

Prioritizing Second-Line Antiretroviral Drugs for Adults and Adolescents: a Public Health Approach

Report of a WHO Working Group Meeting

**World Health Organization
HIV Department**

**Geneva, Switzerland
21-22 May 2007**

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Executive Summary

Introduction

Antiretroviral therapy has dramatically improved the survival of HIV infected individuals and is critically needed to save millions of lives. As resource-limited countries rapidly expand their HIV/AIDS treatment programmes, increasingly countries are faced with the need to make second-line ART regimens available. The 2006 WHO ARV treatment guidelines outline the strategic approaches that should inform updated national treatment guidelines for first- and second-line therapies, and outline which agents should be considered for use in first line and second line. National programmes, however, are requesting additional operational guidance on the composition of their 2nd line ART formularies based on programmatic efficiencies and costs. As the ARV formulary is generally limited in developing countries, there is an increasing and urgent need for principles and criteria by which to prioritize ARV options. Regulatory bodies both nationally and internationally (e.g. the WHO pre-qualification project) are also requesting guidance on how to select the most needed therapeutic ARV agents for rapid appraisal. WHO therefore convened an expert meeting to review the scientific evidence and programmatic data available, in order to develop guidance for national programmes, regulatory authorities and implementing partners on selection, prioritization and planning for second-line ARV drugs.

Meeting objectives

The experts group guided by existing WHO recommendations for ART were requested to:

- Examine programmatic experience in establishing and using second-line ARV agents in national formularies;
- Review data on cost, supply and procurement of, and the range of ARV drugs currently used for second-line ART within national treatment programmes focusing on low and middle-income countries;
- Review existing and projected needs for and costs of second-line regimens, based on forecasts for second-line ARV use, and implications for national programmes;
- Develop key principles to guide rational selection of preferred second-line ARV drugs;
- Develop a list of priority second-line ARV products as recommended by WHO in ART treatment guidelines for use by regulatory authorities, drug manufacturers, national treatment advisory committees, implementing agencies and authorities responsible for drug forecasting and procurement.

Expected meeting outcomes

1. Summary of experience to date on use of ARV products in second line ART;
2. Consensus on key principles for selection and prioritization of second line ARV products;
3. List of priority second-line ARV drugs for use in adults and adolescents to be used for WHO prequalification dossier review.

Working methods

The meeting was conducted over two days. Plenary sessions reviewed current WHO recommendations for second-line ART in low and middle income countries, and programme experience to date, and data on cost, supply and procurement of ARVs. Group work was used to develop prioritization and recommendations for a final list of priority products proposed, which were then reviewed and finalized in plenary..

Outcomes

The working group participants were able to develop consensus on the preferred recommended NRTI background options for second line ART, with two combinations rated as highest priorities. These were **TDF+3TC** and **ABC+ddI**. For the PI component, based on comparable clinical efficacy safety data the working group agreed ranked **LPV/r** and **ATV/r** as the highest priorities. These ARV options are therefore the ones among those recommended in WHO treatment guidelines that producers, development partners, funding agencies and regulatory authorities should be encouraged to make available to national programmes.

Acronyms and abbreviations

3TC	lamivudine
AB	antibody
ABC	abacavir
AIDS	acquired immunodeficiency syndrome
API	active pharmaceutical ingredient
APV	amprenavir
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AZT	zidovudine (also known as ZDV)
bPI	boosted PI
CD4 count	CD4+ T-lymphocyte
CHAI	Clinton Foundation HIV/AIDS Initiative
d4T	stavudine
ddI	didanosine
DRV	darunavir
EC	enteric coated
EFV	efavirenz
FDC	fixed-dose combination
FPV	fos-amprenavir
FTC	emtricitabine
GDG	Guideline Development Group
HAART	highly active antiretroviral therapy
Hb	haemoglobin
HIV	human immunodeficiency virus
IDV	indinavir
ITT	intention-to-treat analysis
LMIC	low and middle-income countries
LPV	lopinavir
MSF	Médecines sans Frontières (Doctors without Borders)
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OT	on-treatment analysis
PAWG	Paediatric ARV Working Group
PEPFAR	President's Emergency Plan for AIDS Relief (from United States of America)
PI	protease inhibitor
PLWHA	people living with HIV/AIDS
/r	low-dose ritonavir
R&D	Research and Development
RLS	resource-limited settings
RTV	ritonavir
SQV	saquinavir
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
UNITAID	United Nations International Drug Purchasing Facility
VL	viral load
WHO	World Health Organization

Background

In December 2006, WHO estimated that 2,015,000 (1.8-2.2 million) people living with HIV/AIDS were receiving treatment in low- and middle-income countries (LMIC), representing 28% (24%-34%) of the estimated 7.1 million (6.0-8.4 million) people in need.[1] Almost all of these have commenced therapy with the WHO recommended first-line regimen of d4T or AZT combined with 3TC and one NNRTI (efavirenz or nevirapine). [2] An estimated 2% (40,000) are receiving second-line ART, the majority of whom are in Brazil.

As low- and middle-income countries rapidly expand their HIV/AIDS treatment programmes, and an increasing number of people living with HIV who have had first line ART go onto need can be expected to go on to need second line regimens. Countries are therefore increasingly faced with the need to make second-line ART regimens available through the public sector. Funding opportunities for second-line agents are available through initiatives such as UNITAID, PEPFAR and the Global Fund and through efforts of implementing partners such as the Clinton Foundation HIV/AIDS Initiative. The 2006 *Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach* [3] outlines the strategic approaches that should inform national treatment guidelines for first- and second-line ART regimens, and includes guidance on which ARV agents are preferred for use in first- and second-line therapies.

In order to achieve affordable pricing and ensure consistent supply of quality assured second-line drugs, national programmes, along with funding agencies and implementing partners, are requesting additional guidance to assist in the selection of the second-line ARVs their ART formularies.

Regulatory bodies both nationally and internationally (e.g., the WHO Pre-qualification Project) are also requesting a shorter selected list of second-line ARVS on which to focus efforts for rapid appraisal.

To improve existing WHO recommendations on ART for adults and adolescents, WHO convened a meeting of selected experts from implementing partners, national HIV programmes and the WHO ART Guideline Development Group (GDG). The meeting reviewed the programme experience, available data on registration/licensing status, cost and availability of the second-line ARV drugs recommended in the 2006 guidelines, and forecasting of need and consumption, with a view to develop a prioritized list of products to assist national programmes, regulatory authorities and implementing partners on selection, of already recommended second-line ARV drugs. The meeting was conducted in Geneva on May 21-22, 2007.

Guiding Assumptions and existing WHO recommendations

- 2NRTI + NNRTI as first-line, fixed-dose combinations preferred.
- 2 NRTI (at least one new) + a PI boosted with ritonavir is the preferred second line ART ,
- One thymidine-analogue NRTI (i.e., d4T or AZT), combined with 3TC, is the preferred 1st line option for NRTI component in resource-limited settings.
- FTC as an acceptable alternative to 3TC, based on similar pharmacological, clinical and resistance patterns profiles.
- Previously unused NRTIs are recommended as second line NRTI component in resource limited-settings, and non-thymidine based NRTIs preferred (i.e. ABC, ddI, TDF).
- Failure of first-line ART is generally identified using clinical and/or immunologic monitoring , as viral load measurements are not routinely available for monitoring resource limited settings.

Meeting objectives

This meeting was convened to:

- Examine programmatic experience in establishing and using second-line ARV agents in national formularies;
- Review data on supply, procurement and cost, of and the range of ARV drugs currently used for second-line ART within national treatment guidelines focusing on low and middle-income countries;
- Guided by WHO ART recommendations review existing and projected needs for and costs of second-line regimens, based forecasts for second-line ARV use, and implications for national programmes;
- Develop principles to assist in prioritization of preferred second-line ARV drugs according to WHO ART recommendations;
- Develop a list of priority second-line ARV products contained within WHO treatment recommendations to guide regulatory authorities, drug manufacturers, national treatment advisory committees, implementing agencies and authorities responsible for drug forecasting and procurement.

Expected meeting outcomes

- Proposed working definitions of first- and second-line ART;
- Principles and criteria for prioritization of preferred second line ARV products;
- List of priority second-line ARV drugs for adults and adolescents;
- Recommendations to WHO on areas for review in existing WHO ART treatment guidelines.

Working methods and development process

The meeting was conducted over two days (See Table 1). Plenary sessions reviewed the current WHO recommendations for second-line ART in LMIC and agreed to supplement these with a smaller limited list of priority recommended second line treatment NRTI and PI drugs for use in national programmes. Other presentations covered new evidence on second-line ARV drugs and the results of a WHO survey on the use of first- and second-line ARV at country level. The process by which the Paediatric ARV Working Group prioritized formulations for children was presented (<http://www.who.int/hiv/events/paediatricmeetingreport.pdf>) with a view to applying a similar methodology to prioritizing second-line adult ARV products. [4] [5] Projections of ARV demand and costs over the next five years were summarized and presented by the Clinton Foundation HIV/AIDS Initiative. Finally, experience and perspectives from four ART programmes were presented. Parallel break-out sessions were followed by group work presentations and discussion forums.

Table 1: Working Group Tasks

	Group 1	Group 2
Day 1	Develop working definitions of first- and second- line ARV drugs and review how programmes are interpreting WHO treatment failure criteria for resource-limited settings(When to Switch ART?)	Develop principles and recommendations to guide rational selection of second-line ARV drugs in LMIC (What to Switch to?)
Day 2	Prioritize second-line ARV agents (NRTI component)	
	Prioritize second-line ARV agents (PI component)	

Plenary sessions

Public health approach to ART and implications for treatment switching

Approximately 2 million people are on ART, which represent 28% of those in need[1]. AZT or d4T, combined with 3TC and an NNRTI, predominate as currently used in first-line regimens in most countries; with limited use of TDF and ABC, and almost no use of PIs in first line, and very limited use of triple NRTIs ART regimens, which is in accordance with current WHO ART guidelines. Available and affordable second-line ARV regimens are a key component of universal access to high quality HIV treatment. In 2007, the range of prices for of second-line ART regimens in LMIC is \$US 1,000-2,500 per year. WHO estimates based on current average switch rates of 3% per year, that by 2010, in the absence of price reductions, 90% of the cost of ART will be required to provide second-line drugs[6].

To simplify second-line therapy options, both at a facility and programmatic level, to help reduce costs, there is a need to identify the most cost efficient second line ARV drugs particularly for people who are currently on a thymidine analogue- (d4T or AZT) based first-line regimens, (95% of the total people estimated to be on ART). It is anticipated that in the near future, modified recommendations for second-line ART will be needed for the increasing numbers of people taking a non-thymidine analogue as their first-line regimen (especially TDF+3TC or TDF+FTC).

Optimizing the second-line formulary

Most patients start first-line ART late in the course of the chronic HIV infection, with a low CD4 count severe or advanced HIV disease (See Table 2). Currently relatively few have failed first-line ART regimens and gone on to need second-line therapy. It is however anticipated that most patients and programmes will switch therapy late due to the limited access to CD4 and viral load testing, with most programmes to date relying on clinical progression alone as the marker of treatment failure. The current WHO guidelines for switching stipulate that clinical disease progression or a drop in CD4 cell count to pre-treatment baseline or fall of 50% from peak value are signs of treatment failure, and are recognized not to be sensitive for detecting early replication of HIV due to emerging HIV drug resistance.

It is also acknowledged in WHO 2006 recommendations that where there is no regular periodic CD4 or viral load monitoring, and reliance is placed on clinical and immunological parameters for recognizing treatment failure, switching will be delayed. When a second line regimen is required WHO recommends use of a ritonavir-boosted PI (bPI), supported by at least one new, previously unused NRTI. In the continued absence of viral load (VL) measurement in most programmes, diagnosing failure of ART and switching regimens late after the initial ART regimen no longer fully suppresses HIV replication, allows the number of cumulative NRTI resistance mutations to ARVs in first-line regimen to increase. This will also allow the HIV to be more likely to develop mutations that result in cross-resistance to all drugs within the NRTI class. This in turn means that even unused NRTIs used in second line regimens may provide limited support to the PI/r, and reduce chances of achieving HIV viral suppression.

Australia	239
Japan	192
United States	187
Argentina	181
Canada	164
China	163
Brazil	159
India	103
Botswana	97
Malawi	97
South Africa	87
Viet Nam	53

Source: Adapted from Egger M, et al. 14th CROI, Los Angeles 2007, abstract #62.

Periodic VL measurements have the potential to detect viral replication at the time of sampling. However viral replication at the time of sampling may result from poor adherence to the existing regimen or loss of viral suppression by an ART regimen.

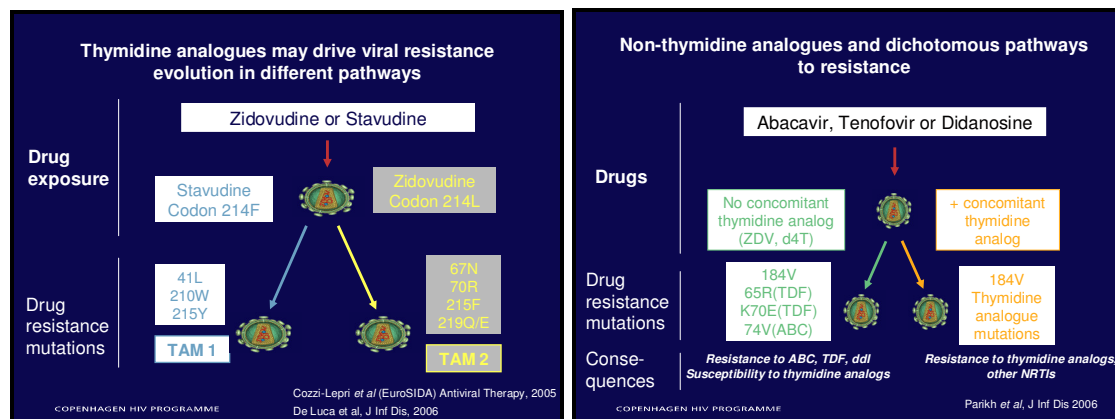
In order to maximize the efficacy and durability of first- and second-line antiretroviral regimens, WHO continues to support the universal availability and use of appropriate and affordable CD4 and HIV viral load testing.

Even where VL testing is available, there is limited agreement as to which threshold of viral load represents treatment failure, and should trigger a clinical decision to switch to a different treatment regimens. Current WHO ART guidelines recommend that 10,000 copies/mL be used as a threshold to switch therapy, this level was selected based on the limited evidence available that demonstrate VL values greater than 10,000 copies/mL with subsequent disease progression and appreciable CD4 count decline. [7] [8] To date definitions of early and late treatment failure have not been formally proposed by WHO and agreed.

Treatment failure and resistance pathways

AZT and d4T direct the virus towards mutations from one of two major pathways, the 41/ 210/ 215 HIV-1 reverse transcriptase (RT) codon mutation pathway, or towards an alternative pathway that involves RT codons 67/ 70/ 219.[9],[10]

Figure 1: Potential Nucleoside/Nucleotide Pathways Resistance



Source: Adapted from "Overview of Current Approaches of NRTI component of 2nd Line ART Regimens". Jens Lundgren, University of Copenhagen, WHO Second-Line Meeting, 21-22 May, 2007.

Viruses carrying the 41/ 210/ 215 combination of RT codon mutations tend to have higher levels of AZT resistance, are more cross-resistant to other NRTIs, and are less likely to become fully sensitized to AZT in the presence of the M184V lamivudine resistance mutation [11]. Those carrying the 67/70/219 cluster of RT codon mutations usually show lower levels of AZT resistance, are less cross-resistant to other NRTIs, and are more likely to remain fully sensitive to zidovudine when the M184V mutation is present. [9] [10]

In contrast ABC, TDF and ddI in combination with 3TC and/or FTC select for mutations in M184V, K65R, L74V and rarely, K70E codons, which compromises the activity of these non-thymidinic NRTIs without accumulating TAM's. Conversely, if a thymidine analog is concomitantly used with these drugs, virus bearing TAM's are selected for - as opposed to the those with the three mutations mentioned above- and therefore susceptibility to AZT and d4T as well as other NRTIs is compromised, particularly after the selection of virus with multiple TAMs (See Figure 1). [12] Of note, the rate of selection of virus with these mutations, once ART no longer completely suppress replication of HIV, differs for different mutations. The TAMs in particular are slowly selected for (See Table 3). In environments without virological monitoring of

ART response, and where failure to first-line ART is identified by the use of clinical and/or immunological progression, it is to be expected that most patients have virologically failed their first-line therapy for extended periods of time.

A study published in 2007 by *Sungkanuparph et al.* in Thailand documents the emergence of resistance and its effect on the choice of second-line therapy, in the context of a resource-limited setting with limited drug available for second line. ART [13] Ninety-eight patients who experienced virological failure while receiving stavudine, lamivudine, and nevirapine had genotypic assays performed. Virological failure was defined as a confirmed rebound of VL to 1,000 copies/mL following a period of sustained virological suppression. Patients had been receiving antiretroviral therapy for a median duration of 20 months at the time that virological failure was determined. High rates of resistance were detected to lamivudine (89%) and NNRTIs (92%); 37% of patients had 1 TAM, 13% had 3 TAMs, and 8% had the Q151M mutation, which is associated with extensive NRTI cross-resistance.

In the DART virology sub study ongoing in Uganda and Zimbabwe, 377 patients received AZT+3TC+TDF for 48 weeks with limited prospective laboratory monitoring. Baseline resistance was detected in 10% of those analyzed (NRTI 6% and NNRTI 4%). Persistent viraemia resulted in increasing accumulation of TAMs between weeks 24 and 48. The proportion of patients with 4 to 6 TAMs increased from 4% at week 24 to 39% at week 48.[14]

Table 3: Likely Mutation patterns on NRTI regimens based on relationship to time of loss of control of viral replication

NRTI Component	Early mutation patterns	Late mutation pattern	Implications for subsequent regimens
ZDV+3TC or d4T+3TC	M184V	M184V+ multiple TAMs	No active NRTIs
TDF+3TC	M184V+K65R	M184V+K65R	AZT will generally remain active

Source: Adapted from "Second-line therapy in MSF: description, clinical outcome and perspectives". Alexandra Calmy, Fernando Pascual, MSF Access Campaign AIDS Working Group, MSF. WHO Second-Line Meeting, 21-22 May, 2007.

Adherence

Adherence remains a key factor in the maintenance of virological control for both first- and second-line regimens. At this meeting, working group members agreed that viral load should be promoted as the most effective way of diagnosing early treatment failure and preserving more active agents for the second line. Measuring viral load is also a useful but expensive tool for assessing adherence. Given that the new NRTI component may provide residual but compromised antiviral activity in a second line bPI-based regimen, comparisons can be drawn with ART simplification studies in which subjects received LPV/r as their only ARV. In a multivariate analysis for virological failure in the OK (21/42 patients) and OK04 (100/198 patients) studies, low adherence, low baseline haemoglobin and a CD4 cell count nadir <100 cells/mm³ predicted failure. [15] [16] In the M03-613 Study (induction with AZT + 3TC + LPV/r, followed by maintenance with LPV/r monotherapy) self-reported low adherence and baseline CD4 count <200 cells/mm³ were associated with the risk of virological rebound. (See Annex 7)

Retaining 3TC in the second-line regimen

Virus harbouring the M184V mutation associated with 3TC resistance has been shown to be less 'fit' than wild-type virus leading to the hypothesis that it may be beneficial to continue 3TC therapy in patients failing a 3TC-containing regimen. An early study of 3TC monotherapy demonstrated a 0.5 log₁₀/mL drop in viral load sustained for 52 weeks. [17] Such sustained virological suppression activity of 3TC, in the face of viral strains completely resistant to 3TC, may be clinically beneficial

in patients on a non fully suppressive ART regimen, and it may assist in preserving and possibly extending the period of immunological benefit seen in patients on ART without complete virological control. [8]

In a study of the antiviral activity of lamivudine in salvage therapy, lamivudine was withdrawn from the regimen in six patients known to be harbouring virus with M184V mutation resulting in an increase of VL of 0.5 log₁₀/mL above baseline six weeks after the withdrawal. Re-introduction of lamivudine resulted in a decrease to baseline VL levels in three subjects. [18]

Castagna et al. randomly assigned HIV-infected patients with HIV harbouring the M184V mutation receiving lamivudine-containing HAART and to monotherapy with lamivudine 300 mg once daily (lamivudine group) or the discontinuation of all antiretroviral drugs (TI group). By week 48, 20 of 29 patients in the TI group (69%; 95% CI 51–83%) and 12 of 29 in the lamivudine group (41%; 95% CI 26–59%) had discontinued the study because of immunological or clinical failure, which was significantly delayed in the lamivudine group.[19]

In the COLATE study [20], 131 patients with virological failure on a 3TC-containing regimen were randomized to continued 3TC or no 3TC in addition to a salvage regimen chosen by their physician. Patients were stratified into two groups; Group A were failing their first 3TC-containing regimen and Group B included patients failing there first, second or later 3TC-containing regimen. There was no difference in the rates of virological suppression in the two arms at week 48 by either ITT or OT analyses. The proportion of subjects with VL < 50 copies/mL in the 3TC arm was 57% and in the non-3TC arm was 44%. There was no difference between groups A and B. However, high success rates in both arms may have masked any impact. Many of the patients enrolled in COLATE had failed only a single previous regimen, and the overall response rate was very good. This left a relatively small group of patients who remained viraemic in which to test the hypothesis that continued 3TC contributes to partial virological control. Hence, in an attempt to preserve the CD4 count, if ART is not able to fully suppress viral replication, it may be considered to add 3TC or FTC in second-line regimens.

Efficacy of ART in individuals infected with HIV-1 non-B subtypes

Natural polymorphisms are often present in HIV-1 non-B subtypes at positions known to be associated with drug resistance in clade B viruses. These changes may influence the emergence of drug-resistant viruses; modify drug susceptibility and/or viral replicative capacity. Different pathways may lead to different drug resistance patterns in non-B subtypes. In the seven main studies (2001-2005) reviewed by *Holguin et al.*, similar virological and clinical outcomes were reported for subjects with non-B subtypes compared to studies in individuals with subtype B were reported. [21] Evidence from programmes with subtype heterogeneity in France and the United Kingdom discussed at this meeting suggest that the subtype response differences to ART are minor.

There are theoretical reasons to support AZT+TDF as the second-line NRTI component in patients with HIV-1 subtype C failing a d4T-containing first-line regimen. There is evidence supporting antagonism between TAMs and K65R. [22] [23] Although the two pathways are not mutually exclusive, the virus would preferentially be driven by one of the two. Subtype C appears preferentially to select for the K65R mutation, more often than subtype B virus even with initial d4T-based regimens.[24] This is not the case with AZT-based regimens. If the virus takes the K65R pathway, then AZT is the preferred option (M184V, which will always be selected for, would not influence AZT activity). TDF would not be active against the K65R-containing virus but it would probably delay the emergence of TAMs. [23] On the other hand, if the virus takes the TAM pathways, TDF (and ddI) would be in general more active than ABC, particularly in the presence of M184V.

Table 4: Main clinical trials comparing the virological and immunological responses to ART in HIV-infected subjects carrying B vs. non-B subtypes

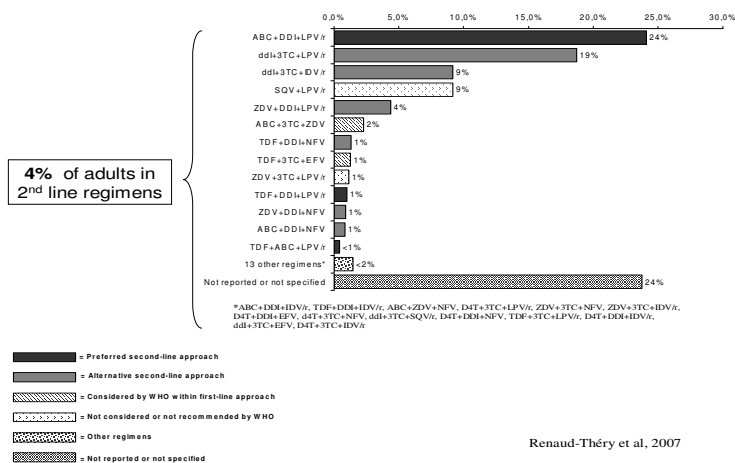
Reference	No. of patients	HIV-1 non-B subtypes (%)	Treatment regimen (months of follow-up)	Virologic response	Immunologic response
Frater, 2001	79	25A,11B,23C,13D,1H,1U,1AC,1AD,3AG (86%)	HAART first regimen 12 months	Similar	Similar
Alexander, 2002	479	1A,459B,11C,2D,5CRF01_AE,1U (4.2%)	ARV 18 months	Similar	-
Nicastrì, 2004	45	1A,34B,1C,3F, 2AG,2CRF02_AG,2J (24.4%)	HAART pretreated 12 months	Similar	Similar
De Wit , 2004	175	21A,56B,25C,8D,8G, 2H,1J,1CRF01AE,22CRF02AG,22 mosaics (68%)	HAART 24 months	Similar	Lower in non-B
Bocket , 2005	416	317B, 99 non-B (not specified) (23.8%)	ARV 12 months	Similar	Similar
Bannister, 2005	684	7A, 547B, 24C, 34 other subtypes (20%)	HAART 12 months	Similar	Similar
Atlas, 2005	172	32A,44B,34C,18D,5G,19CRF01_AE (74.4%)	3 NRTI or HAART 6 months	Different across subtypes	Different across subtypes

Source: Holguín et al; Efficacy of Antiretroviral Therapy in Individuals Infected with HIV-1 Non-B Subtypes. AIDS Reviews 2006 [21]

WHO survey on use of ART in resource-limited settings

Twenty three countries responded to a recent WHO survey entitled '*Survey on the use of ART in Resource Limited Settings in 2006: Distribution and Uptake of 1st and 2nd Line Regimens and Forecast of Demand for ARV Drugs in Low and Middle Income Countries*'. [25] [26] These responding countries represented more than 50% of the total number of patients reported to be on ART in resource limited settings. In the survey, 96% of adults receiving treatment were reported to be on a WHO recommended thymidine-based first-line regimens with 61% of whom are receiving d4T+3TC+NVP. No countries reported patients using a recommended non-thymidine (TDF or ABC) based 1st line 2NRTI+NNRTI regimen. Only 4% of adults were reported to be on second-line regimens, 61% of whose ART regimens concord with WHO guidelines. Approximately 25% of patients were reported to be receiving a WHO preferred second-line regimen (almost all of them using ABC+ddI+LPV/r), 36% an alternative second-line regimen and 12% were on a regimen not recommended as a second-line option by WHO (see Figure 2). According to WHO projections (based on a estimated average switch rate from first to second line ART of 3% per year), approximately 120,000 and 180,000 patients will need 2nd line regimens in 2007 and 2008, respectively.[6]

Figure 2: Use of second-line ARV regimens in low and middle income countries (2006)



Source: Adapted from "WHO Survey on Use of ART in Resource-Limited Settings in 2006", Françoise Renaud-Théry, WHO. WHO Second-Line Meeting, 21-22 May, 2007

Second-line ARV forecasting and pricing

The Clinton Foundation HIV/AIDS Initiative (CHAI) presented market scenarios, based on their internal costing and forecasting models (<http://www.clintonfoundation.org/pdf/chai-arv-price-analysis-082407.pdf>). They predict a progressive market shift, with increasing use of TDF in both first- and second-line regimens as TDF prices fall, with TDF possibly becoming the dominant first-line NRTI, at least for newly enrolled patients, in LMIC by 2010. In the PI market, they predict a likely consolidation around the two PIs that offer a similar profile for efficacy and safety together with the lowest per-patient per-year pricing: ATV/r and LPV/r. A shift from LPV/r, currently the dominant PI on the market in LMIC, towards ATV/r, is predicted to occur once an affordable one pill per day fixed-dose combination of ATV with heat-stable RTV becomes available. This fixed-dose combination is anticipated to be 40% or more cheap than the lowest price currently available for heat-stable LPV/r fixed-dose combination, based on requirements for less active pharmaceutical ingredients (API) per dose. The cost of enteric-coated ddI is also predicted to fall alongside TDF, but ddI and ABC demand is anticipated to remain relatively stable.

Among second-line ARV drugs, generic forms of TDF, TDF+3TC, TDF+FTC, ABC, 3TC, ddI (buffered and EC formulations), SQV, IDV, NFV and LPV/r are currently available. A number of these products, including the TDF products, ddI EC, and LPV/r, have been submitted to WHO and FDA recently and have not yet been approved, though support for their purchase is available to countries using UNITAID or Global Fund financing under Global Fund quality category *c(i)*. Other generic products—including ATV, heat-stable RTV, and heat-stable fixed-dose ATV/r—are reported to be in the pipeline and expected to be launched during 2008. Price ranges for these drugs is anticipated by CHAI to depend largely on limiting the number of different regimens used in second line, which would allow the market to aggregate around a few drugs, and thereby drive down production costs and prices. No data about FPV were presented. More details about ARV pricing are available at Annex 5a and 5b.

Working definitions of first- and second-line ARV drugs in the public health context

The WHO ARV treatment guidelines for adults, adolescents and children follow a public health approach to ART [2], which includes:

- standardised regimens and simplified treatment protocols and :
- simplified clinical decision-making and standardised monitoring.

Existing recommendations outline:

- when to start, substitute, switch and stop ART;
- standard ARV toxicity and drug-drug interaction management on ART.

The current guidelines consider three main ARV classes: NRTI, NNRTI and PI, and treatment options are consolidated into two sequential ARV regimens; a first and then a second ART regimen. Limited guidance is currently available concerning subsequent options, and further evidence is awaited before firm recommendations can be made.

These treatment recommendations refer to first and second-line therapy: however, in practice there remains some confusion about their precise meaning. “First-line” is the term usually used for the initial triple ARV regimen used by an individual, or for patients who are ART naive starting ARV therapy. Subsequent changes being referred to as the “second-line” and “third-line regimens.” Confusion arises when individual drug substitutions within this initial regimen are made (including for toxicity, drug-drug interactions or intolerance). Alternatively, “first-line” and “second-line” may be taken to refer to the ordered sequence of regimens according to the classes of ARV that are recommended. Whilst usually congruent, these definitions are not invariably so. Hence, there remains a need for clear definitions that include reference to the sequence of ARV classes currently recommended.

First-line ART: First-line ART is the initial regimen prescribed for a patient who fulfils national clinical and laboratory criteria to start ART. Current WHO treatment guidelines for first-line ART recommend that two classes of drug for initial treatment, two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and one non nucleoside reverse transcriptase inhibitors (NNRTI) should be the preferred approach.

Second-line ART: Second-line ART is the next regimen used in sequence immediately after first-line therapy has failed (clinically, and or immunologically and or virologically). Current WHO treatment guidelines recommend that the protease inhibitor (PI) class should be reserved for second-line ART and that ritonavir-boosted protease inhibitors (bPIs) are preferred supported by two agents from the NRTI class.

Change of ARVs prescribed should be carefully distinguished:

- 'Failure' defined clinically, and/or immunologically, and/or virologically, refers to the loss of antiviral efficacy and triggers the switch of the entire regimen from first to second line.
- Single drug substitutions of individual ARV (usually within the same class) refers to the replacement of an individual drug for toxicity, drug-drug interaction or intolerance; and do not therefore indicate a second-line regimen is being used.

Countries are encouraged within a public health approach to establish national treatment recommendations to allow consolidated purchase of ARVs for use in the public sector based on one preferred first-line and one preferred second-line ART regimen with alternative agents of the same class provided as substitution for toxicity, intolerance or to avoid drug-drug interactions. The preferred regimens selected nationally are ideally those best suited for all major subpopulations within the country.

Prioritization of new paediatric ARV formulations

The Paediatric ARV Working Group (PAWG) has already undertaken an exercise to recognized similar need to identify priority new or reformulated ARVs products needed to scale up paediatric programmes.[4] Experience and recommendations from this group were summarized and presented to the meeting participants and a meeting report (<http://www.who.int/entity/hiv/events/paediatricmeetingreport.pdf>) is also available. The PAWG based its ranking of paediatric formulations on three major domains; efficacy, safety, and feasibility. Cost was not included. Formulations selected need to be able to provide ARVs at doses consistent with current WHO guidelines A maximum number of tablets to be taken at any one dose was agreed to be not more than three, a preference for solid dosage forms and a restricted number of products that programs need to buy to be able to use the ARV with the programme was also established as three), and these were used to guide the ranking process. Required products identified were ranked and subsequently categorized into three priority groups: urgent, high or important.

Selection of priority second-line ARV drugs for use in adults and adolescents

Rationale for selection of NRTI component

A similar methodology was therefore used to prioritize ARVs required to deliver second-line ART for adults and adolescents. Six domains (**efficacy, simplicity, toxicity, population coverage, potential for low cost and compatibility with paediatric formulations**) were considered by the adult working group. More detail of the domains and parameters used for drugs rating are presented in **Annexes 3 and 4**.

The combination of TDF + ddI was considered based on use of reduced dose of ddI (reduced to 200-250mg OD based on body weight). In the 2006 WHO Guidelines for Adults and Adolescents, caution is advised in using this combination, based on concerns about antagonism; however more recent data suggest that this combination is safe and effective if the ddI dose is reduced. [27-30]

Basis of selection of second-line regimens

- The boosted-PI and NRTI background were considered independently.
- Regimens were for the treatment of HIV-1 only.
- Prior NRTI use in first-line ART was assumed to be thymidine analogue based.
- Selection of NRTIs following non-thymidine based first-line regimens were considered separately.
- The boosted-PI was assumed to be a heat stable formulation.
- ddI was assumed to be available as the enteric coated (EC) formulation.

Of the possible recommended NRTI background options when thymidine analogues are used in 1st line regimens, two options ranked as highest priority; **TDF+3TC** and **ABC+ddI**.

The working group also considered second-line options for NRTI where more people receive non-thymidine NRTIs (TDF or ABC) in the first-line regimen. For patients failing a TDF-containing first line, the working group agreed **AZT+3TC** to be the most suitable priority option. For patients receiving ABC-containing first-line ART, the priority second-line NRTIs are **AZT+3TC** or **TDF+3TC**.

Rationale for the selection of boosted protease inhibitors

For the purposes of the working groups, heat-stable formulations of PIs were assumed, and RTV was considered only as a booster for other PIs. Nelfinavir was not included because it is not recommended to be used boosted with RTV. Five ritonavir-boosted PIs are included in 2006 WHO recommendations for second-line ART: atazanavir + ritonavir (ATV/r), fosamprenavir + ritonavir (FPV/r), indinavir + ritonavir (IDV/r), lopinavir + ritonavir (LPV/r), and saquinavir + ritonavir (SQV/r). Existing originator ritonavir requires refrigeration, limiting its use in some LMIC. Newer, heat-stable ritonavir tablet formulations are becoming available.

In 2007, two further PIs have been approved for clinical use: tipranavir (TPV) and darunavir (DRV). These "second-generation" PIs also need to be boosted with low dose ritonavir. However, currently their use is mainly for salvage therapy in industrialized countries, [31] [32] [33] and they were not considered in the WHO 2006 guidelines, therefore TPV and DRV were not included in the prioritization process.

Based on published clinical efficacy and safety data there is little to distinguish between boosted PIs, with very and limited data comparing different bPIs as part of 2nd line ART. There are few head-to-head comparisons of PIs and many of these studies were conducted in ART-naïve patients. Consequently the 2006 WHO guidelines do not recommend one boosted PI over another. However, there are data which informed the prioritization process:

- IDV/r in its standard dose (800/100 mg bid) appears to be less well tolerated than the other boosted PIs, especially in hot climates, and is therefore likely not to be as effective, and is therefore not preferred. WHO will review evidence for use of IDV/r in a lower dose (400/100 mg bid) to reduce the toxicity. There are some small studies supporting this dose and the WHO European ARV guidelines have adopted this recommendation since 2006;[34-36] [37] [38]
- SQV/r appears to be slightly less potent than the other boosted PIs, although data are scarce. This apparent lower efficacy may relate to the high pill burden needed with the conventional formulation used by generic manufacturers (200 mg tablet). The use of the new 500 mg tablet formulation may be anticipated to improve adherence;

- LPV/r is currently the only available fixed-dose combination of a PI with low dose ritonavir, and is now produced as a heat-stable tablet. LPV/r can cause abnormal lipid profiles;[39] [40] [41]
- ATV/r can cause hyperbilirubinaemia and there have been some reports of ATV/r-related nephrolithiasis;[42] Two studies suggest non-inferiority and better lipid profile with ATV/r compared with LPV/r in ART experienced individuals; [43, 44]
- FPV/r is an oral pro-drug of the protease inhibitor amprenavir, but is not yet widely marketed in LMIC. The major side effects associated with this drug in clinical trials are diarrhoea and skin rash. FPV/r-based regimens have shown good antiviral efficacy and are generally well tolerated in antiretroviral therapy-naive individuals but the experience with this drug even in developed countries is limited, and few comparative data are currently available in treatment-experienced patients with HIV infection;[45] [46]
- There was a consensus that current data suggest ATV/r, LPV/r, and FPV/r are similar with respect to tolerability and potency. ATV/r and FPV/r have the advantage of being dosed once daily. However in a recent trial with patients previously failing to PI based regimens, once daily FPV/r was clearly inferior to FPV/r and LPV/r twice daily [47]

More details about rationale for ranking of PIs are also presented in Annexes 3 and 4.

Patients in LMIC currently face significant barriers in accessing any of these preferred PI options, primarily due to high prices and the absence of registered generic and/or branded versions of each product. Securing price reductions and expanding access to high-quality, heat-stable versions of the preferred priority boosted PI products should be a priority for UNITAID's list of second-line program.

Among the preferred PI options, to date only LPV/r has been included in the initial set of UNITAID second-line products; because originator product is being made available at preferential pricing and generic versions of heat-stable LPV/r are emerging earlier than generic versions of heat-stable ATV/r or FPV/r. In turn, this is due to the greater existing demand for LPV/r in LMIC. ATV/r and FPV/r are newer drugs that originators have not yet widely marketed in the developing world. The originator of ritonavir also manufactures lopinavir; LPV/r was the first boosted PI available, and it has the longest track record. LPV/r is also the first bPI to be produced in a single, co-formulated tablet, and the first available in a heat-stable form. Thus, developing countries currently have more experience using LPV/r and currently national guidelines are more likely to recommend LPV/r as the preferred bPI.

Although generic manufacturers appear not to have begun active R&D on FPV/r, generic versions of ATV and ritonavir (as separate pills) are now appearing on the market in developing countries and will likely be submitted to the WHO and FDA for prequalification over the course of 2007. There is no originator or generic version of a fixed dose combination (FDC) composed of ATV and RTV in the market. This creates an important opportunity for UNITAID to add heat-stable, co-formulated ATV/r to the second-line donation program for 2008. Doing so will create an incentive for generic manufacturers and possibly generic-originator partnerships to fast-track development of heat-stable versions of the product, either heat-stable RTV packaged with ATV, or heat-stable fixed-dose combinations of ATV/r. Other bPI options, including FPV/r can be considered in the future.

Based on production costs related to the significantly higher cost of API per dose of LPV/r, the CHAI market scenario predicts generic ATV/r to be significantly less expensive than LPV/r, perhaps as much as 50%, by the end of the current UNITAID donation program.

Of the PI component, **LPV/r** and **ATV/r** ranked as highest priorities.

Second-line options when thymidine analogs are used in first- line regimens

During this meeting, the working group ranked two nucleoside options (**TDF+3TC** and **ABC+ddI**) and two ritonavir-boosted protease inhibitors (**LPV/r** and **ATV/r**) as highest priorities among the current options recommended by WHO when thymidine analogs were used in 1st line therapy.

Other combinations aligned with current WHO guidelines were also listed in lower priority levels (see Table 5a) considering the six domains selected for the exercise (efficacy, simplicity, toxicity, population coverage, potential for low cost and compatibility with paediatric formulations). According to these parameters and drug availability, countries could then choose second-line regimens from the following options to comply with WHO ART treatment recommendations:

Table 5a: Summary of the prioritization exercise for currently recommended second-line regimens when thymidine analogs are used in 1st line therapy

Ranking	NRTI component	PI component
URGENT	TDF+3TC ¹ ABC+ddI	ATV/r RTV ³ LPV/r
HIGH	TDF+ddI ² ddI+3TC ¹ TDF+ABC AZT+TDF AZT+3TC ¹ +TDF ABC+3TC ¹	SQV/r IDV/r
IMPORTANT	AZT+ddI AZT+3TC ¹ AZT+3TC ¹ +ABC	FPV/r

¹ FTC is an equivalent alternative to 3TC because they are structurally related and share pharmacological properties and resistance profiles.

² The combination of TDF+ddI was rated with consideration of a dose reduction of ddI to 200-250mg OD according to body weight

³ RTV was considered only as a pharmacological booster for other PIs.

Second-line options when non-thymidine analogs are used in first- line regimens

The Table 5b summarizes the ranking options for the NRTI and PI components, according the analysis of the same six domains selected for second-line options in situations when d4T or AZT- was used in first-line therapy.

Table 5b: Summary of the prioritization exercise for currently recommended second-line regimens when non-thymidine analogs are used in 1st line therapy

Ranking	NRTI component	PI component
URGENT	AZT+3TC ¹ TDF+3TC ^{1,2}	ATV/r RTV ⁴ LPV/r
HIGH	ddI+3TC ¹ AZT+3TC ¹ +ABC ABC+3TC ¹	SQV/r IDV/r
IMPORTANT	AZT+TDF AZT+3TC ¹ +TDF TDF+ABC TDF+ddI ³ AZT+ddI	FPV/r

¹ FTC is an equivalent alternative to 3TC because they are structurally related and share pharmacological properties and resistance profiles.

² If ABC was used in 1st line regimen.

³The combination of TDF+ddI was rated with consideration of a dose reduction of ddI to 200-250mg OD according to body weight.

⁴RTV was considered only as a pharmacological booster for other PIs.

Heat stable formulations

Lopinavir co-formulated with ritonavir and ritonavir as a single formulation first became available as a soft gelatin capsules which required refrigeration. They are recommended to be taken with a moderate fat meal. Recently, melt extrusion technology has been used to produce LPV/r tablets which does not require refrigeration and reduces the number of dosage units. *Klein et al.* conducted three separate healthy volunteer studies to assess the bioavailability of the LPV/r tablet formulation with and without food compared to the capsule formulation.[48] The tablet was bioequivalent to the capsule when taken with food. Compared to the capsule the tablet formulation resulted in more consistent lopinavir levels in fasted and non-fasted states.

Heat-stable ritonavir is essential for all boosted PI regimens. A stand-alone formulation of heat-stable ritonavir needs to be made widely available from multiple sources at an affordable price, rapidly qualified, and not limited by patent and registration issues.

Use of rifabutin in TB-HIV co-therapy

The HIV pandemic has led to a resurgence of tuberculosis and the challenge challenges of TB-HIV co-therapy for patients on second-line ART is well recognized. Management of co-infected patients has shown that TB can be cured with standard antituberculosis regimens, including the use of rifampicin-based TB treatment for 6 months.[49] Preliminary evidence and experience has confirmed recommendations in WHO guidelines that for most patients, especially those with CD4 counts < 100 cells/mm³, HIV treatment should not be delayed, but should be started or continued alongside TB treatment.

It is expected that many patients will fail first-line ART with active TB ; and TB will develop in patients on second-line therapy. However, because of well recognized drug-drug interactions, it is difficult to use rifampicin with any boosted PI-based regimens,.[50] For patients who need antituberculosis treatment and who are already on a boosted PI, or who need to be switched to a boosted PI based regimen, two main options exist:

- Increase the ritonavir dose with some bPIs (SQV/r+RTV and LPV/r+RTV) and maintain rifampicin in the anti-TB regimen;
- Substitute rifabutin for rifampicin in the anti-TB regimen and maintain the standard PI-based ART regimen.

Neither option is easily implementable at present in LMIC. Currently rifabutin is considered unaffordable for most TB programs (almost US\$ 2 per day). In many LMIC, rifabutin is not registered, compromising procurement at any price. Similarly, heat-stable ritonavir as a stand-alone medication is single sourced, and is not currently available at an affordable price. Furthermore, dose adjustments for ritonavir are difficult outside of specialized and training centres.

WHO strongly supports key efforts that will enable successful treatment of HIV-TB co-infection:

- Application for rifabutin to the Model List of WHO Essential Medicines should be considered;
- Efforts to secure production of rifabutin at affordable prices should also be encouraged.

Rifabutin is only available from a single-source, and it may have patents pending in countries with capacity of production, which could block competition and price reduction. Countries should consider use of the flexibilities included in the TRIPS agreement in order to increase access to these recommended products.

CD4 and VL testing availability

Significant progress has been made to date towards the goal of Universal Access to HIV Care, Treatment and Prevention in LMIC. Universal Access includes access to both first- and second-line therapies.

Implicit in the call for Universal Access is the ready availability of tools to maximize the effectiveness of the strategic treatment interventions taken. Universal availability and use of appropriate, affordable CD4 testing and HIV viral load testing should maximize efficiency of first and second line therapies.

These laboratory tests are essential components of the cost-effective use of antiretroviral therapy over time, and their use is consistent with the public health approach to treatment. Current assays have been implemented in settings where they are feasible, and their use should be extended. New point-of-care assays for CD4 counts and viral loads are an urgent priority. WHO will use its good offices to mobilize funding agencies and diagnostics companies to address this urgent need.

Annex 1: Meeting Agenda

WHO CONSULTATION FOR GLOBAL RECOMMENDATIONS ON STANDARDIZED SECOND-LINE ANTIRETROVIRAL THERAPY FOR RESOURCE LIMITED SETTINGS

21 - 22 May 2007 - GENEVA, SWITZERLAND (WHO /UNAIDS Building - room D4 46025)

DAY 1 (May 21)

8:30 - 9:00	Registration
9:00 - 9:20	Introduction of the meeting and objectives <i>Teguest Guerma and Charlie Gilks (10´)</i> Introduction of participants (10´)
9:20 - 9:30	Expected meeting outcomes, working methods and development process for the recommendations <i>Marco Vitoria (10´)</i>
9:30 -10:00	Background and new evidence - I Public Health approach to ART and implications for treatment switching <i>Charlie Gilks (15´)</i> Prioritization exercise the development of new paediatric ARV formulations: Experience of the Paediatric ARV Working Group <i>Siobhan Crowley (15´)</i>
10:00 - 10:45	Overview of where we are (<i>Chair: Pedro Cahn</i>) Introduction: Perspectives on Use new ARV drugs and formulations in Resource-Limited Settings: How to protect the limited 2 nd line formulary <i>Pedro Cahn (5´)</i> Overview of current approaches to NRTI component of 2 nd Line ART regimens <i>Jens Lundgren (20´)</i> Overview of current approaches to PI component of 2 nd Line ART regimens <i>Scott Hammer (20´)</i>
10:45 – 11:00	Tea/coffee
11:00 - 11:30	Background and new evidence - II (<i>Chair: Pedro Cahn</i>) WHO Survey on Use of ART in resource limited settings in 2006: distribution and uptake of 1 st and 2 nd line regimens and forecast of demand for ARV drugs in low and middle-income countries <i>Francoise Renaud-Thery (15´)</i> 2 nd line ARV forecasting and pricing: Clinton Foundation HIV/AIDS Initiative <i>Dai Ellis (15´)</i>
11:30-12:30	General Discussion (60´)
14:00 - 15:00	Programmatic Experiences and Perspectives on 2 nd Line ART (<i>Chair: Paula Munderi</i>) <i>South Africa - Robin Wood (15´)</i> <i>ANRS - J. Francois Delfraissy (15´)</i> <i>MSF - Alexandra Calmy (15´)</i> <i>Brazil - Valdilea Veloso (15´)</i>
15:00-15:30	General Discussion (30´)
15:45 – 16:45	Breakout Parallel Sessions - I Group A: Working definition of 1 st and 2 nd line ARV drugs and reviewing how programmes are interpreting WHO treatment failure criteria for resource-limited settings (When to Switch ART?) (<i>Chair: Praphan Pranupak</i>) Group B: Principles and recommendations to guide a rational selection of 2 nd line ARV drugs in resource-limited settings (What to Switch to?) (<i>Chair: William Rodriguez</i>)
16:45 - 17:45	Group work presentation and plenary discussion (<i>Chair: Jean Francois Delfraissy</i>)
17:45 - 18:00	Summary of the day and review the agenda for the next day (<i>Chris Duncombe</i>)

DAY 2 (May 22)

09:00 - 09:15	Introduction on prioritization exercise: Why and How <i>Charlie Gilks</i>
09:15 - 10:15	Breakout Parallel Sessions - II: Group A: Prioritizing 2 nd line ARV agents (NRTI component) (Chair: <i>N Kumarasamy</i>) Group B: Prioritizing 2 nd line ARV agents (NRTI component) (Chair: <i>Alexandra Calmy</i>)
10:15 - 10:30	Tea/coffee
10:30 - 11:30	Group work presentation and plenary discussion (Chair: <i>Joia Mukerjee</i>)
11:30 - 13:00	Breakout Parallel Sessions - III Group A: Prioritizing 2 nd line ARV agents (PI component) (Chair: <i>Valdilea Veloso</i>) Group B: Prioritizing 2 nd line ARV agents (PI component) (Chair: <i>Scott Hammer</i>)
13:00 - 14:00	Lunch
14:00 - 15:00	Group Work Presentations and plenary discussion (Chair: <i>Scott Hammer</i>)
15:00 - 15:15	Tea/coffee
15:15 - 15:30	Next steps <i>Marco Vitoria</i>
15:30 - 16:00	Wrap up and Closing <i>Charlie Gilks</i>

Annex 2: List of Participants

MEETING ON STANDARDIZING SECOND-LINE ART IN RESOURCE-LIMITED SETTINGS WHO-GENEVA, 21-22 MAY 2007

1. Anna Bobrova
Institute of Epidemiology and Infectious Diseases
Academy of Medical Sciences of Ukraine
Department of HIV/AIDS
UKRAINE
2. Pedro Cahn
International AIDS Society
ARGENTINA
3. Alexandra Calmy
Médecins Sans Frontières
SWITZERLAND
4. Kaoeun Chetra
AIDS Care Unit
National Center for HIV/AIDS
Dermatology and STD (NCHADS)
CAMBODIA
5. Jean François DELFRAISSY
Agence Nationale de Recherches sur le Sida et les
Hépatites Virales (A.N.R.S)
FRANCE
6. Alaka Deshpande
Department for Medicine, Grant Medical College
and Sir J.J. Group. Govt. of Hospitals
INDIA
7. Andrea De Luca
Univertità Cattolica del Sacro Cuore
ITALY
8. Marina Dotsenko
Department of Infectious Diseases
Belorussian State Medical University
BELARUS
9. Chris Duncombe
HIV NAT
The Netherlands Australia Thailand Research
THAILAND
10. Dai Ellis
Drug Access Team
Clinton Foundation HIV/AIDS Initiative
USA
11. Scott Hammer
Department of Medicine
Columbia University
USA
12. Bernard Hirschel
Division des Maladies infectieuses, Unité
VIH/SIDA
Hôpital Universitaire de Genève
SWITZERLAND
13. Svilen Konov
HIV i-Base
UNITED KINGDOM
14. N. Kumarasamy
YRG Centre for AIDS Research and Education
INDIA
15. Jens Lundgren
University of Copenhagen
Copenhagen International Coordinating Centre
(ICC) for INSIGHT, Hvidovre University Hospital
DENMARK
16. Joia S. Mukherjee
Partners In Health (PIH)
USA
17. Paula Munderi
MRC/UVRI Uganda Research Unit on AIDS
Uganda Virus Research Institute
UGANDA
18. Lydia Mungherera
National Forum of PLWHA
UGANDA
19. Sylvia Ojoo
National AIDS and STI Control Programme
HIV-NAT Kenyatta National Hospital Grounds
KENYA
20. Fernando Pascual
Médecins Sans Frontières
SWITZERLAND
21. Praphan Phanuphak
Thai Red Cross AIDS Research

Centre
THAILAND

22. William Rodriguez
Harvard Medical School Division of AIDS
Office of International Programs
USA

23 Papa Salif Sow
Dakar University Hospital
SENEGAL

24. Ian Sanne
University of Witwatersrand
SOUTH AFRICA

25. Luis Soto-Ramirez
Molecular Virology Unit
Departamento de Infectologia
Instituto Nacional de Ciencias Medicas Y
Nutrición,
MEXICO

26. Somsit Tansupaswadikul
WHO Collaborating Centre for Training
and Research in HIV/AIDS
Clinical Management and Counselling
Bamrasnaradura Institute
THAILAND

27. Pham Thi Thanh Thuy
Infectious Diseases Department, Bach Mai
Hospital
VIET NAM
E-mail: [pham t thuy@yahoo.com](mailto:pham_t_thuy@yahoo.com)

28. Valdilea Veloso
Centro de Pesquisa Clínica em HIV/AIDS
Instituto de Pesquisa Clínica Evandro Chagas
Fundação Oswaldo Cruz (FIOCRUZ)
BRAZIL

29. Robin Wood
The Desmond Tutu HIV Centre
Institute of Infectious Disease & Molecular
SOUTH AFRICA

WHO/Regional Offices

WHO Regional Office for Americas (AMRO)
Jack Noreen, Senior Adviser, HIV Care and
Treatment, CAREC/PAHO, TrinidadandTobago

WHO Regional Office for Europe (EURO)
Irina Eramova, Senior Medical Officer
STI/HIV/AIDS Programme, Denmark

WHO Regional Office for South Asia (SEARO)
Po Lin Chan, Country Office, India

WHO/HQ
Teguest Guerma, Associate Director, HIV
Department
Charles Gilks, Director-Coordinator, HIV/ATC
Silvia Bertagnolio, HIV/ATC
Siobhan Patricia Crowley, HIV/ATC
Micheline Diepart, HIV/ATC
Peter Graaff, HIV/SSH
Vincent Habiyambere, HIV/SSH
Paulo Meireles, UNITAID
Françoise Renauld-Théry, HIV/SSH
Donald Sutherland, HIV/ATC
Marco Vitoria, HIV/ATC

Conflict of Interest Disclosure Information

The following international experts that participated in the WHO meeting on standardizing 2nd line ART, which occurred in Geneva, from 21 to 22 May 2007, and declared no conflicts of interest: Dr. Bennett, Dr. Bobrova, Dr. Calmy, Dr. Chentra, Dr. Crowley, Dr. Delfraissy, Dr. Deshpande, Dr. Diepart, Dr. De Luca, Dr. Chan, Dr. Dotsenko, Dr. Duncombe, Mr. Ellis, Dr. Eramova, Mr. Graaf, Dr. Habiyambere, Dr. Hirschel, Mr. Konov, Dr. Kumarasamy, Mr. Meireles, Dr. Mukerjee, Dr. Mungherera, Dr. Noreen, Dr. Ojoo, Mr. Pascual, Dr. Phanupak, Dr. Renauld-Théry, Dr. Rodriguez, Dr. Sow, Dr. Soto-Ramirez, Dr. Sutherland, Dr. Tansupaswadikul, Dr. Thuy, Dr. Veloso, Dr. Vitoria and Dr. Wood. Dr. Cahn declared that he serves as advisory board member of Abbott, Avexa, Glaxo-Smith Kline, Tibotec and Pharmassay. Dr. Gilks declared that he receives research support grant from Abbott, Boehringer Ingelheim, Gilead and Glaxo-Smith Kline. Dr. Hammer declared that he serves as a scientific adviser to Merck, Pfizer Progenics and Tibotec. Dr. Ludgren informed that he receives research support grant, and speakers fees and served as an ad-hoc consultant for Abbott, Boehringer Ingelheim, Bristol Meyers-Squibb, Gilead, Glaxo-Smith Kline, Pfizer, Roche and Tibotec. Dr. Munderi declared that she receives research support from Abbott, Boehringer Ingelheim, Gilead and Glaxo-Smith Kline. Dr. Sane informed that he serves as a global advisory board member of Abbott, Glaxo-Smith Kline, Merck Sharp & Dhome, Schering- Plough, Pfizer and TherapyEdge.

Annex 3: Prioritization exercise for second-line regimens

NRTI Component

Domain	Subcomponents
Efficacy	Prior first-line regimen (NRTI), Global failure Ability to push 184 mutation Cross resistance with first-line and with the chosen second-line NRTI Virological suppression and clinical efficacy from clinical trials
Simplicity	No cold chain, Co-formulatability, Dose frequency, Number of pills Food restrictions, FDC availability
Toxicity	Low incidence of toxicity, Minimal monitoring Possible adverse effect on co-morbidities such as hyperlipidaemia
Population Coverage	Suitability or use in special populations, HIV-2 Hepatitis coinfection, TB coinfection, Pregnancy
Potential for low cost	API cost Multiple sourcing Mg per dose large dosing requirements, such as 300mg BID for abacavir, limit potential cost reduction)
Compatibility with paediatric regimens	Family-centered approach

NRTI component (using thymidine-based ART in the first-line regimen)							
	Efficacy	Simplicity	Toxicity	Population Coverage	Low Cost Potential	Paediatric Compatibility	Ranking
ABC+ddI							
AZT+ddI							
TDF+ddI							
ABC+TDF							
TDF+3TC*							
ddI+3TC*							
ABC+3TC*							
AZT+3TC*							
AZT/3TC+TDF							

*3TC and FTC are interchangeable

PI Component

PI Component							
	Efficacy	Simplicity	Toxicity	Population Coverage	Low Cost Potential	Paediatric Compatibility	Ranking
ATV/r							
IDV/r							
LPV/r							
SQV/r							
RTV (boosting only)							

Annex 4: Rationale for prioritization and recommended dosages of second-line antiretrovirals

NRTI component:

RTI component of second-line regimen	Comments
<p>ABC + ddI</p> <p>and</p> <p>AZT + ddI</p>	<ul style="list-style-type: none"> All NRTIs are negatively affected by multiple TAMs. AZT and d4T select for TAMs. TDF, ABC, ddI and d4T select for K65R mutation. 3TC selects for M184V mutation. ABC and ddI are not affected by this mutation if it occurs in isolation (this is very rare). No NRTI second line combination is optimal with current approaches. Factors supporting ddI as a candidate for second-line therapy: <ul style="list-style-type: none"> It is infrequently used in first-line. M184V mutation induced by 3TC seems not to affect the clinical activity of ddI. ≥2 type I TAMs (41L, 210W, 215Y) are needed to reduce ddI activity. Type II TAMs (67N, 70R, 215F, 219Q/E) do not affect ddI activity. ABC/ddI is a suitable option at this moment, particularly in settings where TDF is not available. AZT has a relatively high genetic barrier to resistance and is particularly useful in patients failing an initial ARV regimen with M184V and K65R mutations. HIV-1 with TAMs shows reduced susceptibility to all NRTIs, most notably AZT, whereas HIV-1 with K65R shows reduced susceptibility to all NRTIs except AZT. K65R and TAMs rarely occur together in patients. However, when present together, K65R can restore susceptibility to AZT.
<p>TDF + ABC</p>	<ul style="list-style-type: none"> Some experts that suggest avoiding this combination because of the risk of emergence of the NRTI cross-class mutation, K65R. The emergence of K65R may have limited practical significance in settings where few other drugs are available. In virological terms: <ul style="list-style-type: none"> ABC retains activity with M184V mutation and a few TAMs. TDF has a better performance as requires more TAMs mutations in order to lose the activity. Cost and availability of both drugs in LMIC limit its use, independently of resistance profiles.
<p>TDF + ddI</p>	<ul style="list-style-type: none"> Theoretically TDF+ddI may be the best combination in failing regimens containing d4T or AZT. <ul style="list-style-type: none"> both drugs require a large number of TAMs in order to significantly lose the activity. M184V mutation can increase the activity of both drugs. Some uncertainties about this combination. <ul style="list-style-type: none"> drug interactions and toxicity profile. paradoxical reductions in CD4 counts. higher virological failure rates with NNRTIs and some triple NRTI regimens. When used with PIs, there is no evidence of high failure rate, paradoxical reactions. More studies are needed. However, it is an emerging option to be considered, with close monitoring and only with boosted PIs.
<p>TDF + 3TC</p>	<ul style="list-style-type: none"> The majority of patients switching to second-line have 3TC resistance The presence of M184V mutation can increase the susceptibility to other NRTIs (d4T, AZT and TDF). M184V is associated with reduction of viral fitness. 3TC is useful in patient with co-infection with Hepatitis B (as is TDF) and should be maintained in order to avoid hepatic flares.

NRTI Component (cont'd):

NRTI	Once daily dosing in experienced patients	Availability as FDC	Safety in pregnancy	Safety in Children and Adolescents	Activity against Hepatitis B virus	Major Adverse Reactions
ABC	Yes	Yes	Yes	Yes	No	Hypersensitivity reaction
AZT	No	Yes	Yes	Yes	No	GI intolerance, anemia, neutropenia, lactic acidosis
ddI	Yes	No	Yes	Yes	No	GI intolerance (buffered formulations), pancreatitis, neuropathy, lactic acidosis
TDF	Yes	Yes	Yes ¹	Insufficient data (potential mineral bone toxicity)	Yes	Renal toxicity (renal tubular dysfunction)
3TC ²	Yes	Yes	Yes	Yes	Yes	Pancreatitis (very rare)

¹ Despite be established as FDA pregnancy category B drug (i.e., no teratogenic risk in humans), TDF has been associated with potential mineral bone toxicity, particularly to the fetuses and children. Therefore, its use in 2nd line regimens should be considered with caution in pregnant patients.

² FTC is an equivalent alternative to 3TC because they are structurally related and share pharmacological properties and resistance profiles.

PI Component:

PI	Once daily dosing in experienced patients	Safety in pregnancy	Pill burden with recommended doses (pills/day)	Compatibility with rifampicin
ATV/r	Yes	Yes	3	No
FPV/r	No	Insufficient data	4	No
IDV/r	No	Yes ¹	4-6	No
LPV/r	No	Yes ¹	4-6	Yes ²
NFV	No	Yes	10	No
SQV/r	No	Yes ¹	6-12	Yes ²

1. Qualified as Yes, as it appears to be safe in usage to date (FDA pregnancy category C). Pregnancy registry data demonstrating safety.

2. Usual ritonavir-booster dose need to be increased to 400 mg bid, but it also increases the GI intolerance and toxicity risk.

Source: Adapted from "Approaches to PI Component of second-line ART in Resource Limited Settings". Scott M. Hammer. Columbia University: WHO Second-Line Meeting, 21-22 May, 2007.

**Dosages of Antiretroviral Drugs Used in Second-Line Regimens Recommended in 2006
WHO ART Guidelines for Adults and Adolescents**

Generic Name	Standard Dose	
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors		
Abacavir (ABC)	300 mg twice daily or 600 mg once daily	
Zidovudine (AZT)	250-300 mg twice daily	
Emtricitabine (FTC)	200 mg once daily	
Didanosine (ddI) ¹ buffered tabs or enteric coated (EC) capsules	>60 kg: 400 mg once daily <60 kg: 250 mg once daily	
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily	
Tenofovir (TDF)	300 mg once daily	
Proteases Inhibitors		
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg once daily	
Fos-amprenavir + ritonavir (FPV/r)	700mg + 100 mg twice daily	
Indinavir + ritonavir (IDV/r) ²	800 mg + 100 mg twice daily	
Lopinavir/ritonavir (LPV/r) ³	Capsule Lopinavir 133.3mg / ritonavir 33.3mg	<ul style="list-style-type: none"> • three capsules twice daily (400/100mg twice daily) • four capsules twice daily when combined with EFV or NVP (533/133,33 mg twice daily)
	Tablet (heat stable formulation) Lopinavir 200mg / ritonavir 50mg	<ul style="list-style-type: none"> • Treatment naïve patients • Two tablets twice daily irrespective of coadministration with EFV or NVP (400/100 mg twice daily)
		<ul style="list-style-type: none"> • Treatment experienced patients • Three tablets twice daily when combined with EFV or NVP (600/150 mg twice daily)
Nelfinavir (NFV) ⁴	1250 mg twice daily	
Saquinavir + ritonavir (SQV/r) ⁵	1000 mg + 100 mg twice daily	

- (1) Didanosine dose should be adjusted when coadministered with tenofovir. If weight is above 60 kg, the recommended dose is 250 mg once daily. If weight is below 60 kg, the recommended dose is 200 mg once daily.
- (2) Some recent studies support the use of IDV/r at a lower dose (400/100 mg twice daily) in order to reduce the toxicity.
- (3) In TB/HIV coinfecting patients that require concomitant TB treatment using rifampicin, adjustment in the standard LPV/r dose is required. In this situation, LPV 400 mg/RTV 400 mg twice daily should be used under close clinical and laboratory monitoring.
- (4) Marketing authorization of Roche's nelfinavir (Viracept®) was recently suspended after the product recall motivated by the contamination of the product with a genotoxic substance.
- (5) In TB/HIV coinfecting patients that require concomitant TB treatment using rifampicin, adjustment in the standard SQV/r dose is required. In this situation, SQV 400 mg/RTV 400 mg twice daily should be used under close clinical and laboratory monitoring.

Annex 5a: Availability of recommended 2nd line antiretroviral drugs

International Nonproprietary Name (INN)	Dosage form	Preferred Strengths (adults)	Medium price per patient per year (in U\$)		Suppliers	
			Low income	Middle income	Originator	Generics
Abacavir	tablets	300 mg	637 ^a (520-887)	953 ^a (642-969)	GlaxoSmithKline	Aurobindo Pharma Ltd.; Cipla Ltd.; Eastern Surgical Company; Emcure; Hetero Drugs Ltd.; Laboratorio Elea S.A.C.I.F.y A; Laboratorios Filaxis Argentina; Laboratorios Richmond S.A.C.I.F; Matrix Laboratories Ltd.; Ranbaxy Ltd.
Tenofovir	tablets	300 mg	219 ^a (208-234)	372 ^a (237-1294)	Gilead Sciences	Matrix, Ranbaxy, Hetero; Cipla; Aurobindo; Emcure; Aspen
Didanosine	buffered tablets	100 mg	239 ^a (239-311)	307 ^a (263-569)	Bristol-Myers Squibb	Apotex Mexico (Protein, S.A. de C.V.); Aspen Pharmacare Ltd.; Aurobindo Pharma Ltd.; Cipla Ltd.; Cristalia, productos quimicos farmaceuticos Ltda.; Emcure; Hetero Drugs Ltd.; Laboratorio Dosa S.A; Laboratorios Filaxis Argentina; Laboratorios Richmond S.A.C.I.F; Ranbaxy Ltd.; Zhejiang Huahai Pharmaceutical Co., Ltd.
		150 mg	208 ^b (172-244)		Bristol-Myers Squibb	Aspen Pharmacare Ltd.; Aurobindo Pharma Ltd.; Cipla Ltd.
		200 mg	228 ^a (228-311)	176 ^a (176-343)	Bristol-Myers Squibb	Aurobindo Pharma Ltd; Cipla Ltd.; Laboratorios Richmond S.A.C.I.F; Macleods Pharmaceuticals Ltd.; Ranbaxy Ltd.;
	EC capsules	200 mg	228 ^a (228-311)	176 ^a (176-343)	Bristol-Myers Squibb	Aurobindo Pharma Ltd;
		250 mg	171 ^b (103 - 239)		Bristol-Myers Squibb	Aurobindo Pharma Ltd.; Cipla Ltd.; Ranbaxy Ltd.;
		400 mg	288 ^a (278-289)	695 ^a (406-698)	Bristol-Myers Squibb	Aurobindo Pharma Ltd.; Hetero Drugs Ltd.; Cipla Ltd.; Ranbaxy Ltd.

International Nonproprietary Name (INN)	Dosage form	Preferred Strengths (adults)	Medium price per patient per year (in U\$)		Suppliers	
			Low income	Middle income	Originator	Generics
Lamivudine	tablets	150 mg	51 ^a (50-51)	59 ^a (57-63)	GlaxoSmithKline	Aspen Pharmacare Ltd.; Cambodia Pharmaceutical Enterprise; Cipla Ltd.; Cosmos Ltd.; Cristalia, productos quimicos farmaceuticos Ltda.; Eastern Surgical Company; Emcure; Hetero Drugs Ltd.; Laboratorio Dosa S.A; Laboratorio Elea S.A.C.I.F.y A; Laboratorios Filaxis Argentina; Laboratorios Richmond S.A.C.I.F; Matrix Laboratories Ltd.; Neto Machado, Labogen SA; Ranbaxy Ltd.; Strides Arcolab Ltd.; The Government Pharmaceutical Organization;
		300 mg	61 ^b (55 - 66)			
Zidovudine	capsules	250 mg	242 ^a (242-242)	249 ^a (243-253)	GlaxoSmithKline	Apotex Mexico (Protein, S.A. de C.V.); Aspen Pharmacare Ltd.; Aurobindo Pharma Ltd.; Combino Pharm S.L.; Eastern Surgical Company; Laboratorio Dosa S.A; Laboratorios Filaxis Argentina
	tablets	300 mg	135 ^a (128-165)	136 ^a (122-228)	GlaxoSmithKline	Aspen Pharmacare Ltd.; Aurobindo Pharma Ltd.; Cambogia Pharmaceutical Enterprise; Cipla Ltd.; Combino Pharm S.L.; Cosmos Ltd.; Eastern Surgical Company; Emcure; Hetero Drugs Ltd.; Ranbaxy Ltd.; The Government Pharmaceutical Organization; Xiamen Mchem Pharma Group Ltd.
Lopinavir/ritonavir	gel capsule	133/33 mg	538 ^a (500-646)	2963 ^{a,e} (2123-4440)	Abbott Laboratories	Hetero Drugs Ltd.; Matrix
	heat stable tablet	200/50 mg	507 ^a (500-525)	5658 ^{a,e} (5063-6252)	Abbott Laboratories	Matrix

International Nonproprietary Name (INN)	Dosage form	Preferred Strengths (adults)	Medium price per patient per year (in US\$)		Suppliers	
			Low income	Middle income	Originator	Generics
Saquinavir	capsules	200 mg	1077 ^a (1012-1083)	2154 ^a (1643-2359)	Roche	Cristalia, productos quimicos farmaceuticos Ltda.; Laboratorios Richmond S.A.C.I.F;
	tablets	500 mg	1587 ^b (968-2205)		Roche	
Atazanavir	capsules	150 mg	389 ^b (353-425)		Bristol-Myers Squibb	
		200 mg	487 ^b (439-534)		Bristol-Myers Squibb	
Fos-amprenavir	tablets	700 mg	1524 ^d		GlaxoSmithKline	
Ritonavir	capsules	100 mg	114 ^a (99-141)	351 ^a (81-888)	Abbott Laboratories	Cipla Ltd.; Cristalia, productos quimicos farmaceuticos Ltda.; Hetero Drugs Ltd.
Indinavir	capsules	400 mg	383 ^a (382-435)	695 ^a (406-698)	Merck Sharpe & Dohme	Cipla Ltd.; Cosmos Ltd.; Eastern Surgical Company; Emcure; Hetero Drugs Ltd.; Laboratorio Dosa S.A; Laboratorio Elea S.A.C.I.F.y A; Laboratorios Filaxis Argentina; Laboratorios Richmond S.A.C.I.F; Macleods Pharmaceuticals Ltd.; Ranbaxy Ltd.
Nelfinavir	tablets	250 mg	1021 ^a (992-1108)	2086 ^a (1338-2192)	Roche ^f	Cipla Ltd.; Eastern Surgical Company; Hetero Drugs Ltd.; Laboratorio Dosa S.A; Laboratorio Elea S.A.C.I.F.y A; Laboratorios Filaxis Argentina; Laboratorios Richmond S.A.C.I.F; Macleods Pharmaceuticals Ltd.
		625 mg	9198 ^c		Pfizer	

(a) Prices extracted from WHO Global Price Report Mechanism - (<http://www.who.int/hiv/amds/price/hdd/index.aspx>), accessed in May 2007;

(b) Prices extracted from MSF drug price database for developing countries - "Untangling the web of price reductions" - 10th Edition - July 2007 (www.accessmed-msf.org/documents/Untangling10.pdf);

(c) Price extracted from POC-IT HIV Drug Guide - Johns Hopkins University - USA (<http://www.hopkins-hivguide.org/drug/index.html?navigationId=7591&siteId=7151>), assessed in May 2007;

(d) GlaxoSmithKline information (press release - <http://www.gsk.com/ControllerServlet?appld=4&pageId=402&newsid=840>);

(e) A recent public announcement from Abbott laboratories have informed that the price of LPV/r capsules and tablets was be reduced to US\$ 1,000 per patient per year in low- middle income countries (http://www.abbott.com/global/url/pressRelease/en_US/60.5:5/Press_Release_0442.htm).

(f) Marketing authorization of Roche's nelfinavir (Viracept[®]) was recently suspended after the product recall motivated by the contamination of the product with a genotoxic substance.

Annex 5b: Regulatory status of recommended 2nd line of antiretroviral drugs (as at 19 May 2007)

International Nonproprietary Name (INN)	Formulation	WHO	FDA	EMEA	Registration number in priority countries (97)	
					Originator	Generics
Abacavir	tablets	GlaxoSmithKline	Cipla; Aurobindo; GlaxoSmithKline; Matrix	GlaxoSmithKline	66	11
Tenofovir	tablets	Gilead Sciences, Inc.	Gilead Sciences Inc.	Gilead Sciences, Inc.	26	1
Didanosine	buffered tablets 100mg	Bristol Myers Squibb	Aurobindo Bristol Myers Squibb	Bristol Myers Squibb	32	21
	buffered tablets 150mg	Bristol Myers Squibb	Aurobindo Bristol Myers Squibb	Bristol Myers Squibb	26	6
	buffered tablets 200mg	Bristol Myers Squibb	Aurobindo Bristol Myers Squibb	Bristol Myers Squibb	6	8
	EC capsules 200 mg	Aurobindo				1
	EC capsules 250	Bristol Myers Squibb	Bristol Myers Squibb	Bristol Myers Squibb	22	2
	EC capsules 400	Bristol Myers Squibb	Bristol Myers Squibb	Bristol Myers Squibb	22	3
Lamivudine	tablets 150mg	Cipla Ltd GlaxoSmithKline Aurobindo Aspen Pharmacare Ltd Ranbaxy Laboratories Strides Arcolab	GlaxoSmithKline Aurobindo; Matrix Laboratories Ltd. Ranbaxy Laboratories	GlaxoSmithKline	42	40
	tablets 300mg	Aurobindo	Aurobindo		0	9

International Nonproprietary Name (INN)	Formulation	WHO	FDA	EMEA	Registration number in priority countries (97)	Registration number in priority countries (97)
					Originator	Originator
Zidovudine	capsules 250mg	Combino Pharm S.L. GlaxoSmithKline	GlaxoSmithKline;	Combino Pharm S.L. GlaxoSmithKline	71	5
	tablets 250mg	Cipla Ltd; Combino Pharm Aspen Pharmacare Ltd GlaxoSmithKline Ranbaxy Laboratories Aurobindo Pharma Ltd	Ranbaxy Laboratories Aurobindo Pharma Ltd; GlaxoSmithKline	Combino Pharm GlaxoSmithKline	67	40
Lopinavir/ritonavir	gel capsules	Abbott Laboratories	Abbott Laboratories	Abbott Laboratories	55	1
	heat stable tablets	Abbott Laboratories	Abbott Laboratories	Abbott Laboratories	1	0
Saquinavir	capsules	Roche	Roche	Roche	20	1
	tablets	Roche	Roche	Roche	5	0
Atazanavir	capsules		Bristol-Myers Squibb	Bristol-Myers Squibb	6	0
Fos-amprenavir	tablets		GlaxoSmithKline	GlaxoSmithKline	0	0
Ritonavir	capsules	Abbott Laboratories	Abbott Laboratories	Abbott Laboratories	53	3
Indinavir	capsules	Merck Sharpe & Dohme	Merck Sharpe & Dohme	Merck Sharpe & Dohme	71	31
Nelfinavir	Tablets 250 mg	Roche ¹	Roche ¹	Roche ¹	15	15

(1) Marketing authorization of Roche's nelfinavir (Viracept®) was recently suspended after the product recall motivated by the contamination of the product with a genotoxic substance.

Annex 6: Meeting Minutes - WHO GDG for Anti-retroviral Therapy in Adults

Feb 24th 2007 - West Bonaventure Hotel, Los Angeles, USA

Participants: This group was composed by some Guidelines Development Group (GDG) members who were attending the CROI 2007 (independently of any WHO travel support). The participants were: Alexandra Calmy, Diane Havlir, N. Kumarasamy, Joep Lange, Judith Currier, Marco Vitoria, Mauro Schechter, Paula Munderi, Pedro Cahn, Praphan Pranupak and Scott Hammer. Charlie Gilks, Fabio Scano, Marco Vitoria and Siobhan Crowley attended this meeting as WHO representatives.

Objectives: 1) To establish a priority list of ARV single drugs and fixed dose combinations to be used in adults for WHO drug prequalification program; 2) To discuss potential amendments on 2006 WHO adults ART guidelines and how to disseminate them.

Background

The next Expert Committee on the selection and Use of Essential Medicines will be held in Geneva in 3rd week of March 2007. During this meeting, applications for inclusion, change or deletion of medicines will be evaluated in order to update the Essential Medicine's List (EML). Product applications for some ARV fixed dose combinations (doubles and triples drug combinations) were submitted to the evaluation of the Expert Committee. Some of these products are currently recommended as possible first-line treatment options in the WHO ART guidelines but are not necessarily the most preferred in a Public Health perspective. Furthermore, the global treatment recommendations lack specificity enough to guide the EML committee and prequalification program in terms of priority drugs to be evaluated. Considering these aspects, the Department of Medicines Policy and Standards (PMS) requested HIV Department to establish the **priority list** of these ARV combinations. They would like to use this list as a guidance on what they should focus on during the EML expert committee meeting to be held in March, and also according to the recently procedures established PSM for assessing the acceptability of pharmaceutical products for purchasing by UN agencies.

Considering these arguments, WHO/HIV/ATC would like to get the opinion of Guidelines Development Group on ART (GDG) in order to establish this list, accordingly with the major technical and programmatic parameters.

Furthermore, WHO/HIV/ATC would like to discuss with GDG about some **potential amendments of WHO guidelines**, as d4T and IDV dose reduction and TDF use in pregnancy.

Summary of the rationale, discussions & decisions:

1) Preferred second-line drugs:

The following parameters were considered for each regimen/formulation currently recommended in 2006 WHO adult ART Guidelines:

- Efficacy/Potency;
- Tolerability/Acceptability;
- FDC availability/ Pill burden;
- Clinical experience;
- Use in specific populations (pregnant and breastfeeding women, children, TB/HIV, Hep B & C co-infections, HIV-2 infection);
- Availability;
- Cost.

The preferred approach to 2nd line current global ART guidelines is the use of 2 new nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and a ritonavir-boosted PI.

Considering that AZT/3TC and d4T/3TC has been the major NRTI component used in 1st line regimens, ABC and TDF are considered as the most adequate options to compose the new NRTI component with ddI (which is considered as key drug in the current 2nd line regimens). It is difficult to establish what would be the preferential or alternative drug in this situation, as there is no head to head study comparing TDF or ABC as part of 2nd line regimens and both have different advantages/disadvantages when considering the parameters listed above. However, the price of ABC is significantly higher than TDF (particularly in LMIC, where accordingly the WHO/PRM the median price of ABC is US\$ 887/patient/year and TDF is US\$ 219/patient/year), but TDF is not approved for use in children, adolescents and pregnant/breastfeeding woman. Both has been frequently used as an option in 1st line NRTI component, particularly in situations of mitochondrial toxicity (particularly lipoatrophy) or as the 3rd NRTI in triple nuke approach. In terms of orderly use of these NRTIs, ddI (particularly in enteric coated formulation) should be considered a priority 2nd line drug, followed by TDF or ABC, accordingly with the availability and cost. Ideally, both drugs should be available to permit some toxicity management and specific population coverage.

Regarding PIs, the GDG recognized that this is also a complex decision and there is no adequate studies that perform clinical comparisons among different boosted PIs in ARV experienced patients and reminded that the few recent head-to-head trials were conducted only in ART naive patients or in heavily treated individuals. However, for programmatic reasons, Lopinavir/ritonavir (LPV/r), particularly as a heat stable formulation should be the preferred boosted PI as it is the only PI available as a FDC. Atazanavir boosted with low dose ritonavir was suggested as the most suitable alternative to LPV/r , as it has a low pill burden, a different toxicity profile when compared with other PIs and may become more available and cheap in the near future. However, the group recognize that the manufactures sources for these products are still limited and need to be expanded. Other boosted PI options (SQV, FPV and IDV) can be considered in special situations if the LPV/r and ATV are not available. NFV is considered as less potent than boosted PIs and would be an option only if cold chain is not available.

Considering all these arguments, the list of key products to compose the second-line ARV products is:

- **Didanosine (preferentially as a enteric coated formulation)**
- **Abacavir**
- **Tenofovir**
- **Lopinavir/ritonavir (as a heat stable formulation tablet)**
- **Atazanavir**
- **Ritonavir (as a heat stable formulation tablet)**

The GDG also suggested that a specific note should be drafted to the effect that for now, the newer PIs (e.g., Tipranavir, Darunavir) and drugs of new classes (e.g., Maraviroc, Raltegravir) should be preserved for use in salvage regimens.

2) Priorities for Prequalification Programme: Considering what is currently included and not included in the EOI list, the following priority ranking list of ARV products (including 1st and 2nd line) was proposed for consideration by WHO pre qualification programme:

Urgently required ARVs
• Tenofovir
• Ritonavir (heat stable formulation tablet)
• LPV/r (heat stable formulation tablet)
• TDF/FTC or TDF/3TC (as FDC)
• TDF/FTC/EFV or TDF/3TC/EFV (as FDC)
• Efavirenz (600 mg tablet)

However, this group was unable to prioritize in order the components list above and more discussion is needed. WHO has proposed to convene a specific face-to face meeting or a video conference with the GDG for this discussion (May or June 2007).

3) Potential Amendments of 2006 WHO Guidelines:

3.1) Stavudine (d4T) dose reduction (Amendment proposed that d4T should be dosed as 30mg bid for all patients regardless of the body weight)

Rationale: 1) Antiviral efficacy maintained: a meta-analysis of 8 randomized trials and 3 cohorts, including 11'729 patients study has been recently presented (*Andrew Hill and al, WAC Toronto 2006*) and suggest that antiviral efficacy as defined by the proportion of patients below 50 copies is comparable to with stavudine 30mg and 40 mg bd.; 2)Toxicity dose dependant: polyneuropathy has been shown to be dose dependant in the first phase 1 and 2 dose ranging pre-approval trials (*Browne M et al., JID 1993, Petersen E and al, JID 1995*). Other adverse event such as lipoatrophy (only 4 dose reductions trials evaluated lipoatrophy) and lactic acidosis might be dose related. So far, a study done by *Sanchez-Conde et al. (HIV Clinical Trial 2005)* did show a reduction of MtDNA depletion in patients on 30 mg as compared to patients on 40mg of stavudine.

Expected outcome: Potential benefit: no weight adjustment, increased simplicity at country level, decrease toxicity.

Challenge: Long term monitoring needed, may not be effective enough to prevent the occurrence of toxicity, but may delay it. Also need to maintain an alternative substitution for AZT-related toxicity.

Caveat: Most of the studies reported in the meta-analysis have different design, some of them report data from naive patients, some of them of patients already on d4T regimen, and the endpoint on toxicity are very diverse.

Conclusion: GDG agreed that in view of clinical and virological efficacy data and improved safety data use of the 30 mg formulation for all patients would be safer interim way to enable continued use d4T and could be expected to decrease toxicity. However, the group cautioned that this should not be taken as a message to endorse the use of d4T as a preferred drug. The proposed amendment should be included in WHO website and also in paper format to be added to hard copy version of ART guidelines that was just printed for distribution.

3.2) Indinavir (IDV) dose reduction (Amendment proposed that IDV can be used as 400mg bid when boosted by 100 mg ritonavir twice daily- i.e. IDV/r 400mg/100mg bid - instead of the current standard dose of 800mg/100mg bid)

Rationale: The efficacy of Indinavir/ritonavir (IDV/r) 400mg/100 mg twice daily has been evaluated in several trials: a French study enrolling 40 treatment naïve patients showed in OT analysis at 48 weeks that 96% and 74% of the patients had VL below 400 and 50 copies respectively (*Duvivier et al., Antiviral 2003*). A study have shown that therapeutic C_{min} levels of IDV were achieved in more than 80% of the subject in a small open label pharmacokinetic study (*Boyd et al., Antiviral 2005*). Another open label non randomized study showed that 80 antiretroviral naïve patients were reaching less than 50 copies at week 96 (OT analysis) (*Mootsikapun et al., Antiviral therapy 2005*). Despite the lack of comparative studies, the IDV/r 400mg/100mg bid is recommended by 2005 European Guidelines and the 2006 French guidelines.

Expected outcome: Less toxicity, reduction of cost, provide a new boosted PI available in the drug formulary.

Conclusion: GDG highlighted that this specific dosage is already included in the 2006 version of WHO ART guidelines as a footnote. The wording in this footnote should be revised or considered to be "upgraded" to the main table, as well with inclusion of this information in the text. Need to further discuss with all group if it should be included as a formal amendment in WHO website or as an issue to be fully updated in the next guidelines version.

3.3) Use of TDF in pregnancy (Amendment proposed that TDF could be used in pregnant women and children)

Rationale: Despite to be a RTI drug with a better toxicity profile when compared with AZT and d4T in many clinical trials, new information regarding the safety of TDF in pregnancy and children are urgently needed as there is insufficient data on safety to recommend use in these populations.

This is one of the major limiting factors to adopt TDF as a preferred drug in a programmatic perspective, particularly LMIC were these are key populations to initiate ART.

There is no new info about TDF and pregnancy in the literature than existed before. Lynne Mofenson sent a message reminding that there are some data on pharmacokinetics from a study PACTG 1026 that suggest that the pK of TDF may be somewhat affected by pregnancy. There was a late breaker sent into CROI that looked at TDF pK in 19 women studied during the 3rd trimester and 2 weeks postpartum. The target TDF AUC exceeds the target in 74% (14/19) of women in third trimester and 86% (12/14) of women postpartum. The TDF AUC and peak levels were lower in 3rd trimester than in the same women in the postpartum period ($p=0.02$ and $p=0.069$), but trough levels were not different from postpartum levels. Furthermore, the recent Gilead's application submitted to WHO Essential Medicine's List (to be evaluated by EML Committee in the end of March) were also checked, and their position is that there is no adequate study in pregnant women to clarify this question. Her suggestion was that TDF would not be a preferred drug to use in pregnancy – while it is not contraindicated, it should be used with caution and wouldn't be a first choice of a drug to use in pregnant women on a widespread basis.

This is the same problem with TDF use in children. Data on TDF and bone mineral density in children was published in August 2006 from the NCI, which found an increase in bone markers and calcium excretion and decreases in bone density – the decrease in bone density correlated with decrease in viral load and young age. There was a published report of TDF-related Fanconi's syndrome in a pediatric patient last year (important to say that haven't been

published reports of this previously) so it occurs in kids as well as adults. Thus, TDF can't really be recommended as first-line option in children at this time.

Another point that should be considered is the limited data about renal safety in LMIC, particularly in Africa, where the prevalence of other co-morbidities that can influence the renal function in general population are higher than in industrialized countries. However some pharmacological studies presented at CROI suggested that TDF can cause a reduction in the glomerular filtration rate in long term.

Conclusion: Despite the absence of new clinical suggesting problems, the proposed amendment should not be included at this moment. However, in non-pregnant patients, the group suggested to revise the current text in the guidelines, with maintenance of the support the current statement that TDF can be used where routine screening renal function not undertaken, but highlighting that if available it is the preferred approach. Furthermore, add the statement that if patient develop clinical signs or anaemia on use of TDF containing regimen then renal function should be checked. Need to further discuss with all group if it should be included as an amendment in WHO website or as an issue to be fully updated in the next guidelines version.

Alexandra Calmy and Scott Hammer suggested the proposition below for TDF use:

- 1) The absence of lab tests should not be a contraindication for TDF use.
- 2) If there is access to lab tests, creatinine at the baseline and every 6-12 months is recommended. In older individuals, patients with little muscle mass or if the creatinine value is below the normal range, the creatinine clearance (using the using the Cockcroft-Gault formula) should be calculated to give a better picture of the renal function.
- 3) If risk factors for renal insufficiency (hypertension & other cardiovascular diseases, diabetes, anemia, proteinuria) are present, the creatinine clearance should be calculated at baseline and every 3-6 months.

3.4) Other ART issues:

- **TDF/ddI combinations:** New data from Glasgow Meeting held in end of 2006 support the current guidelines position that the association of TDF + DDI + PI/r can be used. No change required.
- **3rd line ARV regimens:** the initial proposal is to start a discussion on this topic, but do not yet need firm recommendations from the GDG. The current position is to suggest that this will be a country by country decision, but need to ensure UNITAID GFTAM start to consider how this will be included.
- **Unboosted PI use:** No new data and no change required.
- **Saquinavir with Rifampicin:** No new data and no change required.
- **ART and XDR-TB:** Addendum about co-management of HIV (ART) and XDR TB is under elaboration and will be circulated. There is an extremely limited data and experience in this situation, but the current trend is to start ART earlier in this case, particularly in patients with low CD4 count. Starting ART unlikely to worsen outcomes. Some information about drug-drug interaction between ARVs and 2nd line TB drugs will be added.
- **Establishment of a GDG "core" group:** Agree that a smaller group (4-5 persons) from the current GDG could be in more regular contact by conference call or face to face meetings to follow the potential issues to be updated in the WHO recommendations. WHO/HIV/ATC will decide how to organize, as there may be new internal rules on composition of WHO committees and experts groups.

Annex 7: Summary of ATV/r and LPV/r monotherapy studies

ATV/r monotherapy studies				
Study	Study design and authors	Population	Publication or Abstract	Outcomes
ATARITMO trial	Induction-Maintenance Pietro L. Vernazza,	Patients with viral load < 50 copies/mL on current regimen who had no history of drug resistance n=28	3 rd IAS: Abstract WeOa0204. Presented July 27, 2005	Subjects with VL <50 copies/mL were switched to atazanavir/ritonavir (300 mg/100 mg daily) monotherapy. 24 of 30 patients who had reached the 24-week endpoint. 22 patients had viral undetectable load. (Of the 2 virological failures, 1 had discontinued medication and 1 was found to have pre-existing protease resistance.)
Early Virological Rebound in a Pilot Trial of Ritonavir-Boosted Atazanavir as Maintenance Monotherapy	Single-arm single-centre pilot trial In naïve subjects Olle Karlstrom, Filip Josephson, and Anders Sonnerborg,	Adult HIV-1 infected patients, PI naïve subjects, were eligible if they had maintained a viral load <20 copies/mL for a minimum of 12 months on conventional ART n=30	J Acquir Immune Defic Syndr 2007;44:417–422	The trial regimen was atazanavir/ritonavir at a dose of 300/100 mg once daily. The atazanavir dose could be adjusted if plasma concentrations showed a low exposure. The study was intended to recruit 30 patients to be followed over 72 weeks. If 5 cases of virological failure occurred during this period, the study was to be terminated. The study was terminated according to protocol when 15 of the planned 30 patients had been recruited, because 5 cases of virological failure had occurred. In patients failing therapy, viral rebound was seen at weeks 12 through 16. Plasma atazanavir concentrations were not associated with the outcome. T Conclusions: Ritonavir-boosted atazanavir as maintenance monotherapy in HIV-1 infection might not be as potent as conventional ART.
ACTG 5201 Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virological suppression	Regimen simplification Induction maintenance Swindells S, DiRienzo AG, Wilkin et al	HIV-infected adults with virological suppression for 48 weeks or longer receiving their first protease inhibitor (PI)-based regimen n=36	JAMA. 2006 Aug 16;296(7):806-14.	Thirty-four patients were included in the analysis of the primary end point after 24 weeks: 1 withdrew voluntarily, and 33 continued the regimen. Virological success (absence of failure) through 24 weeks of simplified therapy occurred in 91% (31 of 34 patients; lower 90% confidence interval limit = 85%). Three participants experienced virological failure 12, 14, and 20 weeks after simplification, with plasma HIV-1 RNA levels of 4730, 1285, and 28 397 copies/mL, respectively. Resistance testing at failure did not identify PI resistance mutations. Plasma atazanavir concentrations at failure were low or below detection in 2 of 3 participants experiencing failure.

LPV/r monotherapy studies

Study	Study design and authors	Population	Publication or Abstract	Outcomes
MONARK Mono therapy Antiretroviral Kaletra trial	Randomised two arm study of standard HAART versus LPV/r monotherapy. Delfraissy J-F, Flandre P et al.	Naïve patients with a viral load of < 100,000 copies/ml and CD4+ cell count of > 100 cells/ml. n=138	XVI International AIDS Conference, Toronto, Canada (13 – 18 August 2006)	48-week study of LPV/r monotherapy compared to LPV/r + AZT/3TC in naive patients. After 24 weeks of follow up, there were no statistically significant differences between rates of virological suppression of < 400 copies/ml. A larger proportion of patients in the triple-drug therapy group had viral loads of < 50 copies on week 48 (98 versus 84%; p = 0.03).
OK study	Regimen simplification Induction/maintenance. Arribas J, Pulido F, Delgado R et al.	Patients who had been on LPV/r plus 2 NRTIs for ≥ 1 month, had maintained a HIV plasma viral load of < 50 copies/ml for > 6 months and had no history of virological failure during treatment with a PI.	J. Acquir. Immune Defic. Syndr. (2005) 40 (3):280-287.	Participants were randomly assigned to maintain their present regimen (control group) or to stop the NRTIs (OK group). The primary study outcome was the proportion of patients with < 500 copies/ml at 48 weeks. On intent-to-treat analysis, there were no significant differences in the proportion of participants with plasma viral load of < 500 copies/ml (81 and 95% in the OK and control groups, respectively; p = non-significant) at 48 weeks. All patients who achieved a plasma viral load of < 500 copies/ml at week 48 were also below the detection limit using the assay for < 50 copies/ml. Of the 21 patients who were assigned to the monotherapy arm, 3 had a loss of virological suppression defined as 2 consecutive measures of > 500 copies/ml 2 weeks apart; 1 patient discontinued treatment after a first result showed > 500 copies/ml and was subsequently lost to follow up. The two participants were successfully re-suppressed with the re-introduction of the NRTI backbone.

LPV/r monotherapy studies

<p>OK-04 study</p>	<p>Lopinavir/r as single-drug maintenance therapy in patients with HIV-1 viral suppression.</p> <p>Arribas J, Pulido F, Delgado R et al.</p>	<p>Essentially the same as OK study.</p> <p>Patients who had been on LPV/r plus 2 NRTIs for ≥ 1 month, had maintained a HIV plasma viral load of < 50 copies/ml for > 6 months and had no history of virological failure during treatment with a PI.</p> <p>n=205</p>	<p>XVI International AIDS Conference, Toronto, Canada (13 – 18 August 2006).</p>	<p>The primary end point was the proportion of participants without therapeutic failure at 48 weeks. Intensification with NRTIs was permitted in the LPV/r monotherapy arm if virological rebound occurred. These were not considered to be therapeutic failures if, after the re-introduction of the NRTIs, viral load decreased $> 1 \log_{10}$ copies/ml by 4 weeks after re-intensification and to < 50 copies/ml by 16 weeks after re-intensification. The main outcome comparison between the two arms was virological failure during treatment with HAART. At week 48, the proportion of patients without therapeutic failure was 94.0 and 89.8% in the monotherapy arm and in the control arm, respectively (p = non-significant).</p>
<p>Study M03-613</p>	<p>Antiretroviral-naive subjects using LPV/r monotherapy after initial induction treatment.</p> <p>Cameron W Da Silva B Arribas J et al.</p>	<p>Antiretroviral naive subjects and with plasma viral load of > 1000 N=92 randomized to switch to LPV/r monotherapy.</p> <p>n=155</p>	<p>XVI International AIDS Conference, Toronto, Canada (13 – 18 August 2006).</p>	<p>Eligible patients were randomized to start zidovudine plus lamivudine plus efavirenz (the control arm; (n = 51) or to zidovudine plus lamivudine plus LPV/r (n = 104). 92 were switched to maintenance monotherapy with LPV/r. By intent-to-treat analysis, the primary outcome was not significantly different in the two study arms. Low-level viremia (HIV-1 RNA of > 50 copies/ml but < 500 copies/ml) was more frequent in the monotherapy arm, but most participants regained viral suppression in follow-up assessments after re-intensification with zidovudine and lamivudine (2 out of 4 patients) or even when continuing on LPV/r monotherapy (11 out of 12 patients).</p>
<p>KalMo (Kaletra Monotherapy)</p>	<p>48-week efficacy and safety study of simplification to single agent LPV/r regimen.</p> <p>Nunes E Oliveira M Almeida et al.</p>	<p>Patients with a plasma viral load < 80 copies/ml for ≥ 6 months on the present HAART regimen, with no prior virological failure, with a present CD4+ cell count of > 200 cells/ml and a nadir of CD4+ cell count of > 100 cells/ml.</p> <p>N=60</p>	<p>XVI International AIDS Conference, Toronto, Canada (13 – 18 August 2006).</p>	<p>Patients were randomized 1:1 to maintain their present regimen or to switch to LPV/r monotherapy. The primary end point was HIV-1 RNA of < 80 copies/ml by week 96. virological failure being defined as a confirmed HIV-1 RNA of > 1000 copies/ml. Results of an interim analysis at 48 weeks show no significant differences were identified between the 2 groups with regards to the primary outcome by intent-to-treat analysis.</p>

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