treatment to the individual case.

Severity-grading of side effects					
		GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**
anaemia	AZT Cotrim Isoniazide	8-9.5 g/dl	7-7.9 g/dl	6.5-6.9 g/dl	<6.5 g/dl
neutropenia	AZT Cotrim Isoniazide	1000-1500/µl	750-999/µl	500-749/µl	<500/µl
thrombopenia	AZT Isoniazide	75.000-99.000/µl	50.000-74.000/µl	20.000-49.000/µl	< 20.000/µl
Hyperbilirubinemia	NVP EFV	>1 x ULN	>1.5 x ULN	>2.5 x ULN	>5 x ULN
ALT-elevation	AZT NVP EFV LPV/r Cotrim Isoniazide	>1 x ULN	>2.5 x ULN	>5 x ULN	>10 x ULN
CreaClearance	TDF	50-100 ml/min	30-50 ml/min	15-30 ml/min	<15 ml/min
Nausea	AZT 3TC FTC	mild	moderate	severe	Hospitalization required

	TDF LPV/r RAL Cotrim Isoniazide				
vomiting	AZT 3TC FTC TDF Cotrim Isoniazide	mild	moderate	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension	Hypotensive shock OR intravenous rehydration required
diarrhea	3TC FTC LPV/r	mild	moderate	Bloody diarrhea OR orthostatic hypotension OR >7 loose stools/day	Hypotensive shock OR intravenous rehydration required
headache	AZT Cotrim 3TC LPV/r	mild	Moderate (no opiate therapy)	In need of opiates	intractable
rash	EVF NVP FTC Isoniazide Cotrim RAL DRV	Erythema, Mild pruritus	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	mucous membrane involvement OR: Stevens-Johnson OR: exfoliative dermatitis
fatigue	3TC Isoniazide RAL	Daily activity reduced by 10-25%	Daily activity reduced by 25-50%	Daily activity reduced by > 50%	Unable to care for self
depression	EFV Isoniazide	mild	morderate	severe	Suicidal OR Apathic
insomnia	3TC EFV Isoniazide	Sleep reduced by 10-25%	sleep reduced by 25-50%	Sleep reduced by > 50%, daytime capacities significantly affected	Unable to sleep, unable to care for self

Usually Grade 1 conditions need no therapy (by definition), as condition in need of treatment should be graded Grade 2. One exception might be pruritus, which should be treated also as GRADE 1 condition with antihistaminics.

Symptomatic Grade 1 conditions should be taken seriously as they may influence the patient's ability to adhere to ART. ART should not be changed in case of mild or moderate side-effects, but information about harmlessness and/or symptomatic relief should be offered.

Grade 2 conditions may need symptomatic treatment:	
Nausea, vomiting	• Chamomile-, ginger-, mint-tea • Intake with meal (except EFV) • Metoclopramide • Dimenhydrinate • Dimeticon
Diarrhea	• Oral rehydration • Glutamin • Calcium (LPV/r-associated diarrhea: 2 x 500 mg/d) • Loperamide • Opium tincture (not for methadone patients)
Hepatotoxicity	• No specific treatment • Avoid other hepatotoxic medication (e.g. paracetamol)
Creatinine-clearance reduction	• Adjust eventual co-medication • Control hypertension and diabetes mellitus
Insomnia, nightmares and depression due to EFV	• Usually reversible after 2-4 weeks even if EFV is continued • Haloperidole • Benzodiazepines (ONLY very short term! ADDICTIVE!)
Rash, allergic reactions	• Usually reversible after 1-4 weeks even if ART is continued • Antihistamincs
Headache	• Symptomatic treatment (NSAR, paracetamol)

Usually Grade 3 and 4 conditions require stop of medication and treatment of side-effect;

ARV should be replaced in case of Grade 3 or 4 side effects!

In case of NRTI-toxicities, ART should be modified by replacement of either NRTI-backbone ([AZT+3TC] against [TDF+FTC] or vice versa) or the complete regimen should be exchanged ([AZT+3TC+NVP] against [TDF+FTC+EFV] or vice versa).

In case of NNRTI-toxicities, ART should be modified by replacement of either NNRTI (EFV against NVP or vice versa) or the complete regimen should be exchanged ([AZT+3TC+NVP] against [TDF+FTC+EFV] or vice versa).

It is recommended to always stop, continue or modify a complete ART and to never continue only a partial therapy.

Important Contact Numbers/Addresses

For further information please contact:

National AIDS Control Program Afghanistan

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e-mail:

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e-mail:

Address:

HEART ART-Center

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