



World Health  
Organization

REGIONAL OFFICE FOR **Europe**

*Regional consultation on revision  
of the clinical protocols  
“HIV/AIDS treatment and care” for the  
WHO European Region*

*Technical report*

*7 October 2010*

*Kiev, Ukraine*

*WHO Regional Office for Europe*

*United Nations Children's Fund*

Address requests about publications of the WHO Regional Office for Europe to:

Publications  
WHO Regional Office for Europe  
Scherfigsvej 8  
DK-2100 Copenhagen Ø, Denmark

Alternatively, complete an online request form for documentation, health information, or for permission to quote or translate, on the Regional Office web site (<http://www.euro.who.int/pubrequest>).

© **World Health Organization 2010**

All rights reserved. The Regional Office for Europe of the World Health Organization welcomes requests for permission to reproduce or translate its publications, in part or in full.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either express or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use. The views expressed by authors, editors, or expert groups do not necessarily represent the decisions or the stated policy of the World Health Organization.

---

**CONTENTS**

1. Acronyms and abbreviations .....	4
2. Executive summary .....	5
2.1. Introduction .....	5
2.2. Expected outcomes .....	5
2.3. Working methods .....	5
2.4. Outcomes .....	6
3. Summary of plenary sessions .....	6
3.1. WHO Guidelines for guidelines development .....	6
3.2. WHO recommendations on PMTCT .....	7
3.3. WHO recommendations on clinical management of HIV/AIDS in children .....	8
3.4. WHO recommendations on ART in adults and adolescents .....	10
3.5. WHO recommendations on HBV/HIV co-infection management .....	12
3.6. WHO recommendations on management of TB/HIV coinfection .....	12
4. Recommendations of the general discussion .....	13
5. Key results of the group discussions .....	14
5.1. Protocol 1: Patient Evaluation and Antiretroviral Treatment for Adults and Adolescents .....	14
5.2. Protocol 4: Management of Tuberculosis and HIV Coinfection .....	16
5.3. Protocol 7: Management of Hepatitis B and HIV Coinfection .....	18
5.4. Protocol 10: Prevention of HIV Transmission from HIV-infected Mothers to Their Infants .....	18
5.5. Protocol 11: Paediatric HIV & AIDS Treatment and Care .....	20
6. Key recommendations of the meeting .....	21
7. Annexes .....	25
7.1. Meeting agenda .....	25
7.2. List of participants .....	26
7.3. Questions for the working groups .....	29
8. References .....	31

## 1. Acronyms and abbreviations

3TC	lamivudine
ABC	abacavir
Ag	antigen
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AZT	azidothymidine, zidovudine
CD4	cell cluster of differentiation antigen 4 cell
d4T	stavudine
ddI	didanosine
DNA	desoxyribonucleic acid
DR	drug resistance
DRV	darunavir
DST	drug sensitivity testing
EFV	efavirenz
ETR	etravirine
FTC	emtricitabine
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-infection	disease caused by HIV
IDU	injecting drug user
IPT	isoniazid preventive therapy
LPV/r	lopinavir/ritonavir
MARP	most-at-risk population
MDR-TB	multidrug-resistant tuberculosis
MDT	multidisciplinary team
NFV	nelfinavir
NGO	nongovernmental organization
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside or nucleotide reverse transcriptase inhibitor
NVP	nevirapine
PCR	polymerase chain reaction
PI	protease inhibitor
PLWH	people living with HIV
PMTCT	prevention of mother-to-child transmission (of HIV)
RAL	raltegravir
RNA	ribonucleic acid
RTV	ritonavir
SQV	saquinavir
TB	tuberculosis
TDF	tenofovir
VL	viral load
WHO	World Health Organization
XDR-TB	extradrug-resistant tuberculosis

## **2. Executive summary**

### **2.1. Introduction**

Since the WHO Regional Office for Europe published the HIV/AIDS treatment guidelines in 2007, new important evidence regarding the following issues has emerged:

- Criteria of antiretroviral therapy (hereinafter – ART) initiation for patients who need it;
- Efficacy and toxicity profile of selected antiretrovirals (hereinafter – ARVs);
- Clinical management of co-infections, in particular – HIV/HBV and HIV/TB;
- Antiretroviral prophylaxis of HIV transmission from mother to a child.

Due to the above-mentioned points, WHO headquarters issued new global recommendations outlining public health approach to the delivery for pregnant women. The guidelines development process was conducted in accordance with revised WHO requirements for guidelines development which anticipate systematic reviews of new evidence and take into consideration feasibility and cost/financial implications of new recommendations for the treatment delivery.

Since global WHO recommendations cover only some key global issues and do not always take into consideration regional context in terms of existing infrastructure and health care system capacities in the WHO regions, they therefore require regional and country adaptation. Countries of the WHO European Region especially of eastern Europe though are characterized by limited resources for HIV/AIDS response and have similarities in terms of epidemic trends and HIV prevalence in different populations. Besides their health care systems and resources are organized and equipped better than in many other limited resources countries out of the WHO European Region.

This technical consultation intended to have country experts discuss planned revision of HIV/AIDS clinical guidelines for the WHO European Region based on revised global WHO recommendations on ART for adults and adolescents, ART for infants and children, use of ARVs for treatment of HIV-infected pregnant women and infants born to them. Available evidence, countries needs and capacity of health systems for implementation of specific recommendations were taken into consideration during the discussion.

### **2.2. Expected outcomes**

The meeting was planned to provide feedback from clinical experts in terms of acceptability of global recommendations on HIV/AIDS treatment for the countries. It will enable development of suggestions/recommendations for revision of the clinical guidelines for the WHO European Region listed below within regional adaptation of the global recommendations:

- Protocol 1: Patient Evaluation and Antiretroviral Treatment for Adults and Adolescents
- Protocol 4: Management of Tuberculosis and HIV Coinfection
- Protocol 7: Management of Hepatitis B and HIV Coinfection
- Protocol 10: Prevention of HIV Transmission from HIV-infected Mothers to Their Infants
- Protocol 11: Paediatric HIV & AIDS Treatment and Care

### **2.3. Working methods**

Key provisions of the new global WHO recommendations were presented at the plenary and major changes based on the latest evidence highlighted. The consultation continued in the form of two working groups: on ART for adults, HIV/TB and HIV/HBV co-infection management; ART for infants and children and PMTCT. Based on provided questionnaires groups formulated recommendations for adaptation of the global WHO recommendations to European Region and revision of the clinical guidelines listed above. Recommendations proposed by the groups were presented and discussed at plenary session with participation of all involved experts. Clinical experts on HIV/AIDS treatment and care issues from European Region countries who had been directly involved in development of national HIV/AIDS clinical guidelines as well as NGOs representatives who ensured feedback from the target patients groups participated in the meeting.

## **2.4. Outcomes**

As a result of the meeting feedback from clinical experts of the WHO European Region countries has been obtained regarding acceptability, need and extends of the global WHO HIV/AIDS treatment and care guidelines adaptation to the needs and capacity of countries within the region. Recommendations regarding basic directions of revision for five Europe clinical guidelines were formulated:

Protocol 1: Patient Evaluation and Antiretroviral Treatment for Adults and Adolescents

Protocol 4: Management of Tuberculosis and HIV Coinfection

Protocol 7: Management of Hepatitis B and HIV Coinfection

Protocol 10: Prevention of HIV Transmission from HIV-infected Mothers to Their Infants

Protocol 11: Paediatric HIV & AIDS Treatment and Care

This technical report was developed based on the meeting outcomes to reflect main provisions of the plenary session, results of group work and expert discussion. Feedback from the country experts received as a result of the meeting and recommendations developed by them will be used in the process of the Regional Office clinical guidelines updating.

## **3. Summary of plenary sessions**

### **3.1. WHO Guidelines for guidelines development**

Development of guideline for health care is one of the key WHO functions. The guidelines development process was updated in 2009 and described in the “Guidelines for the guidelines development”, regulating issues of keeping standards for the recommendations preparing and using evidence, establishment of experts panel on technical and procedural issues, ensuring absence of intellectual or financial conflicts of interests and transparency of the process, anticipating consultations with the patients’ groups representatives.

Based on assessment of quality of evidence level of confidence in reliability of interaction or interrelation evaluation is classified as high, medium, low or very low. Depending on the quality of evidence, ratio of desirable and undesired consequences of the recommendation execution, probability of accepting recommendation for implementation, acceptability of related expenses recommendations formed based on evidence are defined as strong or conditional. Criteria of quality of evidence and strength of recommendations are reflected in new global WHO recommendations, presented in 2009-2010, In particular:

- Antiretroviral Therapy for HIV Infection in Adults and Adolescents. Recommendations for a public health approach;

- Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Recommendations for a public health approach;
- HIV and Infant Feeding. Revised Principles and Recommendations. Rapid Advice;
- Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a public health approach.
- Global WHO recommendations on intensified TB case finding and TB preventive treatment are being currently revised.

### 3.2. WHO recommendations on PMTCT

The major changes touched the following key recommendations presented in the new WHO guidelines “Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Recommendations for a public health approach”, 2010:

- HIV-infected pregnant women who need for ART for their own health should receive it during whole life;
- ART in pregnant women should be initiated at CD4 count of  $\leq 350$  cells/mm<sup>3</sup> irrespective of the WHO clinical staging;
- In cases when CD4 count testing is not available ART is to be initiated at the WHO clinical stages 3 and 4;
- ARV prophylaxis is prescribed at the WHO clinical stages 1 and 2 and CD4 count of  $> 350$  cells/mm<sup>3</sup>;
- ART should be initiated as soon as it is acceptable and appropriate;
- It is crucial to have an access to CD4 count testing to detect indications to ART;
- Pregnant women who eligible for ART or when these indications are not known ARVs should be started from 14 weeks of gestation (second trimester) or as soon as possible thereafter (*strong recommendation*).

#### Recommended ART regimens for HIV-infected pregnant women and infants with perinatal exposure to HIV

For mother: <ul style="list-style-type: none"> <li>• AZT + 3TC + NVP or</li> <li>• AZT + 3TC + EFV or</li> <li>• TDF + XTC* + NVP or</li> <li>• TDF + XTC* + EFV</li> </ul> *XTC = 3TC or FTC ( <i>strong recommendation</i> )	For infant: <ul style="list-style-type: none"> <li>• AZT during 4-6 weeks OR</li> <li>• NVP during 4-6 weeks</li> </ul> ( <i>strong recommendation</i> )
---	--

When ARV prophylaxis is provided to pregnant women do not need ART for their own health two scenarios are possible:

- A) Maternal AZT, or
- B) Maternal triple ARV prophylaxis.

For breastfeeding mothers it is recommended to prescribe ARVs to a child OR to mother aiming at reducing risk of transmission during breastfeeding period.

**Regimens of ARV prophylaxis to prevent MTCT for HIV-infected pregnant women who do not need treatment for their own health**

Option A	Option B
<b>Mother:</b> <ul style="list-style-type: none"> <li>• Twice-daily AZT antepartum (starting from 14 week of gestation)</li> <li>• Sd-NVP at the onset of labour*</li> <li>• AZT + 3TC during labour and delivery*</li> <li>• AZT + 3TC 7 days postpartum*</li> </ul>	<b>Mother:</b> <ul style="list-style-type: none"> <li>• Triple ARV regimen (starting from 14<sup>th</sup> week of gestation until 1<sup>st</sup> week after all exposure to breast milk has ended)</li> <li>• AZT + 3TC + LPV/r or</li> <li>• AZT + 3TC + ABC or</li> <li>• AZT + 3TC + EFV or</li> <li>• TDF + XTC + EFV</li> </ul>
<b>Infant:</b> <b>Breastfeeding:</b> <ul style="list-style-type: none"> <li>• Daily NVP (from birth until 1 week after all exposure to breast milk has ended)</li> </ul> <b>Replacement feeding:</b> <ul style="list-style-type: none"> <li>• AZT until 4-6 weeks of age OR</li> <li>• NVP until 4-6 weeks of age</li> </ul>	<b>Infant:</b> All infants with perinatal exposure to HIV: <ul style="list-style-type: none"> <li>• AZT until 4-6 weeks of age OR</li> <li>• NVP until 4-6 weeks of age</li> </ul>

\*Sd-NVP and AZT+3TC may be omitted if mother received more than 4 weeks of AZT during pregnancy.

As next steps to efficient prophylaxis of mother to a child transmission it is feasible to ensure further increase in prophylaxis coverage using more efficient regimens, universal CD4 count testing to detect indications to ART, stable funding as well as monitoring of treatment efficacy and quality. There is a need for prompt adaptation and implementation of the new WHO PMTCT recommendations. Attention should also be paid to delivery of care, treatment and support in postpartum period.

### ***3.3. WHO recommendations on clinical management of HIV/AIDS in children***

Revised WHO recommendations on treatment of HIV-infection in children are presented in the guidelines “Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a public health approach”, 2010.

According to the revised WHO recommendations there is a need for early and accurate HIV-infection diagnostic in infants as well as early initiation of ART. HIV-status of a child is to be defined as soon as possible after birth. For testing of infants younger than 4-6 weeks of age it is recommended to use virologic methods:

- HIV DNA on whole blood specimen or dry blood spot (DBS);
- HIV RNA on plasma or DBS;
- Up24 Ag on plasma or DBS.

For infants and children younger than 2 years of age ART is to be initiated as soon as HIV diagnosis is established. Initiation of ART in age group of  $\geq 2$  and  $\leq 5$  is recommended with % CD4 of  $< 25\%$  or CD4 count of  $\leq 750$  cells/mm<sup>3</sup>. For children of more than  $\geq 5$  years of age ART should be started when CD4 count is  $\leq 350$  cells/mm<sup>3</sup>.



When appropriate 1<sup>st</sup> and 2<sup>nd</sup> line ART regimens for children are being selected fixed drug combinations should be preferred with more convenient intake regimen and less strict adherence requirements. For infants with a history NNRTI exposure (when ARVs were taken by the mother during pregnancy) ART regimens based on boosted PIs should be preferred.

### Recommended 1<sup>st</sup> line ART regimens for infants and children

Age	Standard regimen
<b>Infants</b>	
Infants or children <24 months of age not exposed to ARVs	NVP+ 2 NRTIs
Infants or children <24 months of age exposed to ARVs	LPV/r + 2 NRTIs
Infants and children <24 months of age with unknown ARV exposure history	NVP+ 2 NRTIs
<b>Children</b>	
Children from 24 months to 3 years of age	NVP+ 2 NRTIs
Children > 3 years of age	NVP or EFV + 2 NRTIs

There is a need to provide laboratory monitoring of ARVs' adverse reactions. 1<sup>st</sup> line ART regimen failure is an indication to ART regimen switching to 2<sup>nd</sup> line ART. Decision on ART switching should be guided by clinical manifestations and immunological criteria.

### Recommended 2<sup>nd</sup> line ART for infants and children

<b>Recommended 2<sup>nd</sup> line ART regimen: boosted PI component + 2 NRTI components</b>					
		<b>Recommended 2<sup>nd</sup> line ART regimen</b>			
<b>1<sup>st</sup> line ART regimen at failure</b>	<b>NRTI/NNRTI components</b>		<b>PI component</b>	<b>Strength of recommendation</b>	<b>Quality of evidence</b>
2 NRTIs + 1 NNRTI: including AZT or d4T	ABC+3TC or ABC+ddI	<b>plus</b>	LPV/r	<i>Strong</i>	<i>Moderate</i>
or including ABC	AZT+3TC or AZT+ddI		LPV/r	<i>Strong</i>	<i>High</i>
Triple NRTIs	ddI+EFV or NVP				

### Recommendations on ART regimens selection for children with co-infection TB/HIV

<b>Recommended ART regimens for TB/HIV coinfecting children &lt;3 years of age</b>
2 NRTIs + NVP (except for infants and children <2 years if previously exposed to NVP) or 3 NRTIs: (d4T or AZT) + 3TC + ABC
<b>Recommended ART regimens for TB/HIV coinfecting children ≥3 years of age</b>
2 NRTIs + EFV or 3 NRTIs: (d4T or AZT) + 3TC + ABC

Importance of ensuring adequate nutrition in children on ART is emphasized separately as well as interventions on treatment adherence forming and support.

### **3.4. WHO recommendations on ART in adults and adolescents**

Based on available evidence regarding terms of ART initiation, toxicity of individual ARVs as well as benefits of different ART regimens the WHO revised ART recommendations for adults and adolescents in 2010 and presented them in the guidelines “Antiretroviral Therapy for HIV Infection in Adults and Adolescents. Recommendations for a public health approach”, 2010. Global WHO recommendations were developed based on public health principles which anticipate delivery of care to the biggest number of those in need for it, take into consideration significant resources limitations and limited choice treatment and monitoring options allowing providing care with reduced standards though with the maximal coverage.

Evidence indicating higher survival rate, reduced HIV-related morbidity rates and HIV transmission served as a basis for development of corresponding recommendations encouraging ART initiation at:

- CD4 counts of  $\leq 350$  cells/mm<sup>3</sup> regardless of the presence or absence of clinical symptoms (*strong recommendation, medium quality of evidence*);
- WHO clinical stage 3 or 4 irrespective of CD4 count (*strong recommendation, low quality of evidence*).

While selecting ART regimens it is necessary to take into consideration that d4T toxicity according to new evidence is unacceptably high for PLWH. WHO guidelines 2010 recommend starting one of the following regimens 1<sup>st</sup> line ART:

- AZT + 3TC + EFV or
- AZT + 3TC + NVP or
- TDF + 3TC or FTC + EFV or
- TDF + 3TC or FTC + NVP (*strong recommendation, moderate quality of evidence*)
- d4T and ABC are excluded from 1<sup>st</sup> line ARVs.

Assessment of ART efficacy and indications to ART switching is recommended to be provided based on VL monitoring:

- Where available use VL to confirm ART failure (*strong recommendation, low quality of evidence*);
- Where routinely available use VL test is to be provided every 6 months to detect viral replication (*conditional recommendation, low quality of evidence*);
- A persistent VL of  $> 5000$  copies/ml confirms treatment failure (*conditional recommendation, low quality of evidence*);
- When VL is not available, use immunological criteria to confirm ART failure (*strong recommendation, moderate quality of evidence*).

In case of ART failure guidelines differentiate between early and late regimen switching. Based on outcomes of the WHO expert consultation “ART failure and strategies for switching ART regimens in the WHO European Region” (Copenhagen, 7 December 2007) the Regional Office formed recommendations regarding early and late ART switching, described their criteria as well as benefits and disadvantages.

Early ART switching is based on more sensitive monitoring for failure (using VL) and is provided with lower level of VL of  $> 400$  ( $> 50 - < 1000$ ) copies/ml. It allows preserving treatment options, increasing likelihood of effective response, decreasing risk of non-AIDS and AIDS related events but is associated with higher costs and more rapid exhaustion of ARV drug options; need for

routine VL laboratory testing.

Late ART switching is based on using less sensitive criteria of ART failure and is provided at VL of  $\geq 1000 - 10\,000$  copies/ml or a 25% drop in CD4 count. Reduced costs are considered as its advantages whereas disadvantages include greater accumulation of resistance mutations and potential enhanced transmission of resistant virus; may compromise treatment response; may limit the choice of active ARVs for second-line therapy.

In cases of early and late ART regimen switching selection of 2<sup>nd</sup> line ARVs is determined by assumed activity of different ARVs.

In terms of drugs selection for 2<sup>nd</sup> line ART the WHO recommendations of 2010 define following approach:

- PI boosted with rtv (bPI + 2 NRTIs) (*strong recommendation, moderate quality of evidence*);
- Preferred PIs for 2<sup>nd</sup> line ART: ATV/r and LPV/r (*strong recommendation, moderate quality of evidence*);
- Simplification of second NRTI options<sup>1</sup>:  
 1<sup>st</sup> line ART regimen: d4T or AZT  $\Rightarrow$  TDF + 3TC in 2<sup>nd</sup> line ART regimen as the NRTI backbone;  
 1<sup>st</sup> line ART regimen: TDF  $\Rightarrow$  AZT + 3TC in 2<sup>nd</sup> line ART regimen as the NRTI backbone (*strong recommendation, moderate quality of evidence*).

WHO 2010 recommendations regarding ART laboratory monitoring:

- Laboratory monitoring is not a prerequisite for the initiation of ART;
- VL in a targeted approach to confirm suspected treatment failure based on immunological and/or clinical criteria is recommended;
- If resources permit VL is to be measured every 6 months;
- CD4 count testing is provided:
  - before ART initiation (pre-ART);
  - on ART (frequency of CD4 count testing has not been fixed);
- HIV drug resistance test is not recommended.

WHO 2010 recommendations regarding ART 3<sup>rd</sup> line regimens prescription:

- Countries are encouraged to develop policies for 3<sup>rd</sup> line ART regimens that consider:
  - available funding;
  - sustainability;
  - provision of equitable access to ART (*conditional recommendation, low quality of evidence*);
- 3<sup>rd</sup> line ART regimens should include new ARVs likely to have anti-HIV activity:
  - integrase inhibitors;
  - 2<sup>nd</sup> generation PIs and NNRTIs (boosted darunavir plus raltegravir and/or etravirine) (*conditional recommendation, low quality of evidence*);
- If new 3<sup>rd</sup> line ARV options are not available it is recommended to:
  - Continue insufficiently effective 2<sup>nd</sup> line ART if it is well tolerated, or
  - Switch to the drugs previously received by the patient considering their tolerability (*conditional recommendation, very low quality of evidence*).

<sup>1</sup> Late switching is based on CD4 count use or clinical indications as ART failure criteria.

### 3.5. WHO recommendations on HBV/HIV co-infection management

Algorithm for HIV/HBV coinfection diagnostic and treatment depending on indications to HIV and HBV-infection treatment is provided in the clinical protocol for the WHO European Region 2007. Key provisions are also briefly outlined in the WHO guidelines “Antiretroviral Therapy for HIV Infection in Adults and Adolescents. Recommendations for a public health approach”, 2010, containing the following recommendations:

- ART should be started in all HIV/HBV-coinfecting individuals who require treatment for their HBV infection (criteria of treatment initiation are not defined) irrespective of the CD4 cell count or the WHO clinical stage (*strong recommendation, low quality of evidence*);
- While selecting ART regimen TDF and 3TC or FTC are to be administered in all patients HIV/HBV coinfecting individuals needing treatment (*strong recommendation, moderate quality of evidence*).

### 3.6. WHO recommendations on management of TB/HIV coinfection

Ensuring efficient response to HIV/TB coinfection is guided by 12 recommendations for collaborative TB and HIV interventions, including provisions of “Three Is” initiative, as well as recently updated WHO guidelines on Treatment of tuberculosis: guidelines 2010 and Guidelines for the programmatic management of drug-resistant tuberculosis 2008. From 2007 till the present time some WHO clinical recommendations regarding specific issues of TB/HIV coinfecting patients management have been revised and extended.

Recommendations on intensified TB case finding in HIV-positive patients were included into revised WHO guidelines 2010:

- Tuberculin skin test should be performed if it is possible from the programmatic point of view (*strong recommendation*);
- However tuberculin skin test is not a prerequisite (and should not be a barrier) to preventive treatment of latent TB with isoniazid (*strong recommendation*);
- The goal is to provide universal access to sputum culture with drug sensitivity testing (DST) (including using rapid tests).

The guidelines also anticipate provision of IPT:

- Recommended minimal duration of the course is 6 months:
  - Irrespective of CD4 count (*strong recommendation*), or
  - Course 36 months:
    - Irrespective of CD4 count (*conditional recommendation*), taking into consideration following evidence:
      - Protective effect is decreasing with time and lasts only up to 5 years;
      - Improvement of results in case of 36 months IPT duration and longer is observed, especially among PLWH with positive result of tuberculin skin test.

Recommendations regarding TB therapy 2010, in particular – 1<sup>st</sup> line treatment regimens, include:

- Treatment regimens for new TB patients have not been changed comparing to 2007 recommendations;
- Treatment regimens for previously TB-treated patients:
  - In case of relapse and after default if there is no access to rapid molecular methods for DST;

- 1<sup>st</sup> line drugs regimen is no longer recommended to previously TB-treated patients after treatment failure;
- Daily intake of TB drugs during the whole treatment course (*strong recommendation; high quality of evidence*);
- If daily intake during continuation phase of TB treatment is not possible the medications can be administered three times per week (*conditional recommendation; high or moderate quality of evidence*).

Three main strategies of XDR/MDR TB treatment regimes compiling can be applied:

- Standard regimens are administered based on DST results;
- Standard regimens with substitution to individual: modification of standard treatment regimen is performed based on DST results;
- Empirical regimens with switching to individual: individual regimen is based on patient's history data with modification after receiving DST results.

According to the WHO recommendations "Antiretroviral therapy for HIV-infection in adults and adolescents" 2010 ART is to be initiated in all HIV-infected individuals with active TB irrespective of CD4 cell count (*strong recommendation, low quality of evidence*), as soon as possible (within the first eight weeks after initiation of TB therapy) which enables to achieve 55% reduction of mortality rate in this category of patients (*strong recommendation, moderate quality of evidence*). While selecting ART regimens recommendations of clinical protocol for the WHO European Region remain relevant and efavirenz is recommended as the preferred NNRTI in patients starting ART while on TB treatment (*strong recommendation, high quality of evidence*).

Due to drug interactions between ARVs and 1<sup>st</sup> line TB drugs rifabutin is recommended as the drug of choice in case of concomitant ART using PIs (*conditional recommendation, moderate quality of evidence*), whereas rifampicin may be used as an alternative drug in the presence of lopinavir (or saquinavir) with an adjusted, superboosted dose of RTV.

#### **4. Recommendations of the general discussion**

- In the process of clinical guidelines on HIV/AIDS treatment for the WHO European Region updating, it is feasible to anticipate differentiated approach to forming treatment protocols and clinical guidelines. It is recommended to include recommendations on clinical issues as well as more detailed theoretic information containing justification for different approaches in the guidelines. Protocols on the other hand should present brief and simple recommendations in the form of patients' management algorithms free of additional theoretic information, which could be used by all medical specialists providing care to HIV/AIDS patients.
- It is feasible to classify recommendations of clinical guidelines as recommended (preferable) options, alternative options and those which may be used in special situations when other options are not available (acceptable options). Different options of health care provision are to be anticipated including both recommended and alternative approaches applicable when preferable options are not possible (e.g. in the absence of access to one or another diagnostic method or medication).
- Since the WHO 2010 recommendations were formed based on results of clinical studies of 2007-2009 it might be feasible to revise criteria of evidence quality and recommendations strength for those provisions on which new evidence has emerged. If the WHO 2010 global

guidelines do not contain recommendations on specific issues which are relevant for the countries of the European Region it may be necessary to provide additional systematic review and define quality of evidence and recommendations strength.

- Taking into consideration the WHO 2010 recommendation regarding early initiation of ART at CD4 count of  $\leq 350$  cells/mm<sup>3</sup> irrespective of clinical symptoms and significant epidemiological importance of early treatment initiation in terms of reducing population HIV viral load and risk of HIV transmission, accordingly, it is necessary to emphasize importance of performing immunological assessment and VL testing before treatment initiation.

Even in cases when absolute clinical indications to ART are present in patient, laboratory assessment before treatment initiation is necessary to enable evaluation of subsequent treatment efficacy. If ART is provided without appropriate VL, monitoring risk of resistant HIV strains circulation in population is increasing. At the same time in presence of clinical indications, lack of access to laboratory testing should not be considered as an obstacle to ART initiation as it is clearly stated by the WHO 2010 global recommendations. In addition to defining important role of laboratory assessment for ART initiation, clear ART failure criteria for children, adults and adolescents as well as pregnant women are to be provided in the guidelines.

- Issue of forming recommendations on HIV drug resistance testing remains important in particular with regard to indications to testing. Clinical guidelines for the WHO European Region of 2007 recommend HIV drug resistance testing in case of 2<sup>nd</sup> line ART regimen failure and this recommendation remains relevant. There is a need to conduct additional negotiations in countries aimed at increasing access of HIV DR testing, cost of which in eastern European countries may be significantly higher than in western European countries.

If resources permit, HIV drug resistance testing may be provided after 1<sup>st</sup> line ART regimen failure. Though it should be taken into consideration that prevalence of HIV drug resistance in former USSR countries, according to available evidence, remains low and 1<sup>st</sup> line ART regimens efficacy is high if treatment adherence is ensured even in countries like Ukraine and the Russian Federation with relatively old HIV epidemic. Taking the above into consideration, provision of HIV DR testing before any initiation of ART is not grounded from the treatment costs point of view. As a public health matter and considering limited resources of countries of the region, ensuring adequate treatment coverage should be viewed as a priority. As of today the average treatment coverage in the region amounts 15% which is not adequate and HIV-associated mortality remains high. HIV DR testing should be anticipated for pregnant women with PMTCT history.

- In terms of hepatitis C management in HIV-positive patients recommendations of the clinical protocol “Management of Hepatitis C and HIV Coinfection” for the WHO European Region, 2007, remain relevant.

## **5. Key results of the group discussions**

### ***5.1. Protocol 1: Patient Evaluation and Antiretroviral Treatment for Adults and Adolescents***

**Structure of the protocol** (*convenience for use, acceptability of the chapters, modification of the chapters etc.*):

- Overall structure does not require changing;
- It is feasible to include additional information regarding quality of evidence and strength of recommendations;
- Taking into consideration ageing of ART patients' population there is a need to include issues of non-infectious (somatic), including age-related, pathology in PLWH or consider these issues in separate guidelines. Issues of age-related diseases are important for the ART guidelines due to their influence on selecting ARVs;
- There is a need to specify terminology using the term "team approach" instead of "complex brigade" in the Russian version of the guidelines.

**ART initiation criteria – current practice. Increasing CD4 count threshold as ART initiation criteria to 350 cells/mm<sup>3</sup>:** to assess difficulties in implementing and sustainable realization (*risk of increasing costs, decreasing current ART coverage indicators, potential negative consequences for ART scaling up and other risks*):

- This recommendation has already been implemented in many countries or is in the process of implementation;
- VL is taken into consideration as an additional factor in making decision regarding treatment initiation in patients with relatively high CD4 count (350-500 cells/mm<sup>3</sup>).

**Prescribing stavudine – current practice, potential for complete withdrawal:** to assess level of difficulty in implementing and potential sustainable realization:

- Initially stavudine use was limited to "narrow" group of patients and this drug may remain applicable for this group (e.g. patients with anemia, granulocytopenia and renal failure or in the absence of access to tenofovir);
- There is a need to provide clear recommendations on stavudine use, including on indications and duration of its use;
- There is lack of access to tenofovir in Kazakhstan and Kyrgyzstan and availability of tenofovir in Uzbekistan is not stable;
- In Ukraine and Georgia TDF/FTC+EFV or AZT/3TC+EFV are used as basic treatment regimens;
- Strategy of withdrawal from d4T in adults should be reflected in the guidelines and supported by efforts to ensure access to tenofovir where it remains limited.

**Criteria for ART switching (initiation of 2<sup>nd</sup> line ART regimen):** current practice (*early and late ART switching*). *Early switching: to assess level of difficulty in implementing and stable realization (risk of increasing costs, decreasing current ART coverage and ART interruptions, potential negative consequences for ART scaling up, other risks)*:

- Current practices in the countries: in Georgia indications to ART switching are the following: VL of > 400 copies/ml after 6 months of ART; >50 copies/ml after 1year of ART. If VL is of > 1000 copies/ml HIV DR test is performed and ART regimen switching is guided by its results;
- Access to HIV DR testing in other countries of the region remains limited;
- There is a need to clearly define role and interpretation of early and late ART switching strategies in the guidelines;
- It is necessary to highlight criteria of primary treatment failure (inefficacy) and ART regimen failure;
- HIV DR testing strategy should be linked to early and late switching strategies;
- Options and indications (clinical situations) for HIV DR testing after 1<sup>st</sup> line ART regimen failure (e.i. after which regimens testing is indicated, when empirical approach to the regimen switching is not applicable) should be presented;

- HIV DR testing is recommended after 2<sup>nd</sup> line ART regimen failure but it is also desirable in case of initial 1<sup>st</sup> line ART regimen failure;
- It is feasible to anticipate empirical approach as well which is acceptable in case of early regimen switching but aim at implementing and scaling up HIV DR testing;
- It is feasible to keep to “hierarchy” of options (from maximal standard to average and minimal depending on resources available in the country);
- Viral failure is recommended to be established based on detectable VL (exceeding test-kit sensitivity threshold);
- It is necessary to describe algorithm of actions tactics in case of detectable VL (incl. recommendations regarding repeated testing, adherence support);
- There is a need to anticipate different options depending on availability of different testing methods (incl. HIV DR testing), access to ARVs in the guidelines.

**3<sup>rd</sup> line ART regimens:** *HIV DR testing in case of 2<sup>nd</sup> line ART regimen failure – current practice. To assess level of difficulty in implementing and stable realization (risk of increasing costs, decreasing current ART coverage and ART interruptions, potential negative consequences for ART scaling up, other risks):*

- Selection of regimens is provided individually based on HIV DR testing results;
- It is feasible to present more detailed recommendations regarding selection of ARVs for 3<sup>rd</sup> line ART regimens in the guidelines.

## 5.2. Protocol 4: Management of Tuberculosis and HIV Coinfection

**Structure of the protocol** (*convenience for use, acceptability of the chapters, modification of the chapters etc.*):

- Chapter on MDR/XDR TB is to be added;
- Key issues on infection control as a component of “Three Is” principle from the point of patient management are to be added;
- Other chapters are relevant.

### **Preventive treatment of latent TB infection with isoniazid (IPT):**

- *Is the coverage among PLWH adequate?*
- *Which barriers exist? Does limited access to tuberculin skin test create a barrier to IPT?*
- *Switching to 36 month course: is this step feasible taking into consideration TB prevalence, risk of adverse events, increasing costs and other factors?*
- Coverage of PLWH with IPT is not adequate in many countries of the region though formally it is implemented;
- Adherence of patients to IPT is insufficient;
- Problems of collaboration between TB and HIV services, organization of prevention delivery as programmatic issues are relevant;
- Inclusion of recommendations regarding prolongation of IPT course over 6 months, according to the opinion of the meeting participants, is not feasible and is not supported by sufficient evidence relevant for the European Region.

There is a need to specify recommendations on the following issues using existing evidence and results of additional technical and expert consultations:

- Detailed and clear algorithm to exclude active TB diagnosis in patients and criteria for IPT administration?



- Algorithm of actions in case of recurring contact after completion of 6-months prevention course?
- Frequency of prevention courses?
- Duration of IPT course? Prolongation of the course over 6 months?
- Evidence? (Available evidence refers predominantly to the African region. Are there sufficient evidence for the European Region to support corresponding recommendations?)
- Use of isoniazid in conditions of drug resistance spreading?
- Actions in case of IPT course interruption?
- Preventive (relapse preventive) treatment in HIV-positive patients (secondary prophylaxis)?

**TB therapy: selection of regimens for previously TB-treated patients:**

- *Assess need for using standard regimens with 1<sup>st</sup> line TB drugs for TB-treated patients (in case of relapse and after default) taking into consideration access to methods of rapid molecular DST and spreading of MDR-TB;*
- *Is there a need to include description of main approaches to forming individual TB treatment regimens in the guidelines?*
- «Gold standard» according to the WHO recommendations anticipates using results of smear culture test with DST for the regimens selection;
- In previously TB-treated patients with relapse or after default DST is to be performed and standard treatment course according to 2<sup>nd</sup> category prescribed. In case of laboratory confirmed MDR-TB switching to 2<sup>nd</sup> line regimen is indicated;
- Previously treated-TB patients after treatment failure are to be transferred to 4<sup>th</sup> category and be treated with 2<sup>nd</sup> line TB drugs;
- Results of DST should be taken into consideration and the guidelines are to be supplemented with recommendations regarding sensitivity testing.

**TB treatment and MDR/XDR-TB: *treatment regimens with 2<sup>nd</sup> line TB drugs:***

- It is feasible to provide translation of updated global WHO guidelines on MDR/XDR-TB, which are to be launched in 2011, into Russian for its use in the WHO European Region;
- Main clinical decisions are feasible to be included into HIV/TB guidelines and for other issues reference to MDR/XDR-TB guidelines should be provided;
- Peculiarities of monitoring of patients with MDR/XDR-TB, drug interactions etc. are to be covered in MDR/XDR-TB chapter.

**Early ART initiation (*within 2-8 weeks after initiation of TB therapy*) to all PLWH with active TB irrespective of CD4 count: *assess level of difficulties for implementation:***

- There is a need for more detailed explanation of recommendation regarding early ART initiation in patients with active TB after initiation of TB therapy: conditions for the recommendation following are to be specified in view of available evidence (e.g. good tolerability, efficiency of TB therapy);
- There is a need to specify feasibility of early ART initiation in cases when immunological assessment is available for patients with high CD4 count in view of existing evidence;
- It is recommended to justify ART initiation at the background of initial phase of TB treatment;
- It is feasible to specify ART regimens for children based on updated recommendations;
- ART is a key aspect of the patients' management though it is not less important than efficient TB therapy.

**Additional issues which are to be specified:**

- Provision of access to rifabutine;

- Rifampicin versus rifabutin as a drug of choice;
- Duration of TB treatment course in HIV-positive patients in view of existing evidence;
- DOT may be provided not only by medical worker but also by other service providers.

### 5.3. *Protocol 7: Management of Hepatitis B and HIV Coinfection*

#### **Structure of the guidelines:**

- The structure is feasible and do not require changing;
- There is a need to consider adding a chapter on hepatitis B vaccination for PLWH and MARPs.

#### **Screening and diagnostic of hepatitis B in PLWH:**

- Screening is available in the countries of the region;
- Specific diagnostic is provided to assess indications to treatment.

#### **Criteria of hepatitis B treatment initiation and drugs which are in use:**

- There is a need to specify indications to hepatitis B treatment in HIV-infected patients;
- It is feasible to cover aspects of using other hepatitis B drugs in cases when indications to ART are absent taking into consideration available evidence.

#### **Access to TDF, FTC for hepatitis B/HIV coinfection treatment:**

- TDF is not available in Kazakhstan and Kyrgyzstan;
- Availability is not stable in Uzbekistan;
- TDF is available and in use in other countries of the region.

### 5.4. *Protocol 10: Prevention of HIV Transmission from HIV-infected Mothers to Their Infants*

#### **Structure of the protocol** (*convenience for use, acceptability of the chapters, modification of the chapters etc.*):

- During discussion it was suggested to change the guidelines title from “Prevention of HIV Transmission from HIV-infected Mother to Their Infants” to “Antiretroviral Drugs for Treating Pregnant Women and Prevention HIV Infection in Infants” similarly to the title of the new WHO global recommendations on PMTCT. It will stress importance of maintaining health of HIV-positive woman who will take care of growth and development of her child;
- Current structure of the guidelines for the WHO European Region was considered satisfactory by experts. Importance of saving clinical scenarios was emphasized;
- It was suggested to extract organizational and methodological information to separate guidelines on “Principles of Care Delivery to Pregnant HIV-positive Women”. This will allow strengthening clinical scope of the guidelines, maximize their value for health care providers, including infectologists, obstetric and gynecologists, midwives and nurses. Organizational and methodological guidelines will in their turn define principles of care delivery to HIV-positive pregnant women, specify target groups of women who need care and outline order of care delivery. For example, imprisoned women and female IDUs remain groups inadequately covered with prophylaxis and need special attention;
- It was recommended to insert additions regarding strength of recommendations (low, moderate, high);
- Among scenarios which are not reflected in the current guidelines there are PMTCT in case of preterm delivery and management of preterm infants. There is also a need to include scenario of labour management in case of premature rupture of fetal membranes;

- Recommendation to include information in the form of additional schemes and algorithms (flowcharts) which could be used for printing of posters, booklets, leaflets etc. was expressed.

**Criteria of prophylaxis initiation in pregnant women who do not need ART for their own health:**

- It is recommended to stress importance of timely assessment of the WHO clinical stage, early CD4 count and VL testing. It is recommended to determine VL at early stage of gestation with subsequent assessment at 22-24 weeks;
- VL test result is to be used to determine time of ARV prophylaxis initiation in pregnant women who do not need ART for their own health (e.g. in case when VL is of > 100,000 copies/ml ARV prophylaxis should be initiated right after completion of the first trimester of pregnancy or earlier).

**Time of ARV prophylaxis initiation:**

- Regarding time of ARV prophylaxis initiation in pregnant women who do not need ART for their own health a request was expressed to maintain current recommendations of the clinical guidelines for the WHO European Region of 24-28 weeks, taking into consideration that earlier ARV prophylaxis initiation would increase infant exposure to ARVs, increase costs of prophylaxis though will not significantly improve its outcomes;
- It was noted that majority of countries did not face problems in covering women with antenatal observation with the exclusion of vulnerable groups of population: IDUs, migrants. For these groups earlier ARV prophylaxis initiation may be recommended starting from 14 weeks of gestation.

**Use of monoprophyllaxis in pregnant women:**

- Use of triple drug regimens and withdrawal from zidovudine monoprophyllaxis were recommended for PMTCT;
- If laboratory assessment can not be performed it is feasible to prescribe the safest and the most efficient regimen.

**ART regimens for pregnant women, ARV prophylaxis in infants:** *Comments by scenarios of the clinical protocols for the WHO European Region 2007:*

Scenario 1.1. HIV-positive pregnant women who do not need ART for their own health:

- It was suggested to completely withdraw from use of zidovudine monotherapy as a prophylaxis scenario given that all countries have access to ART;
- It was recommended to use AZT/3TC/LPV/r as a preferred ART regimen taking into consideration the most significant experience of its use and convenience of drug intake whereas use AZT/3TC/SQV/r as an alternative regimen, or other boosted PI;
- It was recommended to provide prophylaxis to infant until 1 month of age using syrup of zidovudine.

Scenario 1.2. HIV-positive pregnant women who need ART for their own health:

- It was suggested to revise indications for ART initiation recommending to start ART for all pregnant women with CD4 count of  $\leq 350$  cells/mm<sup>3</sup>;
- As an alternative treatment option AZT/3TC/NVP regimen is to be indicated.

Scenario 1.3. HIV-positive pregnant women who started ART before pregnancy:

- It was suggested to continue taking ARVs;
- In case if woman is taking efavirenz she should potential negative influence on fetus in the first trimester of pregnancy is to be discussed with her.

Scenario 1.4. HIV-positive pregnant women who present at labour:

- Previous scenario of the clinical protocol for the WHO European Region is to be maintained;
- Using triple ARVs regimen (AZT/3TC+NVP) in infants is to be considered.

**Use of cesarean section:**

- Previous recommendations of the clinical protocol for the WHO European Region 2007 should be preserved in the updated version of the guidelines;
- Planned (pre-labour) cesarean section should be anticipated for all women with VL of > 1000 copies/ml or lack of access to VL testing;
- Recommendations for cases of preterm labour or premature rupture of fetal membranes are to be provided.

**Selection of ARV prophylaxis depending on infant feeding option:**

- It is recommended to supplement this chapter with the new WHO global recommendations of 2010 regarding feeding of infants born to HIV-positive mothers;
- At the same time for the eastern European countries priority and importance of avoidance of breastfeeding should be stressed as well as need for providing replacement feeding for infants;
- As an alternative (in cases when mother chooses breastfeeding) it is important to continue ARV prophylaxis which was started during pregnancy for the whole period of breastfeeding.

**Laboratory monitoring of HIV-positive pregnant women:**

- It was recommended to add table indicating time and frequency of HIV-infection laboratory monitoring in pregnant women, incl. CD4 count and VL testing.

**Prevention and treatment of TB in HIV-positive pregnant women:**

- It was recommended to add short chapter on clinical management of HIV/TB coinfection in pregnant women.

**Other recommendations:**

- It was recommended to preserve recommendation on performing HIV PCR test within first days after birth for infants born to women of MARPs: IDUs, mothers who did not receive ARVs, preterm infants;
- It was suggested to add short chapter on clinical management of HIV/HBV and HCV coinfection in pregnant women;
- As well it was recommended to cover issues of clinical tactics in management of pregnant women with PMTCT history in case of subsequent pregnancy.

## **5.5. Protocol 11: Paediatric HIV & AIDS Treatment and Care**

**Structure of the protocol** (*convenience for use, acceptability of the chapters, modification of the chapters etc.*):

- It was suggested to preserve the current structure of the protocol.

**Early HIV-infection diagnostic in infants younger than 6-8 weeks of age:**

- It was recommended to extend chapter on early HIV-infection diagnostic in infants through adding of HIV DNA PCR testing on whole blood or DBS, HIV RNA PCR on plasma or DBS, Up24 Ag testing.

**Immunological and clinical criteria of ART initiation, time of ART initiation in children:**

- It is necessary to revise immunological and clinical indications and time of ART initiation in infants and children in accordance to the global WHO recommendations 2010;
- Issue of ART initiation in infants of < 1 year of age needs to be clarified and duration of ART in children after its early initiation should be specified;
- Option of ART initiation in children older than 2 years of age with the WHO clinical stage 2, CD4 count of >25% and high VL is to be considered;
- Clear criteria (clinical and immunological) of ART failure and regimen switching in case of limited access to VL testing are to be developed.

**ART regimens in infants and children:**

- Regimens based on ABC and 3TC are preferred options for ART initiation in children;
- It should be recommended not to combine ABC and NVP at the treatment initiation due to similar profile of adverse events, difficulties in differential diagnostic and need to substitute two drugs at once if adverse events emerge;
- For Lpv/rtv possibility of its concomitant use with ABC is to be indicated;
- It should be recommended to withdraw from d4T use in children as a drug of choice;
- Issue of 4-drugs ART regimens use is to be considered for children younger than 1 year of age with very high VL.

**Prevention and treatment of hepatitis B and C in children:**

- It was recommended to consider option of TDF administering to children of younger age with viral hepatitis coinfection;
- Issue of hepatitis C treatment using pegylated interferon and ribavirine in children is to be considered.

**Prevention and treatment of TB in children:**

- There is a need to develop and include in the protocol issues of TB diagnostic, TB treatment regimens for children, MDR-TB treatment regimens, concomitant use of TB and ART regimens (in particular in case of combining rifampicin and EFV), as well as issue of TB prevention in infants born to HIV-positive mothers.

## **6. Key recommendations of the meeting**

**General recommendations:**

- To anticipate development of both more detailed clinical guidelines and brief protocols (algorithms) of treatment for the WHO European Region;
- To categorize recommendations to preferred and alternative as well as those which may be used when other options (including due to staffing issues) are not available;
- To revise criteria of quality of evidence for those recommendations of the global WHO guidelines for which new evidence have emerged in the period of 2007-2009 and provide additional systematic review of evidence, define criteria of quality of evidence and strength of recommendations for those issues which are not covered by the global guidelines but will be included into recommendations for the WHO European Region.

## **Recommendations to separate protocols/guidelines**

### **1. Protocol 1: Patient evaluation and antiretroviral treatment for adults and adolescents**

- To stress need for providing laboratory assessment for CD4 count and VL before ART initiation and recommend considering VL as an additional to clinical and immunological criteria of treatment initiation;
- To include clear recommendations on stavudine use in particular groups of patients for whom use of other NRTIs is not possible, define indications and duration of its use;
- To reflect strategy of withdrawal from d4T for adult patients in the guidelines and stress need for ensuring access to tenofovir in the countries where it is still limited;
- To provide definition and interpretation of early and late ART regimen switching strategies in the guidelines;
- To include criteria of primary inefficacy and failure of ART regimen;
- To recommend using of detectable (i.e. exceeding test-kit sensitivity threshold) VL as a treatment failure criteria and provide detailed algorithm of actions in case of detectable VL;
- To reflect linkage between HIV DR testing strategy to early and late ART switching strategies;
- To define feasibility and indications for HIV DR testing in case of 1<sup>st</sup> line ART regimen failure, 2<sup>nd</sup> line ART regimen failure. To include recommendations on using empiric approach to the regimen switching in cases when resistance testing is not available. Thus it is recommended to anticipate different options for patients management in case of treatment failure depending on access to laboratory assessment;
- To recommend individual designing of 3<sup>rd</sup> line ART regimens based on DR testing results and provide more detailed recommendations on selecting ARVs for 3<sup>rd</sup> line treatment regimens in the guidelines.

### **2. Protocol 4: Management of Tuberculosis and HIV Coinfection**

- To supplement the protocol with a chapter on diagnostic and treatment of MDR/XDR-TB in HIV-positive patients including key clinical issues and decisions as well as references to the global MDR/XDR-TB guidelines for more detailed information on other aspects;
- To supplement the protocol with a chapter on TB infection control;
- To include detailed recommendations on the following aspects of IPT for latent TB infection: algorithm of active TB diagnosis exclusion and criteria of IPT initiation; algorithm of actions in case of subsequent TB exposure after completion of 6-months IPT; frequency and duration of IPT; use of isoniazid at the background of spread resistance; actions in case of treatment default; preventive (relapse-preventive) TB treatment in HIV-positive patients (secondary prophylaxis). Additional technical consultations may be required;
- To include and justify based on available evidence recommendations regarding selection of TB treatment regimens in previously TB-treated patients, particularly in case of relapse and after default, indications to 2<sup>nd</sup> line treatment regimens and DST;
- To provide more detailed explanation of recommendation regarding early ART initiation in patients with active TB after initiation of TB therapy, in particular to specify conditions for ART initiation from the point of TB therapy efficacy and tolerability.

### **3. Protocol 7: Management of Hepatitis B and HIV Coinfection**

- To consider including chapter on hepatitis B vaccination for PLWH and risk groups in the guidelines;
- To specify indications to hepatitis B treatment in HIV-positive patients;
- To include information regarding use of other medications and hepatitis B treatment regimens? than ARVs with dual activity, which may be used in cases when indications to ART are absent.

#### **4. Protocol 10: Prevention of HIV Transmission from HIV-infected Mothers to Their Infants**

- To change the guidelines title from “Prevention of HIV Transmission from HIV-infected Mother to Their Infants” to “Antiretroviral Drugs for Treating Pregnant Women and Prevention HIV Infection in Infants”;
- To present organizational and methodological issues in a separate guidelines on “Principles of health care provision to pregnant women with HIV-infection”;
- To add scenario of PMTCT in case of preterm labour and recommendations on management of premature infants, as well as scenario of labour management in case of premature rupture of fetal membranes;
- To include recommendation for VL testing at early gestation stage and subsequently at 22-24 weeks of gestation and clarify using of VL test results use to define time for ARV prophylaxis initiation in pregnant women who do not need ART for their own health;
- To revise indications for ART initiation in pregnant women and recommend treatment initiation in all women with CD4 count of  $\leq 350$  cells/mm<sup>3</sup> irrespective of the clinical symptoms;
- To preserve recommendation of the clinical protocol for the WHO European Region regarding ARV prophylaxis initiation in pregnant women who do not need ART for their own health at 22-24 weeks of gestation although recommend earlier ARV prophylaxis initiation at 14 weeks of gestation for women of MARPs: IDUs, illegal migrants etc.;
- To recommend using triple ARV regimen for PMTCT and withdrawal from monotherapy use;
- To recommend AZT/3TC+LPV/r as preferred ART regimen for HIV-positive pregnant women who do not need ART for their own health and AZT/3TC+SQV/r as an alternative one;
- To recommend AZT/3TC+NVP as a regimen of choice for HIV-positive pregnant women who need ART for their own health;
- To recommend continuing ART for HIV-positive pregnant women who started ART before pregnancy but consider potential negative impact of efavirenz on fetus development in first trimester of pregnancy;
- To preserve current scenario for HIV-positive pregnant women who present at labour but consider using triple ARVs regimen in infant;
- To preserve recommendations of the WHO European Region clinical protocol regarding provision of cesarean section, to anticipate pre-labour cesarean section for all women with VL of  $> 1000$  copies/ml or when VL testing is not available;
- To stress importance of avoiding breastfeeding and need to ensure replacement feeding for infants but include recommendations on breastfeeding as an alternative option for exceptional cases when use of replacement feeding is not possible provided that ART is administered to a woman and/or an infant according to the corresponding recommendations of the global WHO guidelines 2010;
- To supplement the protocol with a table indicating time and frequency of HIV-infection laboratory monitoring in pregnant women;

- To preserve recommendation on PCR HIV provision within first days after birth for infants born to mothers of MARPs: female IDUs, mothers who did not receive ARVs, preterm infants etc.;
- To add brief chapters on management of pregnant women with coinfections HIV/TB and HIV/viral hepatitis;
- To cover issues of clinical management of women with PMTCT history in case of subsequent pregnancy;
- To add reference to Clinical protocol for the WHO European Region “Prevention of HIV Transmission from HIV-infected Mothers to Their Infants”, 2007, which covers issues of family planning and contraception in HIV-positive women.

#### **5. Protocol 11: Paediatric HIV & AIDS Treatment and Care**

- To extend chapter on early HIV-infection diagnostic in infants through adding of recommendations on DNA HIV PCR testing on whole blood or DBS; RNA HIV PCR testing on plasma or DBS; Up24 Ag testing;
- To revise immunological and clinical indications and time of ART initiation in infants and children in accordance to the global WHO recommendations 2010 as well as provide detailed information regarding duration of ART in case of its early initiation, to consider option of ART initiation in children older than 2 years of age with the WHO clinical stage 2, CD4 count of >25% and high VL;
- To develop and provide clear criteria of ART failure and therapy switching in case of limited access to VL testing;
- To include ART regimens based on ABC and 3TC as preferred options for children but not recommend combining ABC with NVP due to similar toxicity profile and indicate possibility to combine ABC with LPV/r;
- To cover issues of potential use of tenofovir in children of younger age with viral hepatitis coinfection as well as hepatitis C treatment using pegylated interferons and ribavirine in children;
- To recommend withdrawal from stavudine use as drug of choice in children;
- To consider prescribing 4-drugs ART regimen in children younger than 1 year of age. with very high VL;
- To reflect issues of TB diagnostic and treatment in children, in particular of concomitant TB and ART treatment.



## 7. Annexes

### 7.1. Meeting agenda

Update of some HIV/AIDS clinical protocols for the WHO European Region WHO/UNICEF Technical Consultation		
Agenda Thursday, 07 October 2010		
Time	Session	Presenter
09:30 – 09:40	Introduction and welcome	Denis Broun, UNAIDS Irina Eramova, WHO Regional Office for Europe Ruslan Malyuta, UNICEF
09:40 – 09:50	Objectives of the meeting Logistic information	Irina Eramova, WHO Regional Office for Europe Ruslan Malyuta, UNICEF
09:50 – 10:10	WHO guidelines development process	Irina Eramova, WHO Regional Office for Europe
10:10 – 11:00	PMTCT, ART for children Questions, comments	Ruslan Malyuta, UNICEF
11:00 – 11:15	Coffee Break	
11:15 – 11:45	ART for adults, Management of HBV/HIV co- infection Questions, comments	Irina Eramova, WHO Regional Office for Europe
11:45 – 12:15	Management of TB/HIV co-infection Questions, comments	Gabit Ismailov, WHO Regional Office for Europe
12:15 – 13:00	Work in two working groups <ul style="list-style-type: none"> <li>• ART for adults, HBV/HIV, TB/HIV</li> </ul> PMTCT, ART for children	
13:00 – 14:00	Lunch	
14:00 – 15:30	Work in two working groups <ul style="list-style-type: none"> <li>• ART for adults, HBV/HIV, TB/HIV</li> <li>• PMTCT, ART for children</li> </ul>	
15:30 – 15:45	Coffee Break	
15:45 – 16:30	Presentations from the groups Questions, Discussion	

16:30 – 17:00	Summary Next steps	Ruslan Malyuta Irina Eramova
---------------	-----------------------	---------------------------------

## 7.2. *List of participants*

### LIST OF PARTICIPANTS

#### ARMENIA

Armen Mkrtchan,  
Head  
Treatment department  
National HIV/AIDS centre  
0040 Yerevan

Jackeline Khakobjan  
Physician  
Treatment department,  
National HIV/AIDS centre  
0040 Yerevan

#### AZERBAIJAN

Esmira Almamedova  
Deputy Director  
Republican HIV/AIDS centre  
1022 Baku

#### REPUBLIC OF BELARUS

Anna Vasilenko  
Assistant,  
Department of infectious diseases  
Belarus State Medical University  
220136 Minsk

Nikoalai Goloborodko  
Assistant,  
Department of infectious diseases  
and infections in children  
Belarussian Medical Academy  
Postgraduate education  
220013 Minsk

#### GEORGIA

Pati Gabunia  
Head,  
Patient Department for AIDS treatment  
Tbilisi

Lasha Tvaliashvili

Director  
Real People Real Vision  
Kodjori, Tbilisi

#### KAZAKHSTAN

Saule Doskazhaeva  
Head, Department of Infectious Diseases  
Almaty State Institute of  
Advanced Medical education  
Almaty

Natalia Petrova  
Professor, Department of Infectious Diseases  
Almaty State Institute of  
Advanced Medical education  
Almaty

#### KYRGYZSTAN

Ainura Kutmanova  
Head,  
Department of infectious diseases  
Kyrgyzstan State Medical Academy  
720000 Bishkek

Anarkul Sultanova  
Head, Treatment department  
National AIDs centre  
720040 Bishkek

Erkin Tostokov  
Physician, Treatment department  
National AIDs centre  
720040 Bishkek

#### REPUBLIC OF MOLDOVA

Igor Kilchevsky  
Chairman, PLWH league  
Kishinev

Svetlana Popovici  
Specialist, HIV/AIDS treatment  
National HIV/AIDS centre  
Kishinev

**RUSSIAN FEDERATION**

Larisa Afonina  
Deputy Head  
Republican Clinical City Hospital  
Ust-Izora  
196645 St. Petersburg  
Oleg Yurin  
Deputy Director  
Federal AIDS centre  
111123 Moscow

**TAJKISTAN**

Tatiana Madzitova  
Specialist  
Republican AIDS centre  
Dushanbe

Turakhon Sharipov  
Head of department  
City Infectious Diseases Hospital  
Dushanbe

**UKRAINE**

Svetlana Cherenko  
Head  
Committee on control of HIV/AIDS  
and other socially dangerous diseases  
Ministry of Health of Ukraine  
Kiev

Elena Eschenko  
Deputy Head  
Committee on control of HIV/AIDS  
and other socially dangerous diseases  
Ministry of Health of Ukraine  
Kiev

Svetlana Antonyak  
Head, HIV/AIDS department  
Research Institute of  
Epidemiology and infectious diseases  
named after L.V. Gromashevskij  
Ukrainian Academy of medical sciences  
Kiev

Svetlana Komar  
Head  
Clinic for treatment of HIV infected children  
NCSH "Okhmatdyt"  
01135 Kiev

Vladimir Kurpita

Executive Director  
All-Ukrainian Network of PLWH  
04071 Kiev

Natalia Nizova  
Director  
Ukrainian Center for  
Prevention and AIDS control  
Ministry of Health of Ukraine  
Kiev

Ljudmila Storozhuk  
Deputy director  
Ukrainian Center for  
Prevention and AIDS control  
Ministry of Health of Ukraine  
Kiev

Olga Nikolaeva  
Associate Professor of phthysiology  
National Academy of Medicine  
Postgraduate Education named after P.L. Shupik  
Kiev

**UZBEKISTAN**

Djamilja Usmanova  
Physician  
Republican HIV/AIDS centre  
100135 Tashkent

Kamila Fitikhova  
Coordinator  
NGO "Kalditgosh"  
100037 Tashkent

Mamlakat Shermukhamedova  
Obstetrician-gynecologist  
Republican HIV/AIDS centre  
Tashkent

**World Health Organization (WHO)**

**WHO, Ukraine**

Iurii Kobyshecha  
Coordinator a.i  
Department of infectious diseases

Anna Bobrova  
HIV/AIDS/STI treatment specialist

**WHO Regional office for Europe**

Irina Eramova  
Senior Medical Officer  
HIV/AIDS, STIs and Viral Hepatitis Programme  
E-mail: ier@euro.who.int

Gabit Ismailov  
Medical specialist  
TB control programme

**UNICEF, Ukraine**

Tatiana Tarasova  
HIV/AIDS specialist

**UNICEF, Regional office**

Ruslan Malyuta  
Programme specialist  
HIV/AIDS, health and youth development

Nina Ferencic  
Senior Advisor, HIV/AIDS for CEE and CIS

**UNAIDS**

Denis Bruun  
Regional Director  
Joint United Nations Programme on HIV/AIDS (UNAIDS)  
for Europe and central Asia

### 7.3. *Questions for the working groups*

#### **Group 1: ART for adults; TB/HIV, HBV/HIV coinfections**

##### Protocol 1: ART for adults

- **Structure of the protocol** (convenience for use, acceptability of the chapters, modification of the chapters etc.);
- **ART initiation criteria – current practice. Increasing CD4 count threshold as ART initiation criteria to 350 cells/mm<sup>3</sup>:** to assess difficulties in implementing and sustainable realization (risk of increasing costs, decreasing current ART coverage indicators, potential negative consequences for ART scaling up and other risks);
- **Prescribing stavudine – current practice, potential for complete withdrawal:** to assess level of difficulty in implementing and potential sustainable realization;
- **Criteria for ART switching** (initiation of 2<sup>nd</sup> line ART regimen): current practice (early and late ART switching). Early switching: to assess level of difficulty in implementing and stable realization (risk of increasing costs, decreasing current ART coverage and ART interruptions, potential negative consequences for ART scaling up, other risks);
- **3<sup>rd</sup> line ART regimens:** HIV DR testing in case of 2<sup>nd</sup> line ART regimen failure – current practice. To assess level of difficulty in implementing and stable realization (risk of increasing costs, decreasing current ART coverage and ART interruptions, potential negative consequences for ART scaling up, other risks).

Are there any other issues which are not provided with answers by the guidelines or updated recommendations?

The data may be presented in the table format by countries or groups of countries if the answers vary.

##### Protocol 4: TB/HIV coinfection

- **Structure of the protocol** (convenience for use, acceptability of the chapters, modification of the chapters etc.);
- **Preventive treatment of latent TB infection with isoniazid (IPT):**
  - Is the coverage among PLWH adequate?
  - Which barriers exist? Does limited access to tuberculin skin test create a barrier to IPT?
  - Switching to 36 month course: is this step feasible taking into consideration TB prevalence, risk of adverse events, increasing costs and other factors?
- **TB therapy: selection of regimens for previously TB-treated patients:**
  - Assess need for using standard regimens with 1<sup>st</sup> line TB drugs for TB-treated patients (in case of relapse and after default) taking into consideration access to methods of rapid molecular DST and spreading of MDR-TB;
  - Is there a need to include description of main approaches to forming individual TB treatment regimens in the guidelines?
- **TB treatment and MDR/XDR-TB: treatment regimens with 2nd line TB drugs;**
- **Early ART initiation** (within 2-8 weeks after initiation of TB therapy) to all PLWH with active TB irrespective of CD4 count: assess level of difficulties for implementation.

Are there any other issues which are not provided with answers by the guidelines or updated recommendations?

The data may be presented in the table format by countries or groups of countries if the answers vary.

Protocol 7: Hepatitis B/HIV coinfection

- **Structure of the guidelines;**
- **Screening and diagnostic of hepatitis B in PLWH;**
- **Criteria of hepatitis B treatment initiation and drugs which are in use;**
- **Access to TDF, FTC for hepatitis B/HIV coinfection treatment.**

Are there any other issues which are not provided with answers by the guidelines or updated recommendations?

The data may be presented in the table format by countries or groups of countries if the answers vary.

**Group 2: PMTCT, ART in children**

Protocol 10: PMTCT

- **Structure of the protocol** (convenience for use, acceptability of the chapters, modification of the chapters etc.);
- **Criteria of prophylaxis initiation in pregnant women who do not need ART for their own health;**
- **Time of ARV prophylaxis initiation;**
- **Use of mono-prophylaxis in pregnant women;**
- **ART regimens for pregnant women, ARV prevention in infants;**
- **Use of cesarean section;**
- **ARV prophylaxis depending on infant feeding option;**
- **Laboratory monitoring of HIV-positive pregnant women;**
- **Prophylaxis and treatment of TB in pregnant women;**
- **Other recommendations.**

Are there any other issues which are not provided with answers by the guidelines or updated recommendations?

The data may be presented in the table format by countries or groups of countries if the answers vary.

Protocol 11: ART in children

- **Structure of the protocol** (convenience for use, acceptability of the chapters, modification of the chapters etc.);
- **Early HIV-infection diagnostic in infants younger than 6-8 weeks of age;**
- **Immunological and clinical criteria for ART initiation, time of ART initiation in children;**
- **ART regimens in infants and children;**
- **Prevention and treatment of hepatitis B and C in children;**
- **Prevention and treatment of TB in children;**

- **Adherence support in children;**
- **Transition of the treatment from children to adolescent age.**

Are there any other issues which are not provided with answers by the guidelines or updated recommendations?

The data may be presented in the table format by countries or groups of countries if the answers vary.

## 8. References

1. Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Recommendations for a public health approach. WHO, 2010 revision.
2. Antiretroviral Therapy for HIV Infection in Adults and Adolescents. Recommendations for a public health approach. WHO, 2010 revision.
3. Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a public health approach. WHO, 2010 revision.
4. “ART failure and strategies for switching ART regimens in the WHO European Region”, Report of the WHO expert consultation, Copenhagen, 7 December 2007.
5. HIV and Infant Feeding. Revised Principles and Recommendations. Rapid Advice. WHO, 2009.
6. Rapid advice. Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. WHO, November 2009. Revised June 2010.
7. “ART failure and strategies for switching ART regimens in the WHO European Region”, Report of the WHO expert consultation, Copenhagen, 7 December 2007.
8. WHO Handbook for Guideline Development. WHO, March 2008.
9. Rapid advice. Antiretroviral Therapy for HIV infection in adults and adolescents, WHO, 2009..
10. HIV/AIDS Treatment and Care. Clinical protocols for the WHO European Region. WHO Regional Office for Europe, 2007.