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WHO Collaborating Centre on HIV and Viral Hepatitis

WHO mission on ART optimization in Belarus March 30-31, April 1, 2016

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List of Abbreviations

3TC	Lamivudin
ABC	Abacavir
ART	antiretroviral treatment
AZT	Zidovudin
ddI	Didanosin
DRV/r	Darunavir boosted by Ritonavir
EFV	Efavirenz
FTC	Emtricitabin
LPV/r	Lopinavir boosted by Ritonavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	Nevirapin
PLHIV	People Living with HIV
RAL	Raltegravir
TDF	Tenofovir

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1. Background

1.1 Introduction

In November 2014, WHO conducted a HIV Program Review in Belarus with the purpose to assist the country in developing a Concept Note for The Global Fund. The WHO mission identified several key priority areas for interventions and developed key recommendations to be considered for the National Strategic Plan on HIV and Concept Note (1).

During the preparation of the concept note on HIV to The Global Fund in 2015 some difficulties were experienced in quantifying the required ARV drugs and it was agreed to plan a review of this issue.

WHO and the Global Fund have extended a Cooperative Agreement on delivering technical assistance to the countries during Grant making process. Belarus has approached WHO Regional Office for Europe with a request for a technical assistance in optimization of ART regimens. There is a need for specific recommendations on reducing their number including ways on adequate substitution of the specific currently existing ART regimens in line with a public health approach to ART administration and WHO recommendations.

1.2 Objectives

The objective of this assignment was to develop a time-bound plan to further accelerate reduction and optimization of ART regimens in Belarus. The plan should clearly:

- Indicate number of new patients and ART regimens within The Global Fund grant time period
- Indicate number of current patients on ART who need their regimens to be optimized, suggest new ART regimens and a time schedule for switching to the WHO recommended regimens

1.3 Methodology

During the country mission the WHO expert worked closely with clinical experts of Minsk city infectious diseases hospital. It was discussed in depth why some PLHIV are receiving other ART regimens than the ones recommended by the WHO. The clinical experts of Minsk city infectious diseases hospitals outlined the treatment history, co-morbidity, toxicity profile and laboratory indicators for both adult and child patients that had led to these decisions. The WHO mission participants Dr Ristola and Dr Rusovich visited Infectious Disease Treatment Office in Soligorsk Central District Hospital and reviewed ART regimens there with the local staff.

The mission included also meetings at the Ministry of Health in the beginning and at the end of the mission. Preliminary goals for the first line ART recommendations and switching of ART regimens in order to harmonize the ART recommendations of Belarus with WHO guidelines were presented in debriefing at the Belarus Ministry of Health at the end of the mission to harmonize the national ART recommendations with the WHO guidelines (2,3).

2. The current epidemiological situation of HIV infection in Belarus

2.1 Epidemiological overview

As of February 1, 2016 in the Republic of Belarus there were registered cumulative 20 038 cases of HIV infection, the registered number of people living with HIV was 15 557. 1st of January 2014 in the Republic of Belarus - 15 711 cases of HIV-infections were registered, the number of people living with HIV were – 12 213. The increase in the number of PLHIV was 3341 in 25 months, thus the mean annual number of newly diagnosed HIV cases has been 1604 persons. The annual number of newly diagnosed PLHIV has been increasing in recent years (2012: 1223 persons, 2013: 1553 persons).

The main reported route of HIV transmission is sexual (January 2016: 72 %). Parental transmission of HIV amongst injecting drug users is also common (January 2016: 26 %)(4). Nosocomial transmission of HIV is extremely rare in Belarus; according to the Belarus experts there have been two known occasions of nosocomial transmission of HIV during the last 10 years.

Within Belarus, as of February 1, 2016, the prevalence of HIV is highest in the Gomel Region 448 persons per 100,000 inhabitants with 17 % increase from 2014, followed by Minsk region 164 per 10^5 with increase of 21 % from 2014, and City of Minsk 155 per 10^5 with an increase of 52 % from 2014 (4). The specialists at the Minsk City Infectious Disease hospital consider the increase in the use of illegal synthetic drugs as the main cause for the increased incidence of HIV infection in City of Minsk.

As of February 1, 2016, there were 294 children (275 natives of Belarus) diagnosed with HIV infection living in Belarus (4). The annual number of children aged 0 – 1 year diagnosed with HIV for the last three years has been 7, 3, and 7 in 2013, 2014, and 2015, respectively. The data for children >1 – 10 years old is not routinely collected.

2.2 Coverage of antiretroviral therapy in Belarus

According to national guidelines, the threshold for starting ART for adults is CD4 count below 350 cells per mm^3. However, ART is started earlier in some situations, e.g. PLHIV in a sero-discordant couple.

There were 7,388 PLHIV who received ART on December 31, 2015. Thus, the overall coverage of ART amongst the diagnosed PLHIV was 48 % in 2015.

There were 5 181 PLHIV who received ART in 2014. The number of PLHIV in Belarus was 12 213 of whom 42 % received antiretroviral therapy.

There were 235 children aged 0 – 18 years receiving ART in Belarus as of January 01, 2016. The epidemiological data for HIV-infected children was provided for 0 – 14 years, which were 294 children. It appears that ART coverage is higher among children than among adults, but it is not possible to calculate the exact coverage with the data available.

There were 6 568 (89 %) PLHIV on 1st line ART, 767 (10 %) PLHIV on 2nd line ART, and 53 (<1 %) PLHIV on 3rd line ART on December 31, 2015.

2.3 Production of antiretroviral drugs in Belarus

There is local production of antiretroviral drugs in Belarus. The aim of local production is to reduce the costs of antiretroviral drugs and to secure a constant supply of ARVs and to prevent stock-outs.

Currently AZT, AZT/3TC, EFV, NVP, TDF, TDF/FTC, ABC, DRV are produced locally in Belarus. National production covers 79 % of the overall treatment schemes. The fixed dose combination of TDF/FTC/EFV is currently procured through GF, but national production is being organized at present.

According to the national HIV experts there is a quality control starting from the stage of registration: Entry control during the process of delivery, monitoring of the production, control before shipment. There is also system of registration of adverse drug reactions.

2.4 Current antiretroviral regimens in Belarus

Paediatric regimens

Paediatric regimens for children 0 – 3 years include 4 regimens of which one is a second line regimen (see table in appendix 1). The regimens are in accordance with WHO recommendations, although only four of 31 children receive a regimen with lopinavir/r that would be a preferred regimen for this age group.

Paediatric regimens for children 4 – 10 years include 8 regimens for 87 children, of whom 11 are on a second line regimen. The regimens are in accordance with WHO recommendations, although only 26 of 107 children receive a regimen with efavirenz that is the preferred regimen for this age group. In addition there are two children with a regimen that includes only three nucleosides.

All children receive a nucleoside combination on either AZT+3TC (63 %) or ABC+3TC.

Regimens for adults

As of January 01, 2016 there were 14 ART regimens identified as first line regimens. These regimens included 6435 patients aged over 10 years (88 % PLHIV receiving ART). There were six first line regimens that do not have acceptable antiretroviral efficiency. There were 265 PLHIV receiving these regimens. Five of these regimens included only three nucleosides.

Nevirapine was used by 643 and lopinavir/r by 717 PLHIV in first line regimen.

There were 23 second line regimens of which three regimens did not have sufficient antireroviral activity.

There were not reported any patients on stavudine or didanosine. AZT was used by 4 412 PLHIV (61 % of PLHIV on ART).

Regional differences

The Gomel region had 23 ART regimens, which was the highest among the regions. There were 100 PLHIV on AZT+3TC+ABC in Gomel region. The region has the longest history and had the highest numbers of PLHIV who inject drugs, which may explain at least in part the situation.

The multitude of regimens was explained by local experts to be due partly to problems of availability of antiretrovirals and partly due to higher cost of tenofovir-containing regimens, e.g. annual cost of (AZT+3TC)+EFV is 300,24 US$ compared to (TDF/FTC)+EFV 664,44 US$. The annual cost of a one pill a day regimen of TDF/FTC/EFV is 1591,80 US$, because it is purchased as a brand drug through GF.

According to the national HIV experts the situation of ARV regimens in the Gomel region relates to overall big number of patients, high rate of treatment interruptions among them, relatively higher proportion of IDU to compare with the other regions, more prolonged history of ART prescription to compare with the other regions.

The infectious disease unit at Soligorsk Hospital provides a good example in keeping the number of ART regimens limited. There are 1 275 PLHIV in the encatchment area of the hospital and 600 are receiving ART. The proportion of those on ART with undetectable viral load was 78 %. The number of the regimens provided is 11.

2.5 Availability of viral load measurements to monitor ART

There was a national tender for the provision of laboratory kits for HIV viral load measurements. The Amplisense kit was chosen on basis of the tender. However, the company that made the winning offer of the Amplisense kits announced after the tender that the company is not capable to provide the Amplisense kits for the price agreed in the tender.

As a result HIV viral load has not been routinely available to monitor ART since November 2015. The Republican Scientific and Practical Center for Microbiology and Epidemiology has provided limited number of VL tests for special situations, e.g. pregnant women on ART.

2.6 National database on HIV care and ART

A database for HIV care and ART for was briefly demonstrated at Soligorsk Hospital by a clinical doctor. It was understood that the database is in a pilot phase.

3. Priority areas for optimization of ART in Belarus

3.1 Priority area 1: When to start ART

Currently the clinical protocol in Belarus recommends starting ART in patients with a CD4 count below 350 cells per mm^3. It is recommended that Belarus revises and updates the clinical protocols in accordance with 2015 WHO recommendation to initiate ART in everyone living with HIV at any CD4 cell count (2, 3, see also 4) although full implementation is not feasible at present the target should be to implement this fully by 2020.

Until this is fully implemented, prioritization should be given to start patients on ART with CD4 count below 350 cells per mm^3 , patients clinical symptoms and patients with special needs (e.g. with an HIV sero-negative spouse with coinfections TB/HIV, HepB/HIV or HepC/HIV, pregnant women and children).

Recommendations

- Revise and update national clinical protocols in accordance with 2015 WHO recommendation to initiate ART in everyone living with HIV at any CD4 cell count
- Until this is implemented fully, prioritization should be initiate ART for patients with CD4 count below 350 cells per mm^3, clinical symptoms and/or special needs (e.g. with an HIV sero-negative spouse with coinfections TB/HIV, HepB/HIV or HepC/HIV, pregnant women and children).

Target: Although full implementation of 'treat-all' is not feasible at present, the target should be to implement this fully by 2020.

3.2 Priority area 2: Scale-up of ART coverage

The number of PLHIV on ART in Belarus increased from 5 181 by the end of 2013 to 7 388 by the end of 2015. The enrolment of PLHIV to ART has to be accelerated. As mentioned, there are approximately 1 600 new cases of HIV infection diagnosed annually, which indicates that there will be about 22 000 PLHIV in Belarus by 2020.

This means that in 2020 Belarus should have 20 000 PLHIV on ART in order to fulfil the second of the 90 – 90 – 90 goals. To reach this goal, 2 800 PLHIV would need to start ART annually and by the end of 2017 Belarus should have 13 000 PLHIV on ART.

Recommendation

- The enrolment of PLHIV to ART has to be accelerated so that 2 800 additional PLHIV start ART annually

Target: In 2020 Belarus should have 20 000 PLHIV on ART in order to fulfil the second of the 90 – 90 – 90 goals

3.3 Priority area 3: What to start with

In Belarus there are currently 14 different 1st line regiments used for treating adult PLHIV (Table 1). WHO recommends to utilize one preferred 1st line regimen (3; see also appendix 1).

3.3.1 Optimization of choices of ART in adults already on 1st line ART

There are 6 568 adults currently on 1st line ART (Table 1). Approximately 1 in 4 are receiving the WHO's preferred 1st line regimen (TDF/FTC+EFV).

Table 1. ART composition at 1 January 2016 among adult PLHIV on 1st line treatment

1st line ART adults (>10 years)	Percentage of patients 01.01.2016
6 568 patients	89 % of all PLHIV on ART
TDF/FTC/EFV (WHO preferred 1st line regimen)	**24 % (1 552 PLHIV, includes 342 on TDF+3TC+EFV)**
TDF/FTC + LPV/r (intolerant to EFV due to CNS side effects)	none
AZT + 3TC + LPV/r	none
AZT/3TC + EFV	43 % (2847)
AZT/3TC + NVP	8 % (534)
ABC/3TC + EFV	6 % (362)
TDF/FTC + NVP	2 % (148)
ABC/3TC + NVP	9 % (616)
2 NRTI + LPV/r	11% (717)
Regimens with three nucleoside analogues	3 % (178)

Based on WHO recommendations and existing scientific evidence it would be medically safe to switch the composition of ART for a large majority of the remaining 3/4 of adult patients in order for more patients to receive the preferred regimen. Based on the distribution of combinations used, three strategies for switching are proposed (Table 2).

Table 2. Drug switched considered as part of optimisation of 1st line ART

• **AZT to TDF**
• **ABC to TDF**
• **LPV*/r to either ATV/r, EFV or NVP**

**Reasons why some first line patients receive LPV/r are diverse: Teratogenic concerns with use of EFV; Prior treatment-limiting toxicity to EFV; Patient choice; Physician choice; Prior limited access to EFV*

The suggested switches should be feasible for most patients (likely 80-90%) and this would result in substantial cost savings. Average cost per patient for one year of treatment can possibly be reduced to 120-140 US$ per patient per year if optimization as described in table 2 is implemented. The financial surplus could be channelled towards providing ART to more PLHIV and possibly attract additional international support as such optimization is a prerequisite for many international donors including the Global Fund.

In case Belarus decides to implement a switching strategy a proposal has been outlined for how to switch patients to other agents as part of process to optimise ART programme in Belarus, how patients can be instructed and the recommended HIV RNA monitoring around the time of the switch (see Table 3).

Table 3. Proposal for how to switch patients using Zidovudine, abacavir, and LPV/r-based regimens as part of 1st line ART to other regimens

Other drug: reason for being on this	Proposed drug to switch to	Need for HIV RNA monitoring post-switch (pre-switch relevant)	Comments
ZDV: preferred choice at the time	TDF	Not necessary but can be done	TDF is a safer drug than ZDV (less risk of anaemia and lipoatrophy)
ZDV: current severe kidney impairment	Stay on ZDV or switch to ABC	Not necessary but can be done	TDF may further impair kidney function
ABC: preferred choice at the time	TDF	Not necessary but can be done	TDF is a cheaper and probably more effective and safer drug than ABC
ABC: current severe kidney impairment	Stay on ABC or switch to ZDV	Not necessary but can be done	TDF may further impair kidney function
LPV/r: Teratogenic concerns with use of EFV	EFV*	Yes (prioritised if earlier use of EFV or NVP)	Current evidence does not suggest that this concern is relevant to humans
LPV/r: Prior treatment-limiting toxicity to EFV	NVP**, ATV/r*** or EFV*	Yes if switching to either one of the two NNRTI's (prioritised if earlier use of EFV)	Choice of drug to switch to depends on circumstances when original switch was done (if well documented, EFV should be avoided; if not EFV may be considered); drug to possible switch to depends on which drugs national programme is focusing on
LPV/r: Prior limited access to EFV	EFV*	Yes (prioritised if earlier use of EFV or NVP)	Reason no longer relevant
LPV/r: prior switch from nelfinavir (the preferred PI/r) at the time	EFV*	Yes (prioritised if earlier use of EFV or NVP)	Switching from one drug call to another with lower genetic barrier is safe if patient remains adherent
LPV/r: Currently having accepted contraindications to using EFV	NVP** or ATV/r***		Recognised contraindications to EFVs; drug to possible switch to depends on which drugs national programme is focusing on
LPV/r: current using methadone	EFV*	Yes (prioritised if earlier use of EFV or NVP)	EFV and methadone can be safely co-administrated
LPV/r: Patient	EFV*	Yes (prioritised if	Patients are to be reassured by their

choice (other than above)		earlier use of EFV)	health care professionals that EFV is a safe drug
LPV/r: Physician choice (other than above)	EFV*		Health care professionals are to be reassured that EFV is a safe drug when prescribed under the correct medical conditions*
	TDF/FTC fixed dose combination with LPV/r		**For PLHIV for unable to take TDF/FTC/EFV for central nervous system side effect**
	AZT + 3TC + LPV/r (AZT and 3TC as separate pills)		**The second alternative for PLHIV with renal problems. AZT and LPV/r can be used with standard doses until CreaCl is 10 ml/s and with dose reductions 3TC can be also used until CreaCl is 10 ml/s.**

**: Patients should be informed prior to the switch about possible adverse drug reactions of EFV and that these usually diminish within days or a few weeks; if the patient experiences these adverse effects he or she should continue to take the drug until instructed otherwise in consultation with ART centre.*
***: Patients should be informed to contact ART centre in case of rash and liver toxicity; these toxicities are reduced for persons with higher CD4 counts if HIV RNA is suppressed at time of switch.*
****: Patients should be informed to contact ART centre if icteric sclerae is cosmetically debilitating; this manifestation is not health threatening.*

It is recommended that the use of zidovudine is reduced, because zidovudine causes lipoatrophy when it is used for several years. Furthermore, zidovudine does not allow for one daily dose. Zidovudine should be replaced in the first place by tenofovir. However, the price Belarus pays for tenofovir containing regimens is two times more expensive than that of zidovudine containing regimens. Starting domestic manufacturing of the WHO recommended ARVs in fixed dose tablets may be a strategy to combat the current price of tenofovir in fixed dose combinations tablets.

Dolutegravir is needed for the third line in antiretroviral therapy and to avoid drug-to-drug interactions in PLHIV with other therapies (e.g. tuberculosis). It is important to continue negotiations through the global programs to make darunavir available at a more reasonable price in Belarus. The aim should be to limit the number of protease inhibitors used in Belarus to two (LPV/r and DRV/r).

Recommendations

- Reduce the number of first line antiretroviral therapies from 16 to 10 as quickly as possible taking into account the need for national expert consultations, and procurement and logistics affecting antiretroviral drugs
- Reduce the number of second and third line antiretroviral therapies from 24 to 18 as quickly as possible taking into account the need for national expert consultations, and procurement and logistics affecting antiretroviral drugs
- Develop a strategy that will result in switches to the WHO recommended 1st line ART for a substantial % of patients currently on other 1st line ART combinations. This strategy should have at least three components:

- Institute post-graduate training of health care professionals to ensure that this community is supporting the strategy.
- Make a decision on which drugs in addition to WHO preferred 1st line ART Belarus will be prioritised for procurement – this depends in part on price of the drug.
- Follow recommendations as outlined in table 3

- Consider asking WHO to review strategy document prior to implementation.
- Ensure domestic manufacturing of the WHO recommended ARVs in the FDC tablet: TDF/FTC/EFV
- Secondly, ensure domestic manufacturing of the WHO recommended ARVs in the FDC tablet: TDF/FTC

Target: By the end of 2018 are 90% of all patients on standard WHO 1st line ART regimen (TDF/FTC/EFV)

3.3.2 Optimization of choices of 1st line ART for children

Currently 3 different 1st line regiments are used for treating children aged 0-3 years with HIV infection in Belarus (see table in Annex 1) – none of them is 1st line regimen ABC+3TC+LPV/r which WHO recommends.

For children aged 4-10 with HIV infection there are currently used 7 ART regimens in Belarus, and only 10% of the children are receiving the WHO's preferred 1st line regimen (ABC+3TC+EFV).

As part of implementing this ART optimization, it is recommended to make HLA-B5701 testing available at least for children in order to facilitate switch from zidovudine to abacavir to allow well tolerated ART regimens to be easily available for children.

Moreover, WHO recommendations that antiretroviral therapies for children <10 years always are reported separately from therapies for children ≥10 years, adolescents and adults. This is not the case currently in Belarus.

Recommendations

- Apply ARV therapies to children according to WHO recommendations
- Reported antiretroviral therapies for children <10 years separately from therapies for children ≥10 years, adolescents and adults in accordance with WHO recommendations

Target: By 2018 approximately 70% of the children aged 0-3 should be on the WHO recommended 1st line regimen ABC+3TC+LPV/r.
Target: By 2018 approximately 70% of the children aged 4-10 should be on the WHO recommended 1st line regimen ABC+3TC+EFV.

3.4 Priority area 4: Laboratory monitoring of ART

Belarus has adopted WHO recommendations on monitoring of patients on ART. However, they have not adopted the recommendation to monitor ART efficacy using viral load monitoring (and thereby cease using CD4 cell count as an indicator) because there is limited access to VL testing products in the country.

Viral load monitoring is a central and necessary tool in monitoring success targets for antiretroviral therapy, and it also constitutes the "last 90" of the UNAIDS 90-90-90 targets. It is therefore crucial that routine viral load monitoring is available for clinical HIV care without any interruptions.

Recommendations

- VL monitoring should be prioritised and the stable provision of laboratory kits for HIV viral load measurements secured

Target: All newly initiated people receive one measurement after proximately six months of therapy

3.5 Priority area 5: ART to key populations

Approximately 26% of PLHIV in Belarus have been infected due to injecting drug use – increasingly of illegal synthetic drugs. The number is highest in the Gomel region, which has a long history of providing antiretroviral therapy to injecting drug users, which is a hard to treat population group. The region will probably need additional help in streamlining the provision and the regimens of ART.

Firstly, an inquiry should be conducted to explore whether the rate of ART interruptions could be reduced by e.g. streamlining of delivery of ART. Secondly, the national HIV experts should be consulted to assess whether the number of health care staff is adequate and how the number of ART regimens can be reduced in the region.

Recommendation

- Streamline the provision of ART and the regimens to secure better adherence among injecting drug users

3.6 Priority area 6: National Reporting on HIV care and ART

In order to secure national level data collection and allow for easy up-to-date reviews of HIV care and ART it is important to finalize the development of the national database on HIV care and ART.

Recommendation

- Urgent finalization of the development of the national database on HIV care and ART

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Appendix 1: Currently used ARV regimens and Plan to Optimize ART regimens with the Goals to Keep in Pace to Achieve 90 – 90 – 90 by 2020

1st line ART adults (>10 years)	**Percentage of patients 01.01.2016**	**Percentage of patients 01.01 2017**	**Percentage of patients 01.01.2018**
Optimization process	**14 regimens**	**10 regimens**	**3 regimens**
Number of PLHIV on ART (89 % of PLHIV on ART)	**6 568**	**8 600**	**11 600**
TDF/FTC/EFV (standard WHO)	**24 % (1 552 PLHIV, includes 342 on TDF+3TC+EFV)**	**51 % (4 343 PLHIV)**	**90% (10 440 PLHIV)**
TDF/FTC + LPV/r (intolerant to EFV due to CNS side effects)	none	5 % (430)	7 % (812)
AZT + 3TC + LPV/r	none	3 % (258)	3 % (348)
AZT/3TC + EFV	43 % (2847)	26 % (2236)	0
AZT/3TC + NVP	8 % (534)	<6 % (500)	0
ABC/3TC + EFV	6 % (362)	4 % (344)	0
TDF/FTC + NVP	2 % (148)	<2 % (140)	0
ABC/3TC + NVP	9 % (616)	<4 % (300)	0
2 NRTI + LPV/r	11% (717)	5 % (430)	0
Regimens with three nucleoside analogues	3 % (178)	0	0
2nd line ART adults			
Number of PLHIV on 2nd line 10 % of PLHIV on ART	767	955	1300
TDF/FTC+LPV/r (standard WHO)	51 % (391 patients)	75 % (716)	88 % (1144)
ABC+3TC+LPV/r	32 % (248)	22 % (210)	10 % (130)
AZT+ABC+LPV/r	0.5 % (3)	0	0
Regimens not recommended because of insufficient			

antiretroviral efficiency (consider also 3rd line):			
- ABC+TDF+EFV	6 % (44)	0	0
- ABC+TDF+LPV/r	5 % (41)	2 % (19)	0
- LPV/r +/- 3TC	0,3 % (2)	<0.3 % (1 to 2) Consult national experts ')	<0.2% (1 to 2) Consult national experts ')
Additional 2 to 3 other 2nd line regimens decided by national experts		1 % (10) Consult national experts ')	2 % (26) Consult national experts *)
			*) allowed if drug intolerance problem
3rd line ART adults			
On Jan 01, 2016 there were 53 patients on 10 different regimens. In future TDF/FTC should be the preferred nucleoside backbone. DRV/r and DTG will replace ATV/r and RAL			
PLHIV on 3rd line **1% of PLHIV on ART**	53	96	130
TDF/FTC+DRV/r **(standard WHO)**			70 % (91)
TDF+FTC+DTG			20 % (26)
Other regimens based on the treatment histories			10 % (13)
			DRV/r will replace ATV/r, and DTG will replace RAL
			TDF+FTC will be the preferred nucleoside backbone

1st line ART children	**Percentage of patients** **01.01.2016**	**Percentage of patients** **01.01 2017-31.12.2017**	**Percentage of patients** **01.01.2018**

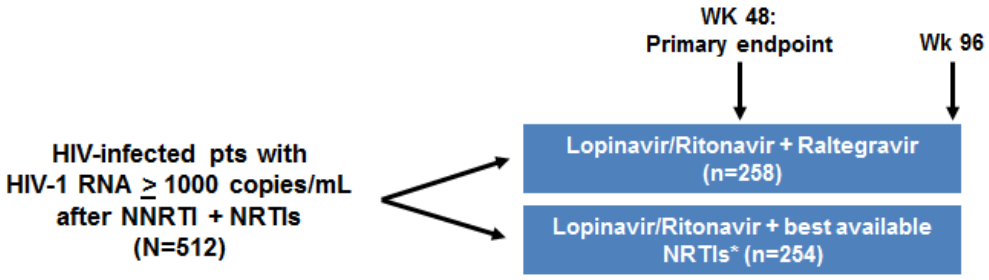
Children 0-3 years			
Total of PLHIV on ART	**30**		**20**
ABC+3TC+LPV/r (Standard WHO)	**0**		**70 % (14)**
AZT+3TC+NVP	**63% (19 patients)**		**10 % (2)**
ABC+3TC+NVP	**27 % (8)**		**10 % (2)**
AZT+3TC+LPV/r	**10 % (3)**		**10 % (2)**
Children 4-10 years			
Total PLHIV on ART	**76**		**76**
ABC+3TC+EFV	**10**		**70 % (53)**
ABC+3TC+LPV/r	**5**		**14 % (11)**
AZT +3TC+NVP	**27**		**4 % (3)**
ABC+3TC+NVP	**21**		**4% (3)**
AZT+3TC+EFV	**16**		**5 % (4)**
AZT+3TC+LPV/r	**4**		**3 % (2)**
AZT+3TC+ABC	**2**		**0**
Total	**76 patients**		
2nd and 3rd line ART children			
Children 0-3 years	**1**		1
Children 4-10 years	**10**		10
There are few children on 2nd line and none on 3rd line ART. The regimens will depend on the treatment histories and availability of paediatric formulas.			

Appendix 2: Key studies supporting current WHO recommendations

A) Current Role of New ARV Options in 2015 WHO Guidelines (2)

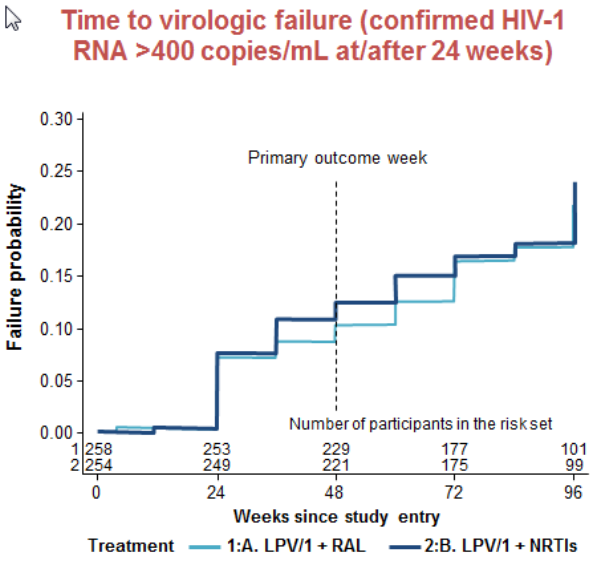
ARV	Population	1st line	2nd line	3rd line	Comments
EFV_{400}	Adult/Adol	✓			• No dose reduction studies in children is needed
DTG	Adult/Adol	✓		✓	• Not approved in children less than 12 years old . • Twice daily dose probably needed in TB patients using RMP
	Children			✓	
RAL	Adult/Adol		✓	✓	• Currently preferred as 3rd line option in adults and as 2nd line option in children • Limited use as alternative 2nd line option in adults. (RAL+ LPV/r)
	Children		✓	✓	
DRV/r	Adult/Adol		✓	✓	• Currently preferred as 3rd line option
	Children			✓	

B) The randomized trial of second-line ART called ACTG A5273 (SELECT), which was a phase III, open-label, randomized, non-inferiority study (6)



- Study objective: to determine noninferiority of raltegravir arm vs NRTI arm at Week 48
- Study powered to detect noninferiority at 10% margin
- Primary endpoint: time to virologic failure, defined as confirmed HIV-1 RNA >400 copies/mL after ≥ 24 weeks of first-line ART

*NRTIs selected according to algorithm, including substitution of zidovudine for tenofovir DF and vice versa



C) Meta-analysis of studies on HIV-1 Drug Resistance in ARV-naïve populations (7)

287 studies: N=50,870 persons from 111 countries

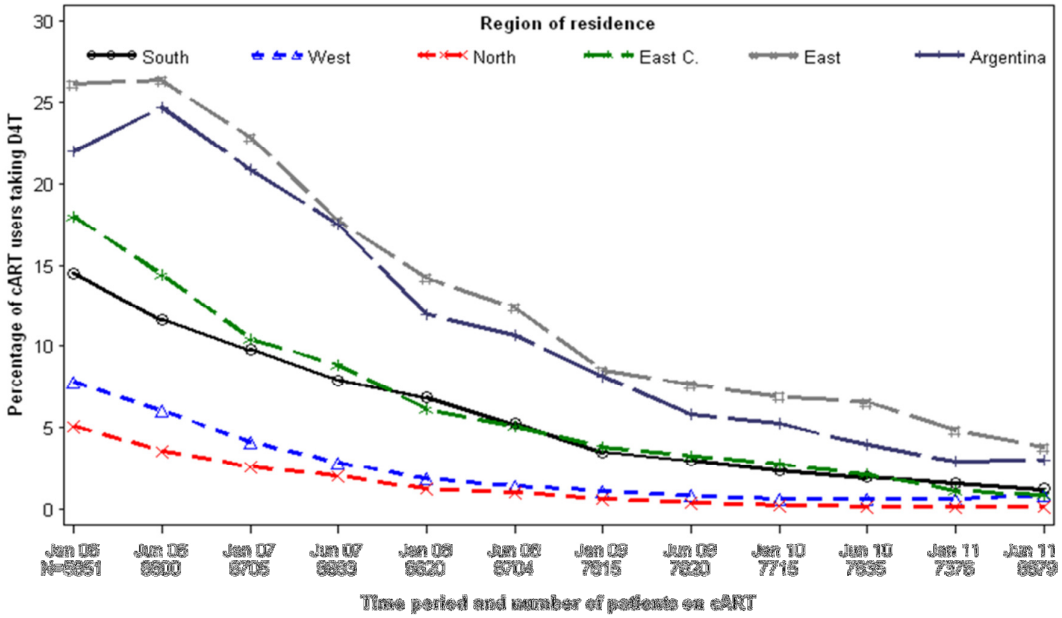
*N=50,870 persons from 111 countries

D) Studies on ART simplification strategies

Study	Intervention	Major outcomes	N	Country	Expected Completion
DREAM	Maintenance with LPV/r monotherapy or TDF/FTC/EFV	Efficacy, and tolerability (Phase II/III)	420	France	2014
SALT	Maintenance with ATV/r + 3TC OD	Efficacy/non-inferiority (Phase III)	325	Spain	2014
PROTEA	Maintenance with DRV/r (800/100 OD) monotherapy	Safety, tolerability and efficacy (Phase IIIb)	274	Multicountry (13)	2015
MOBIDIP	Maintenance with mono or bi-therapy with bPIs (±3TC)	Efficacy (Phase III)	264	Burkina Faso, Cameroon, Senegal	2017

*Dream (8); Salt (9); PROTEA (10); MOBIDIP (11)

E) Decreasing prevalence of D4T use across Europe & Argentina (12)

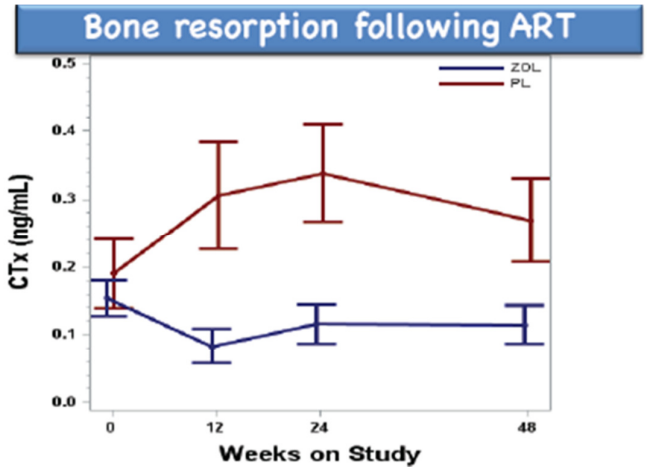


F) Association between abacavir usage and myocardial infarction risk - absolute risk difference only if elevated underlying risk* (13)

	Pre-March 2008	Post-March 2008
Events	672	269
PYRS	210,250	157,309
Rate	0.32 (0.30, 0.34)	0.17 (0.15, 0.19)
Recent exposure	1.97 (1.68, 2.33)	1.97 (1.43, 2.72)

*See also refs: 14, 15, 16.

G) A Single Dose Zoledronic Acid Prevents Antiretroviral-Induced Bone Loss (17)



- Phase 2, double-blind randomized, placebo controlled trial
- 63 non-osteoporotic treatment naïve HIV+ subjects were randomized to receive ART (ATV/r + TDF/FTC) and 1 dose ZOL (5 mg IV) or placebo
- Treatment with ZOL associated with a 73% and a 65% reduction in bone resorption relative to PL at 12 and 24 weeks, respectively, an effect that lasted through 48 weeks