Antiretroviral sequencing meeting report

Geneva

22 - 23 September 2011

1. Introduction

For just over a decade now, people living with HIV and HIV treatment providers have been grappling with how to ensure that quality treatment is available in resource-limited settings and an environment of permanently constrained budgets. Providing people with medicines that have as few side effects as possible in a form that is practical to take, easy to adhere to, and affordable, has been a challenge. HIV treatment is not only the best way to reduce HIV/AIDS morbidity and mortality, but also to reduce HIV transmission.[1]

With more and more countries moving to implement World Health Organization's (WHO) 2010 Guidelines recommending improved treatment, it is time to think about the next steps that will allow us to deliver antiretroviral therapy (ART) on a very large scale in high prevalence, low resource settings. And with new drugs from new classes now having gained a foothold in developed countries, it is a good opportunity to look at these, as well as drugs in the pipeline, and open a discussion about which of these drugs should be used when, and how.

People living with HIV and treatment providers have a stake in the decisions that will be taken over the coming months that could alter how HIV is managed for the next decade. Some of the main tension lies in how much to optimise treatment for the individual, while keeping an eye on ensuring as many people as possible can be treated. Compromises that have been made in the past because of price—such as the use of stavudine in developing countries long after its phase-out in developed countries—should not be repeated.

Constrained budgets should not stand in the way of fighting for access to the best possible treatment. But in order for those working on access to affordable medicines to direct their efforts most effectively, it is critical to narrow down the range of treatment options that will be considered ideal in the future. The price of medicines is not static as we know from experience over the last decade; first-line prices have come down around 99% since 2000, from over US$10,000 per person per year to roughly $150 today.

A decade ago, treatment literacy was the cornerstone of AIDS activism across the globe, and has helped build the foundation that led to the important level of treatment scale-up that has been achieved. In the same way, literacy about treatment options that lie in the near, medium, and long term should drive advocacy for improved care in developing countries.

This report resulted from a meeting convened in September 2011 by Médecins Sans Frontières (MSF) with participants from Ensemble pour une Solidarité Thérapeutique Hospitalière en Réseau (Esther) and Solidarité Thérapeutique & Initiatives contre le SIDA (SOLTHIS). These organisations convened a meeting of HIV treatment experts to look at antiretroviral (ARV) regimens and strategies to support the further scale up treatment and long-term sustainability in resource limited settings (RLS). The list of participants is at the end of this document.

The group considered the challenges of treating people earlier, treatment as prevention, and how and when to use the most promising compounds in the pipeline, for both children and adults.

The meeting objectives were to:

- Develop a set of recommendations for sequencing existing and pipeline ARV drugs for adults and children in resource-limited settings in the short term (one to two years from now), in the medium term (three to six years from now) and long term (seven to ten years from now);
- Define the specifications of the regimen and formulations that will be needed in the future to treat HIV in the community; and
- Develop recommendations and principles to guide treatment and diagnostic strategies and an operational research agenda.

The report also looks at possible alternative ways of delivering drugs that could become a reality in the next several years, which would allow treatment to be administered in much less frequent intervals.

This independent report is intended to complement ongoing work by the WHO in defining treatment guidelines, the drug optimization work performed by the WHO/UNAIDS Treatment 2.0 initiative, and to serve as a base for systematic review of evidence and operational research for future guidelines.

2. Dream regimen

If ART is life-long, why can't I have just one regimen in my lifetime? Why second line or salvage therapy?
-- Nelson Juma Otwoma

Across the broad range of stakeholders participating in the meeting, the same characteristics of a 'dream regimen' arose again and again. Ideally this regimen would be so safe, effective, tolerable and durable that the need for switching to a new regimen would be very rare. There was consensus that the dream regimen needs to be:

- **Efficient and simple** – Able to be given by health or community care providers with minimal training, and in decentralised health facilities or in the community. A drug regimen composed of one formulated pill, to be taken once a day as a fixed dose combination is most ideal. A once–a-month injectable regimen (or other novel delivery system) might be possible for the future.
- **Tolerable** – As drug side effects are a major driver of treatment interruption, change, and discontinuation amongst people living with HIV, the ideal regimen should have minimal or no side effects, and also minimal laboratory requirements for its use. Reformulation and dose reduction studies of existing drugs may help to improve tolerability. Participants noted that "new drugs need to have superior

tolerability to those currently used", and "adherence is the most critical factor for success".

- **Durable** – Regimens that are more lenient in their adherence, that have a high genetic barrier to resistance, and have drug components with long half-lives are required. "Drug regimens which you cannot occasionally miss doses, and have food or liquid requirements, don't work for us", one participant noted.
- **Heat stable** – This aspect is particularly problematic for protease inhibitors (PIs), which require a low dose of ritonavir as a pharmacological booster, and need to be kept cool to maintain their stability in settings with no electricity and high ambient temperatures. One participant observed that "we need drugs like paracetamol, which can be stored for months without needing a fridge".
- **Universal** – The regimen must be safe and effective for use across all CD4 cell count strata; in individuals with high viral load; in men and women; during pregnancy; in infants and children; in adolescents and adults; and with concomitant co-infections such as tuberculosis or viral hepatitis. 'One size fits all' is an ideal requirement.
- **Affordable** – Last year, the Kaiser Family Foundation and UNAIDS announced global donor funding had decreased by ten percent[2]. This is not expected to recover in the near future. Meanwhile, ARV coverage does not yet meet the estimated needs, and evidence is mounting for treating earlier and for prevention, increasing treatment demand. To do 'more with less', strategies to cut treatment costs - including using drugs as fixed dose combinations, dose reduction, improved drug bioavailability, active pharmaceutical (API) cost reduction through improved chemistry process, and novel drug delivery systems and strategies - must be investigated. As one participant stated, "in developed countries production price of original drugs is typically only one to five percent of the selling cost, whereas it reaches 95% of the cost of generic drugs.[3]
- **Different from pre-post exposure prophylaxis (PreP)** – Little is known in practice about the consequences of the broad use of drugs as a method of prevention, and the potential resistance that could jeopardise the use of the same drugs as backbone components of an initial treatment regimen.

Note: The UNAIDS/WHO Treatment 2.0 initiatives and the work done on antiretroviral drug optimization have not been discussed here, although it is supported by the group[1].[4]

All recommendations arising from this meeting are made taking these issues into account.

3. Adult first line ART for decentralisation and scaling-up

It is likely that patients "in need" of ART will include more people than only those with documented immune suppression; for example, pregnant women, those with co-morbidities, or individuals living with a HIV serodiscordant partner.
-- Alexandra Calmy

[1] In June 2010, the UNAIDS Secretariat and WHO launched *treatment 2.0 ,* an initiative designed to achieve and sustain universal access and maximize the preventive benefit of antiretroviral therapy. The aim is to expand access to HIV diagnosis, treatment and carte through a series of innovations in five priority areas: drugs, diagnostics, costs, service delivery and community mobilization. Source: WHO & UNAIDS HIV/AIDS Programme. The treatment 2.0 framework for action: catalysing the next phase of treatment, care and support,2011.

Pre Exposure Prophylaxis - PreP

Can a molecule be used in PreP and in first line treatment?

There is a theoretical risk of selection for drug resistance with prolonged use of HIV PreP with no serological assessment of HIV infection/seroconversion. However, the IpreX trial[56] showed no cases of people who acquired resistance who were infected during the trial. Only three cases of resistance were observed among the ten patients seroconverting at baseline.

Modelling the future impact of PreP and ART on drug resistance prevalence in South Africa in 2022 showed that ART is predicted to contribute more to resistance than is Prep.[7] More evidence is needed to document the efficacy and safety of PreP strategies, feasibility in practical situations in high prevalence settings, and the real presence or absence of selection of HIV drug resistance.

Ideally, drugs used for HIV PreP should not be used for HIV treatment.

3.1. Short-term recommendations for adult first line ART: one to two years' time

There was consensus among the expert group that **the current best first line regimen for use in HIV-infected adults and adolescents is the WHO-recommended combination of tenofovir/lamivudine/efavirenz** (TDF/3TC/EFV), given once daily as a one tablet fixed-dose combination (FDC) tablet.

However, some concerns with this regimen are the potential risk of teratogenicity with EFV use during the first trimester of pregnancy, and whether 3TC and emtricitabine (FTC) are fully equivalent. WHO is preparing position statements on both these issues following reviews of all relevant data, which will be available in the first half 2012. Already, new United Kingdom draft guidelines on the management of HIV infection in pregnant women recommend that efavirenz-based treatment should no longer be avoided by pregnant women or women who want to have a baby.[8]

Recently, a meta-analysis did not show any increased risk of teratogenicity of EFV compared to other ARVs during pregnancy and it is unlikely that better evidence will ever emerge.[9] It was agreed by the expert group that, considering the trade offs in a public health perspective, **women living with HIV who are of child bearing age and eligible to commence ART should use regimens with EFV**, as the benefits outweigh the risks. A more clear recommendation on its use is needed and implementation of pharmacovigilance to follow up this issue should be promoted.

The investigation into dose reduction with EFV (ENCORE 1 - study currently ongoing) is also important, both for the potential cost savings and for the reduction of central nervous system toxicity, which is being looked at in a sub-study.

Continued pharmacovigilance is also needed to learn more about toxicity with TDF use. More information on long term renal and bone toxicities are needed as there could be cause for concern. The tenofovir 'pro-drugs' currently in pipeline development (GS-7340 and CMX-157) may have better toxicity profiles.

The expert group stressed the importance of the **introduction of viral load testing to monitor first-line treatment**. Immunological and clinical criteria have been found to have poor sensitivity and specificity in detecting virological failure.[10][11][12][13] Viral load preserves further treatment options through early detection of poor adherence and virological failure. The consequences of inadequate detection of treatment failure are: increased mortality; increased AIDS-related events; accumulation of resistant mutations that will jeopardise the efficacy of other regimens and may be transmitted to others; and inadequate use of limited available antiretroviral regimen. For these reasons, access to viral load testing will improve retention in care and patient survival.

Co-infection with hepatitis B (HBV) should not be forgotten; **all people should be tested for HBV** and HBV-HIV co-infected people should be kept on a 3TC/TDF treatment combination, as TDF is also active against HBV.

Finally, **induction/maintenance ART strategies[2], as well as appropriate strategies for earlier treatment initiation, need to be explored now** if they are to be considered for 2015 WHO guidelines.

3.2. Medium-term recommendations for adult first line ART: three to six years' time

For the medium-term agenda, the group discussed the use of once-daily ritonavir-boosted PIs atazanavir (ATV/r) and darunavir (DRV/r), or second generation NNRTI as etravirine (ETR) as first-line anchor drugs. The robustness of a boosted PI-based regimen was weighed up against the usual good tolerability and convenience (more easily formulated as a full FDC) of an NNRTI-based regimen.

Access to rifabutin and replacement of rifampicin in tuberculosis (TB) regimens could influence the use of ATV/r and DRV/r[14]. All boosted PIs (at standard doses) are contraindicated with rifampicin. Currently, double boosting with ritonavir is almost the only option that has been rolled out in countries using LPV/r combinations, but this is associated with high levels of toxicity and requires close clinical and laboratory monitoring. To date, the recommendation is to use rifabutin 150mg three times per week, with normal doses of LPV/r and SQV/r. [15][16]

The production of an FDC tuberculosis treatment containing rifabutin would make adherence easier. For this to be possible, pharmacokinetic studies have to be performed in order to define an adequate dose of rifabutin to accompany PIs like ATV or DRV, which are likely to become preferred second-line.

The NNRTI rilpivirine (RIL) was also considered as an option, either as a maintenance regimen within an induction/maintenance strategy at the currently approved dose (25 mg/day – which is fragile in the presence of higher viral loads compared to efavirenz)[17], or with the possibility of investigating a higher dose (50 mg/day) to ensure potency at high viral loads without the cardiac toxicity observed with higher doses. [18][19][20]

[2] Induction / maintenance strategy: means the patient will receive an induction treatment composed of 3 to 4 drugs in order to decrease viral load quickly and hopefully restore immunity more quickly, and when viral load is under control and cd4 at appropriate level, the treatment is simplified: less drugs to take, the aim then to maintain an adequate drug pressure on the virus without side effects, less drug toxicity and maximize adherence.

Finding whether the current boosting dose of ritonavir (RTV) can be reduced needs to be established, as well as whether the investigational boosters such as cobicistat (COB) have advantages over RTV (currently the only booster available in the market).

The group also considered the use of integrase inhibitors in first-line regimens, of which only one – raltegravir (RAL) – is currently US Food and Drug Administration (FDA) approved. Elvitegravir (EVG) is the furthest along the development pipeline and has been submitted to the US FDA for approval. EVG requires boosting and has been submitted to the FDA both as a stand-alone compound (with COB booster) and as part of an FDC of TDF/FTC/EVG/COB (Gilead's 'quad pill').However, the group considered **dolutegravir (DTG) to be the most promising integrase inhibitor currently in the pipeline**, as it does not require boosting, can be used once daily, has a low milligram dose (50mg) and the potential to be produced at low cost[21]. DTG may also be co-formulated with abacavir/3TC for commercial reasons (the manufacturer of abacavir and 3TC being the same as for DTG).

For the NRTI backbone, the tenofovir pro-drug (GS-7340) has been found to be more potent than TDF at less than one tenth of its current dose (25mg)[22]. The development of CMX-157, which has been considered for use even in a weekly dose, also needs to be followed carefully.

Many operational questions are also related to reducing drug exposure via HIV maintenance therapy, most likely using PI/r or integrase inhibitor mono therapy after induction with combined regimen. Questions include who could benefit from maintenance therapy?; which could be the adequate drugs to use?; how would these strategies cope with the HIV reservoir?; will drugs have enough activity or penetration into the CNS?; would we use mono- or bi-therapies?; what could be the role of new drugs like PRO140[3] or injectable rilpivirine[23]?

3.3. Long-term recommendations for adult first line ART: seven to ten years' time

Hope was expressed for long-acting drug formulations and new drug delivery systems - for example, issued from nanotechnologies - to be developed with several of the drugs in the ARV pipeline (see below).

Sequencing first-line treatment recommendations and potential options

First-line TDF/(3TC or FTC)/EFV
Open questions: EFV 400mg may be better tolerated, but if used in co-administration with rifampycin. Would it preserve efficacy?

- **First-line intolerance -** for people who do not tolerate usual first-line therapy due to side effects:
- **Rilpivirine/FTC/TDF**: a FDC exists but it is not robust enough if there is a high initial viral load (fragile at 25mg of rilpivirine, availability of a viral load test is critical, rifampicin interaction is a problem[24]
- **Nevirapine slow release formulation:** XR (nevirapine immediate release formulation is still needed for initiation phase; there are safety and efficacy concerns of putting ABC and NVP in the same regimen, a FDC containing NVP XR will need slow release companion drugs)

[3] PRO-140: new entry inhibitor, from Progenics, a sub-cutaneus once weekly dosing under development

If no biological monitoring available? TDF /3TC/EFV is appropriate

Other fixed dose combinations potentially interesting for first–line treatment:

- Approved and marketed:
    - Quad pill: TDF/FTC/EVG/COB: may be more robust even if patient adherence is not perfect and can be co-administered with Rifabutin; however, interaction with rifampicin is expected[25].
- Not yet developed:
    - DRV/COB in combination with ABC/3TC or TDF/FTC or GS-7340/FTC, as it is probably not robust enough as a monotherapy treatment.
    - ATV/COB in combination with optimized background regimen
    - GS-7340 (TDF pro drug)/FTC/ATV/COB or low dose ritonavir?

Reducing drug doses, drug exposure:

- AZT 600 mg against 400mg (MINIZID)
- Weekly/monthly ARV regimens (long-acting drugs)
- Explore added value of nanomedicines
- Explore added value of drugs with long half lives such as GSK 744, some TDF pro-drugs, RIL

HIV-2: less treatment options:

- Cross resistance of NRTIs, in most cases selection of K65R even with AZT and d4T.
- Natural resistance for NNRTIs (EFV, NVP, ETV, RIL)
- Limited number of active PIs: only LPV/r and DRV/r are recommended
- High activity of raltegravir
- Only two lines: after LPV/r use DRV/r/RAL.

4. ART sequencing for second-line and salvage regimens for adults

In treatment-experienced people the group agreed that:

- a new regimen should contain at least two active compounds;
- switching earlier is better - a failing strategy should be modified even in case of low viral load and high CD4 cell count;
- the less access to new drugs you have, the more potent the regimen needs to be.

4.1. Short-term recommendations for second-line and salvage regimens in adults

The current WHO recommendation is a boosted ATV or LPV- (second line) or DRV- (third line) based combination. In order to simplify this regimen, heat stable ATV/r- or DRV/r-based FDCs (with co-blister packs[4]) are needed.

Some participants considered that first-line regimens should be PI-based because of the high genetic barrier. But it is not established that NNRTI-based first line regimens have

[4] Ideally any regimen should be FDC.

resulted in increased transmission of resistance. Primary acquired resistance levels in Africa are still less than 5% in a large majority of settings, according to WHO HIV Resistance Network.

Boosted PIs could be combined with an integrase inhibitor as an NRTI-sparing option. It may also be possible to give DRV/r or integrase inhibitor monotherapy as maintenance after induction.

Currently, DRV/r is given in doses of 800/100 mg once a day and 600/100 twice a day to people without and with PI mutations, respectively. In order to formulate a FDC with DRV/r, a single ratio of DRV/r needs to be established for adults and children[5]; reformulation of DRV/r may reduce the dosage. The drug-drug interaction with rifampicin also needs to be investigated on how to overcome interactions with rifampicin, in association with rifabutin.

The development of alternative boosters to RTV – such as COB - is useful.

PI monotherapy after induction and NRTI-sparing combinations also need to be field-tested.

Recommendations for second-line ART and TB drugs: potential options

- Investigate alternative treatment strategies - control HIV earlier and treat TB early;
- Shorten TB treatment, adapt HIV treatment to be compatible with TB treatment, isoniazid prophylaxis to avoid TB and give ART earlier.
- Improve access to rifabutin by lowering price (current actual price discount offered by Pfizer is $1 per pill).
- Identify other rifamycins or fluoroquinolones. These would have cost implications and be a long term solution at best.
- Alternative ART: Cobicistat boosting, higher doses of LPV or RTV?

Raltegravir and two NRTIs.

- Alternative formulations such as nanosuspensions or nanoparticules.
- Alternative TB drugs: to be investigated. Pharmacokinetics of bedaquiline (TMC 207) and LPV/r are being studied.

Some people will need to go on to a third-line regimen, even if there are robust first- and second-line regimens. The selection of drugs can be genotype-based or by selection of new drugs the patient has not been previously exposed to. Ideally three new drugs (DRV/ r/RAL/ETR) should be recommended. If genotyping is not available, the algorithms developed by the Agence Nationale de la Recherche Scientifique (ANRS) can be very useful[6]. Access to new drugs for salvage therapy remains very limited in resource-limited settings.

The price of new drugs like DRV, ETR and RAL, needs to decrease substantially in order for people to have other options available now. ARV price dynamics can be followed online through MSF's landmark publication, *Untangling the Web of Antiretroviral Price Reductions*, currently in its 14th edition[26].

[5] The problem is to co-formulate DRV and its booster.
[6]These ANRS algorithms will soon be available: adresse:hivfrenchresistance.org network.

4.2. Medium-term recommendations for second-line and salvage regimens in adults

For the medium–term, the group discussed use of an integrase inhibitor in second-line regimens. RAL is already approved – but is currently very expensive – and it appears to not interact with rifampicin, so it may be useful for people also on TB treatment[2728].

The promising development of DTG continues, with the drug appearing to be potent, safe, and phase two study data suggest a high genetic barrier to resistance[29]. Pending further clinical evaluation, it is possible that a DTG/DRV/r-based regimen could become a recommended second-line option within five years, with the further possibility it could be manufactured at low cost. Whether a NRTI strategy using DRV/r/DTG is a good option needs to be further investigated.

However, drug-drug interaction between DTG/DRV/r and rifampicin is expected, so RAL could be substituted for DTG during TB treatment.

The group was also interested in potential new delivery systems of pipeline drugs in the longer term.

Recommendations: sequencing after first-line treatment failure

Short-term issues:

- Viral load testing is recommended for all people
- If d4T or AZT was used in first-line treatment, switch to TDF/3TC
- If TDF was used in first–line treatment, switch to AZT/3TC
- ATV/r co-formulated (approved November 2011) or LPV/r or DRV/r (but DRV currently too expensive)
- If a person was on d4T, was then switched to TDF/3TC and developed treatment failure - there was no consensus on switching to TDF/3TC/LPV/r as the risk of providing a PI monotherapy versus added value of residual nucleoside effect.
- People on treatment for TB should be given rifabutin co-formulated treatment to improve adherence
- Establish HBV status for all people and keep TDF/3TC or TDF/FTC for HBV positive as component of first and second-line treatment option

<u>New drugs in the medium term</u>

- Integrase RAL or DTG plus DRV/boosted with or without two NRTI
- With no access to genotyping, move to the most robust and the better-tolerated combinations, DRV/COB and integrase inhibitors.
- Necessary to study if it is safe to alternate ARVs and TB drugs[7]

Why don't you push for the drugs you would take yourself or give to your children! --Christine Katlama

Take the best drugs now, don't wait! - Gilles Raguin.

[7] Alternate means temporarily stop one of the treatments.

Table 1: Antiretroviral pipeline compounds in phases 2 and 3

Compound	Company	Class	Status and Comments
Elvitegravir (EVG)	Gilead	INI	48-week phase 3 data demonstrated non-inferiority to raltegravir. Needs boosting with COB. Filed with FDA (as boosted single agent) December 2011.
Cobicistat (COB)	Gilead	PK booster	Phase 3 48-week Ph2 results comparing to ritonavir showed similar efficacy. Filed with FDA for use as a boosting agent.
Dolutegravir (DTG)	ViiV / Shionogi	INI	Phase 3 naïve study compares 50mg QD with EFV Ph2b data 50mg BID effective in people with raltegravir-resistance Approval anticipated in 2013
BMS-663068	BMS	Attachment inhibitor (gp120)	Phase 2b New therapeutic class. Oral formulation. Study in treatment experienced currently recruiting.
Lersivirine	ViiV	NNRTI	Phase 2 Ph2 data similar activity to EFV in naïve people at 48 weeks.
BMS-986001	BMS	NRTI	Phase 2 Structurally close to d4T but hopefully without associated toxicity. Phase 2b study in treatment naïve enrolling soon.
Apricitabine	Avexa	NRTI	Phase 2 Recently resumed development. Structurally close to 3TC/FTC.
GS-7340	Gilead	NRTI	Phase 2 New formulation (oral pro-drug) of tenofovir suggesting improved PK.
CMX-157	Chimerix	NRTI	Phase 2 Long acting pro-drug of tenofovir.
S/GSK-1265744	ViiV/Shiongi	INI	Phase 2a Intramuscular injection with potential for once monthly dosing.

Source: Updated from 2011 i-Base/TAG Pipeline Report
Clinical trials.gov

Table 2. Pipeline combined products including FDCs, and patent information

Regimen	Classes	Companies	Comments
Quad: Elvitegravir/cobicistat/ tenofovir/emtricitabine	Integrase inhibitor/booster /2NRTIs	**Gilead** Licensed to Medicines Patent Pool (MPP); this means Indian manufacturers can produce and sell the combination to 112 developing countries	Filed with FDA October 2011, approval anticipated 2012
Darunavir/cobicistat	PI/booster	Licensing agreement between **Gilead** (COB) and **Tibotec** (DRV); cobicistat licensed to MPP. No patent on darunavir in India on single molecule.	Once daily boosted PI.
Atazanavir/cobicistat	PI/booster	Licensing agreement between **Gilead** (COB) and Bristol-Myers Squibb (atazanavir)	
Darunavir/cobicistat /emtricitibine/GS7340	PI/booster/2 NRTIs	Licensing agreement between **Gilead** (COB/FTC/GS7340) and **Tibotec** (DRV) COB FTC are in MPP: it will depend if GS 7340 is patented in India or not.	First PI-based FDC. GS7340 small molecule less than1/10 300mg dose TDF: 25mg makes co-formulation possible.
572-Trii Dolutegravir/abacavir/ lamivudine	Integrase inhibitor/2 NRTIs	**ViiV/Shionogi** ViiV=GSK and Pfizer, they have their own licensing agreements. There might be a future agreement with Aspen or any WHO PQ facilities to manufacture the product (in Zimbabwe, Kenya, Uganda, South Africa) India is out: Viiv does not include India in their royalty-free licensing policy. DLG: patents are filed in India.	PK completed but not presented Ph3 with naïve patients begun

4. Infants and children

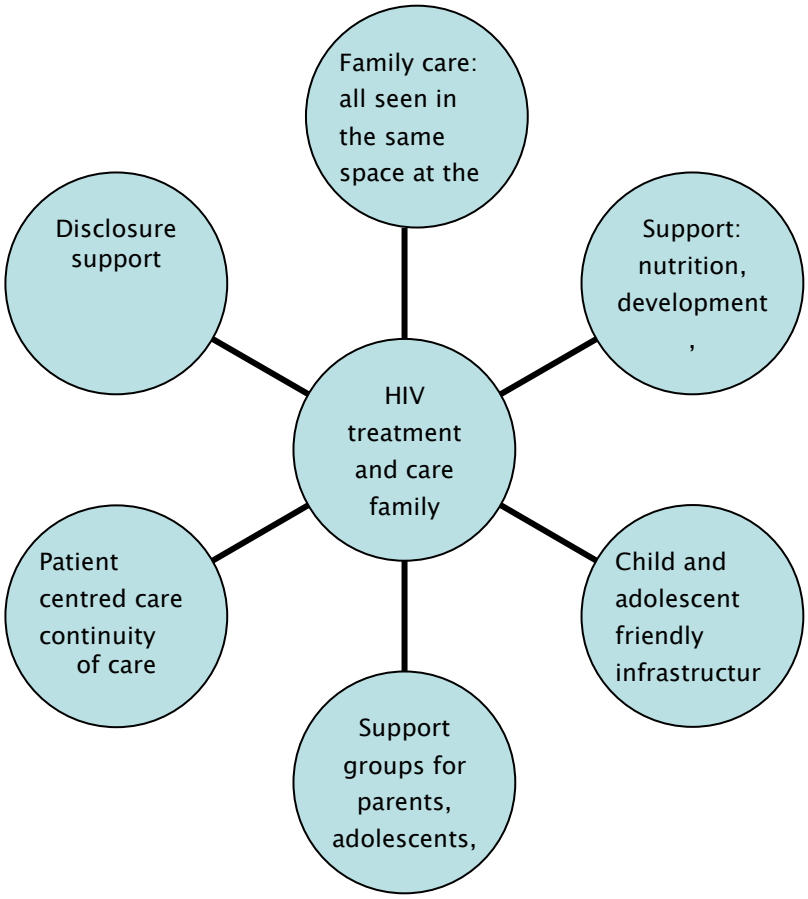
We need mother and baby-friendly care. At the moment there are family planning visits, early childhood development centre visits, baby ART visits, immunisation week 14 week visits, mum ART clinic visits…Each clinic visit takes a whole day and city visits may even take longer… --Siobhan Crowley.

The integration of paediatric and adult HIV care at community level is urgently needed. This requires family-friendly health systems in order to scale up access to TB/HIV care efficiently within, or close to, communities.

To achieve this we need:

- Leadership and governance: greater focus on family-friendly packages and client satisfaction;
- Health workforce: mentored, motivated and supported nurse-led primary health care services (PHC);
- Medical products and technologies: child-friendly medicines and diagnostics;
- Health information systems: age disaggregation, tracking family-friendly health indicators;
- Service delivery: one-stop, quality, comprehensive and accessible information; and
- Appropriate health financing: clear budget lines for paediatric treatment and diagnostics.

Fig 1: What do we mean by child-friendly care?



We have too many formulations and yet too few real options. -- Shaffiq Essajee

At first glance the area of paediatric formulations already seems quite crowded; country programmes currently use over 45 single agents and co-formulations. But the market is small, and broken up further by different regimens and weight band doses. This fragmentation threatens access and market sustainability because of low volume orders. Therefore, there is the need to focus on a smaller number of products that offer the best options for children.

It may be possible to align recommendations for adults and children who are three years of age and above. With TDF powder and 150, 200 and 250mg tablets now approved for treatment in children aged 2 to 12 years this looks more feasible. WHO is also reviewing the existing data on the use of TDF in younger children.

An ideal formulation for first-line treatment for children would be a scored (once on one side and twice on the other for weight band dosing), adult strength, dispersible FDC tablet of TDF/3TC/EFV. This would mean programmes could use the same pill for all people, aged three to adult, if this treatment recommendation was supported by new WHO evidence-based guidelines.

Infants exposed to NVP for prevention of mother-to-child transmission (PMTCT) currently need a non-NNRTI-based regimen, which precludes alignment with adult dosages for infants and young children. The group stressed the importance of taking the same approach for NVP-exposed and -unexposed infants and children.

For the younger age group, a better formulation of lopinavir/ ritonavir (LPV/r) is needed. The syrup is highly unpalatable for children, requires refrigeration, and has a very high ethylene glycol and ethanol content. The paediatric tablet must be taken whole. A heat stable sprinkle formulation is in development and may be available this year.

A heat stable 25mg formulation of RTV for “super-boosting” LPV/r to overcome interactions with RIF is also needed, which is anticipated to be available in 2012 at the earliest, possibly in 2013.

Induction/maintenance strategies may be appropriate in this age group with three NRTIs + NNRTI or two NRTIs + PI reducing to two NRTIs + NNRTI.

If a LPV/r based regimen is used as a first-line treatment, a second-line option could be either NNRTI or DRV/r (only above age three and DRV to RTV ratios are complicated); RAL, ETR (depending on paediatric approval) may also be possible.

As with adults, alternative boosters to RTV are anticipated and COB is being developed for children.

For the medium-term, the Drugs for Neglected Diseases initiative (DNDi) is specifically working on developing regimens for children aged three years and under. Products under consideration are a sprinkle formulation of LPV/r or pro-drugs/nanoformulations of RTV and LPV to be assembled with an appropriately dosed NRTI backbone, as well as a stand-alone solid formulation of RTV for superboosting when children are on rifampicin based anti-TB therapy.

Second generation NNRTIs ETR and RIL may be suitable for this age group. It is not certain that the resistance profile of children exposed to NVP for PMTCT will allow use of ETR or RIL in young children with a high viral load.

For children age three years and above, the regimens will depend on adult recommendations and approval of pipeline formulations for children. For children failing a PI-based first-line regimen, a boosted DRV/DTG regimen has strong potential for this age group and needs to be studied.

Long-acting formulations and novel drug delivery systems are particularly ideal for children.

Since children are likely to be treated for decades, efficacious, safe, well-tolerated child-friendly regimens are essential.
--Marc Lallemant.

As immediate needs and treatment options differ according to age, strategies are likely to differ. Newly infected adolescents will require a once a day FDC; perinatally infected adolescents will need more complex second- or third-line regimens; and younger children will have fewer treatment options, due to a lack of dosing studies.

Recommendations: sequencing paediatric formulations and strategies

First-line recommendations
More data will be available by end 2012 on key drugs and strategies:

- A new LPV/r formulation is needed that addresses the issue of requiring a cold chain;
- Most children are still on d4T triple FDC, but should take a AZT/3TC or ABC/3TC FDC as recommended by WHO
- A review of data on TDF use in children is needed for a recommendation by WHO, starting with four-drug NNRTI.

Young children (under age two/three versus over age three)

- A formulation with higher efficacy is required because of high viral load and risk of NVP exposure during PMTCT; an intensive phase (higher barrier to resistance or higher efficacy) for first two to three years could be used as below
- First-line regimen recommendation: PI/two NRTI (ex. LPV/r/AZT/3TC) or NNRTI /three NRTI (ex. NVP/ABC/3TC/AZT) - evidence in NNRTI-exposed children is needed.
- Child doses could be aligned with adult doses if possible.

Three to twelve years and adolescents

- Align with adults through a FDC tablet which can be scored
- Use WHO weight bands which should be consistent across ages and diseases (HIV and TB) wherever possible.
- TDF is preferred over AZT-based triple combination.

Considerations with first line:

- Overcome problems with LPV/r; LPV/r better taste, RTV 25 mg for TB interaction.
- 4-drugs NNRTI intensive-maintenance using 3NRTIs + NNRTI or 2 NRTIs+PI reducing to 2NRTIs+NNRTI: more data on the length of time of children have to be kept on four drugs is needed.(data from European children, ARROW trial)
- Induction maintenance strategies for three to twelve years and adolescents have to be studied.
- For TB treatment: Drop NVP for duration of TB treatment (for toxicity). Use of superboosting in PI regimen with a new 25mg ritonavir; should we add extra

NVP (how much? using 50mg NVP?), versus switch to 3 NRTIs.
- Ability to change children regimen to maintenance adult formulation (preferably TDF/3TC/EFV) triple.

Second-line recommendations:
Second-line following NNRTI based first-line.
- Currently LPV/r. In the future ATV/r may be recommended.
- Need to sort RTV (or alternative) booster to co-formulate.
- Issues about TB co-treatment.
- Pharmacokinetic data on ATV/r in infants and children

Second-line following LPV/r based first-line : a boosted DRV/DTG regimen has strong potential for children age three years and above. Other treatment options like DRV/r monotherapy, use of ETR, use of DLT have to be studied.

Open questions on second-line:
- Safety and PK data ATV/r in young children
- Need FDC with ATV/r once daily pharmacokinetic data is available.
- Use of ATV/r during TB treatment in children (what boosting ratio)
- DRV: make an FDC with RTV and integrase inhibitor[8].
- Safety data on ATV/r in children.

New drugs in the longer term
Three to five years:
- New NNRTI with no overlapping resistance with NVP/EFV: can ETR or RIL do the job?
- Integrase inhibitor: DTG
- Long-acting formulations, innovative delivery systems.

Five to ten years:
- Alternative NNRTI to NVP for < 3 years: RIL? ETR?
- Integrase inhibitor as an intensifier; alternative in young children.

Table 3: Paediatric ARV pipeline

Compound	Company	Class	Formulation and dose	Status and comments
Atazanavir (ATV)	Bristol-Myers Squibb	PI	Oral powder 50mg sachet Capsule 100, 150, 200, 300mg	Ongoing phase 2 naïve and experienced with or without RTV from three months to six years
Darunavir (DRV)	Janssen	PI	Oral suspension 100mg/ml 75 and 150mg tablets	FDA approved > 3 years of age (waiver for children< 3)

[8] This combination needs to be studied first, and the integrase inhibitor has to be carefully selected.

				Dosage of DRV and RTV is based on body weight and should not exceed the treatment experienced adult doses. DRV/RTV ratios vary according to weight and treatment experience so cannot simple weight band dosing.
Dolutegravir (DTG)	Shionogi/ViiV	INI	Older children tablets 10, 25, 50mg Younger children to be decided. Granule formulation being evaluated.	Phase 1 and 2 from six weeks to 18 years Phase one PK completed. Exposure of granules with different liquids exceeded that of tablets in healthy adults, so can be given without liquid restriction or directly to mouth
Elvitegravir/ cobicistat (booster)/Quad (EVG/COB)	Gilead	FDC INI	To be decided. Solid and liquid forms in development, separately and co-formulated as Quad (solid tablet only)	EVG treatment experienced 12 to18 years Integrated plans for paediatric studies under discussion
Etravirine (ETR)	Janssen	NNRTI	Dispersible tablets 25 (scored), 100mg	Ongoing Phase 2 treatment experienced 6 to17 years. Phase 1 and 2 naïve/experienced two months to six years planned.
Lopinavir/ritonavir (LPV/r)	Cipla	PI	Sprinkles 40/10 mg (equivalent to 0.5 mL liquid)	Similar PK to solution in healthy adults PK in children

				being evaluated
Maraviroc (MVC)	Pfizer/ViiV	CCR5 receptor antagonist	Oral suspension 20mg/mL	Phase 4 Experienced CCR5 tropic 2 to12 years
Raltegravir (RAL)	Merck	INI	Oral granules for suspension 6mg/kg (100mg sachet)	Phase 2, two weeks to two years Granules achieved good target exposure in six months to under 2 years, similar to that with older children Neonate passive PK
Rilpivirine (RIL)	Tibotec/Johnson and Johnson	NNRTI	Oral granules 2.5mg base/g	Phase 2 planned 0-12 years

Source: Updated 2011 i-Base/TAG Pipeline report
clinicaltrials.gov

5. New drug delivery systems and long acting formulations

We have one pill a day – why not one a week or one a month? Or an injection once a month?
-- Nelson Juma Otwoma

In the long term perspective, there was consensus among the group that there was great potential for longer lasting formulations (weekly or monthly) and novel delivery systems (patch, injection or implant).

These may be of particular importance for paediatrics. Perhaps even greater for adolescents; 160,000 adolescents are infected each year in South Africa alone and a subcutaneous removable implant associated with family planning could be an important option. These formulations have the potential to completely alter the current standard of care.

There are opportunities for longer-acting formulations with products currently in development - RIL, S/GSK 744, CMX 157, DTG - for weekly or monthly dosage forms, including injectable products. Low milligram dosage and long half-lives mean that once-weekly oral or once-monthly depot injection formulations might be possible.

Still further along the pipeline is the possibility of nanomedicines; a nanosuspension and injection of RIL is currently in development.

There was strong consensus on the importance of engaging with communities on the acceptability of different dosing schedules and delivery systems. This means getting answers to these questions: What does the community need? What problems need solving? Currently there is lack of a good proxy for understanding the potential of long-

acting treatments for HIV. Is a once-weekly oral or once-monthly depot injection a 'better' option than a daily pill? What challenges come with a new solution? Drug developers need clarity on the target product profile.

What is nanomedicine? What are its implications in the treatment of HIV?

Don't be afraid of nanomedicine. It's out there and being used.
--Steve Rannard

Nanotechnology conventionally means technology on the scale of less than 100 nanometers but can range to sizes just below one micron. The aim of nanotechnology is to derive new benefits or behaviours from the manipulation of atoms, molecules and particles.

Nanoparticles have a dramatically increased surface area to volume ratio compared to much larger micronized particles. Nanoparticles also generally stick to surfaces more efficiently. They offer options to overcoming the insolubility of pharmaceuticals – PIs and efavirenz have poor solubility, for example - by dispersing drugs as whole particles of API.

Nanomedicines are used in the successful treatment of many medical conditions. Nanotechnology offers potential benefits for future HIV treatment including modifying the behaviour of existing ARVs:

- Targeting tissue and cellular sanctuary sites
- Improving pharmacokinetics
- Improving toxicity profiles

Nanotechnology also presents target opportunities related to enhanced ARV behaviour:

- reduce toxicology,
- enhance activity,
- modify bioavailability,
- provide stable formats that can be dosed as a liquid,
- combination therapies,
- target macrophage sanctuary sites.

More targeted delivery should reduce the quantity of raw materials needed. This, is turn, has the potential to have a huge impact on the drugs used in resource-limited settings. More investment and research in this field is required and the regulatory position needs to be clarified.

6. Viral load

Viral load testing is essential to monitor treatment efficacy. Testing can be used to monitor adherence early on and better inform decisions about treatment modifications or switches. Viral load testing can also be used to diagnose HIV-infected infants and to monitor virological suppression in pregnant women to reduce the risk of mother-to-child transmission.

The group considered viral load to be essential during this next phase of programme scale up, but that it must not be a barrier to ART. Ideally, every patient should have access to viral load monitoring and any failure should be investigated, with adherence and possible drug-drug interactions checked, and treatment changed, if necessary.

Point of care (POC) viral load tests - including SAMBA and Alere – are urgently needed to support decentralised implementation on a large scale. The SAMBA (simple amplification based assay), is currently being developed by the Diagnostics Development Unit at the University of Cambridge. They are developing two variations; a semi-quantitative test for monitoring ART, and a qualitative test for early infant diagnosis (EID). The tests use isothermal amplification and visual detection by dipstick. SAMBA is being field tested by MSF in Malawi and Uganda.

The Alere NAT system is a generic platform designed to detect various nucleic acids. This test – anticipated to be commercially launched this year – is a real time detection method for measuring quantitative HIV RNA. The sample – which can be from a finger-prick, whole blood, or plasma – is applied directly onto the disposable cartridge and is then processed by a compact, battery-driven instrument.

POC tests are not yet available and will have to undergo field validation using large sample sizes – as well as be included in cost-effectiveness and patient outcome analyses compared to current lab-based tests - before any conclusions about implementation can be made. There is currently only an estimate as to when these tests will be commercially available and quality approved. UNITAID have provided a landscape overview[30],[31] .

Currently, there are only four big suppliers of viral load tests, which offer integrated closed systems that are highly automated and supplied as 'black boxes'. Although discounts are offered for larger orders, these may not be sufficient to enable affordable access.

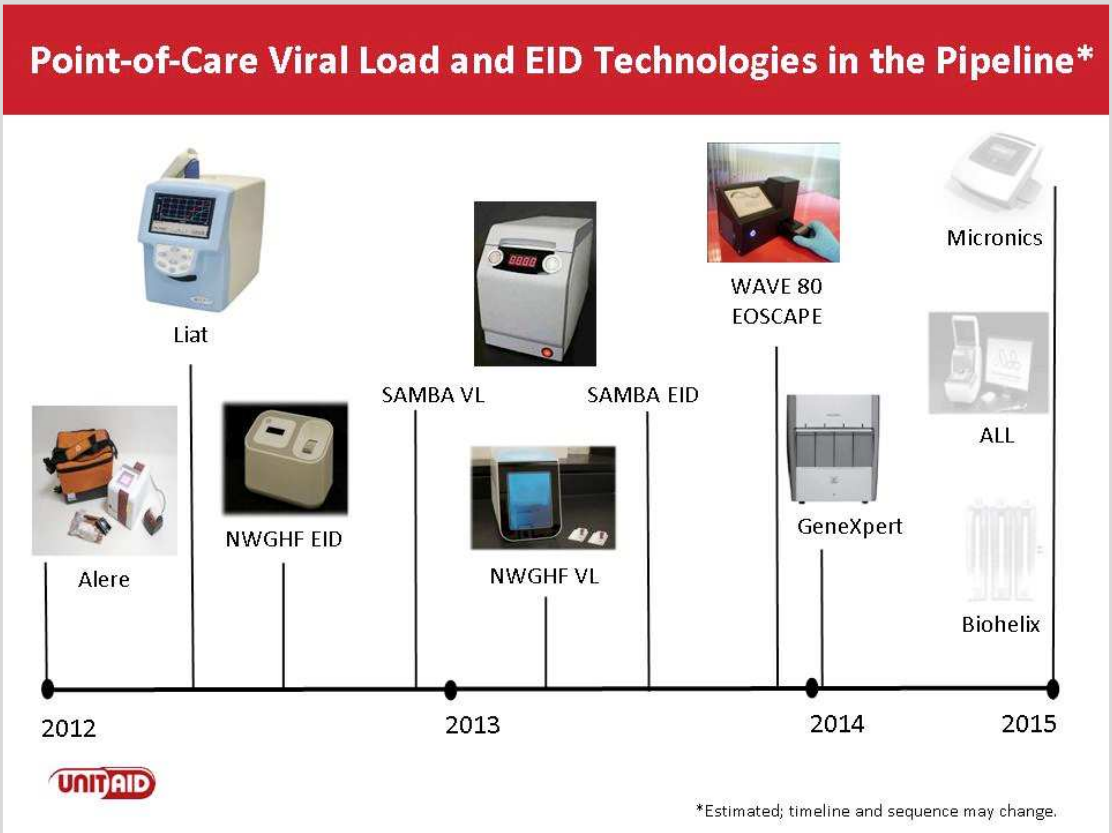
Open Polyvalent Platforms (OPP) can help improve access to VL and EID in resource-limited settings. This means that separate components (extractors, RT-PCR machines and reagents, etc) can be assembled from different manufacturers. They can also be used for other diseases such as TB. They could offer a bridge between the (largely inaccessible) integrated automated systems and the new POC technologies in the pipeline. They could also enhance competition between suppliers, changing the market structures and pushing down prices.

The ANRS Generic HIV-RNA assay is a proof of concept OPP, and is now commercialised by Biocentric, and is being used in Asian and African countries.[323334]

The optimal frequency of testing, effect on outcomes and cost effectiveness of viral load are uncertain and are an important area for operational research.

Pipeline point of care (POC) tests

This overview is taken from the UNITAID landscape analysis referenced above:



All platforms, except for the SAMBA and GeneXpert, are true POC tests that are self-contained, able to process a result from a finger-prick blood sample, and able to be located at the clinic level. They may be battery-run or powered from solar-panels. The SAMBA and GeneXpert tests, on the other hand, require a simple laboratory set-up with reliable access to electricity and the availability of trained laboratory technicians. Importantly, they are low-through-put (only the 4-plex GeneXpert instrument falls under the FIND preferential pricing agreement) but can be decentralised to district level and stacked for greater through-put. None of these tests has yet to be commercialised, quality approved, or field validated, and thus the reliance on traditional lab-based tests will continue in the short- to medium-term.

7. Conclusion

This independent expert meeting, organised by Médecins Sans Frontières, with Esther and SOLTHIS, has allowed productive discussion of the issues currently facing the diagnosis, treatment and management of people living with HIV and their proposed solutions appropriate to the resource limited settings in which we work.

Participants recognised that the long-term support of people living with HIV needs to occur in a decentralised manner, in order to cope with the massive scaling-up of the numbers of people on HIV treatment. The future management of people living with HIV

and HIV and TB will happen at the community level. However, this shift to decentralised care will require new tools and changes to the way in which we work, including:

- Antiretroviral drugs will need to be very efficient, well-tolerated, durable, heat stable, safe and effective for use across all CD4 cell count strata, in individuals with high viral loads, in men and women, in infants and children, in adolescents and adults, and with concomitant co-infections such as tuberculosis and viral hepatitis, and, most importantly, affordable. Drugs for HIV treatment will need to be different from those given for PreP.
- Health care providers will have to work in a more decentralised way, through health posts at the community level, and services will need to become family-friendly and mainly community health worker- or patient group-based.

Discussion included an overview of the best use of existing and pipeline antiretroviral drugs for resource limited settings with a five to ten year outlook. Possible immediate, mid- and long-term therapeutic options were also discussed. It was acknowledged that the current best first-line regimen is TDF+3TC or FTC+EFV. For the medium-term agenda, the group discussed the use of once-daily ritonavir-boosted PIs atazanavir (ATV/r) and darunavir (DRV/r), or second generation NNRTI as etravirine (ETR) as first-line anchor drugs. Access to rifabutin and replacement of rifampicin in tuberculosis (TB) regimens could influence the use of ATV/r and DRV/r. The group also considered the use of integrase inhibitors in first-line regimens. Hope was expressed for long-acting drug formulations and new drug delivery systems - for example, issued from nanotechnologies - to be developed with several of the drugs in the ARV pipeline in a long term perspective.

Second-line regimens will likely remain protease inhibitor-based, with ATV/r or DVR/r co-formulated improving the pill burden and drug adherence. The companion drug in three to five years' time could be the pipeline integrase inhibitor dolutegravir as the backbone regimen. More third-line options are still needed and the approach of these will remain genotype-based or by substitution of at least two new active components. The preferred salvage regimen is RAL+ETV+DRV/r.

Participants agreed that paediatric HIV treatment needs to focus on a smaller number of products that offer the best options. Infants exposed to NVP for prevention of mother-to-child transmission (PMTCT) currently need a non-NNRTI based regimen. The group stressed the importance of taking the same approach for NVP-exposed and -unexposed infants and children. At age three years and above, it may be possible to align recommendations for adults and children. It was agreed that an ideal formulation for first-line would be a scored, adult strength, dispersible FDC tablet of TDF/3TC/EFV, which would enable programmes to use the same pill for everyone aged three and upwards. Adolescents present a different challenge, needing FDCs and innovative ART delivery systems allowing monthly or three monthly drug delivery (for example, an injectable contraception).

Participants recognised that access to viral load will be a key issue for long-term adherence monitoring, early detection of treatment failure and timely treatment adaptation. Polyvalent open platforms at field level and development of viral load point of care tests are urgently needed.

It was also recognised that new delivery systems issued for nanotechnologies, with combinations of long-acting ART formulations that would allow weekly, monthly, or three monthly administration of ART would be of great added value in five to ten years' time.

Finally, access to health care, including integrated TB and HIV care, has to improve and continue to be more affordable so that people living with HIV can be confident that they will able to lead long, healthy and productive lives.

8. Appendices

8.1. List of abbreviations

ABC: abacavir
ANRS: Agence National de la Recherche Scientifique
API: active pharmaceutical ingredient
ARV: antiretrovirals
ASAP: as soon as possible
ATV: atazanavir
AZT: zidovudine
CD4: Lymphocyte CD4 count
CNS: central nervous system
COB: cobicistat
DNDi: drug for neglected diseases initiative
DRV/r: darunavir/ritonavir
EID: ealy infant diagnosis
EFV: efavirenz
Esther: Ensemble Solidarité Thérapeutique Hospitalière en réseau
ETV: etravirine
EVG: elvitegravir
FDA: Food and drug administration
FDC: fixed dose combination
HBV: hepatitis B virus
LSV: lersivirine
NRTI: nucleotide reverse transcriptase inhibitor
NNRTI: non nucleotide reverse transcriptase inhibitor
OPP: open polyvalent platform
PI: protease inhibitor
POC: point of care test
RLS: resource limited settings
RNA: ribonucleic acid
RT-PCR: real time polymerase chain reaction
PreP: pre exposure prophylaxis
RIL: rilpivirine
RTV: ritonavir
TB: tuberculosis
TDF: tenofovir
3TC: lamivudine
POC: point of care
PHC: primary health care centre
UNAIDS: Joint United Nations programme on HIV/AIDS
Solthis: Solidarité Thérapeutique et Initiatives contre le sida
VL: viral load
WHO: World Health Organisation
XR: extended release

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8.3. Declarations of interest

Dr Alexandra Calmy has been supported by travel grants from BMS and Janssens; these grants are unrelated to the current work.

Pr. Vincent Calvez: Advisor and receiving research grants from BMS, ViiV, Roche, JNJ, Tibotec, Gilead and MSD

Dr Andrew Hill has received consultancy payments from Tibotec/Janssen"

Pr Christine Katlama has received travel grants, fees for conference or consultancy fees from various pharmaceutical companies such as Abbott, Bristol Myers-Squibb, Gilead, Janssen Cilag, MSD and ViiV Healthcare.

Pr Yazdan Yazdanpanah has received travel grants and honoraria for presentations at workshops and consultancy honoraria from Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, Roche, and Tibotec.

Dr Pedro Cahn is an advisory board member for Avexa- Gilead- GSK- Myriad -Merck-Pfizer-Pharmasset- Schering Plough-Tibotec, an investigator: Avexa- Boehringer Ingelheim - Gilead- GSK- Roche-Merck-Pfizer- Pharmasset- Schering Plough-Tibotec-Abbott- BMS, has acted as a speaker (content and design performed by the speaker, no company control) for Abbott-BMS-Boehringer Ingelheim-GSK-Merck-Pfizer-Tibotec, as a Scientific Advisor for Merck Sharp & Dohme- Pfizer- GSK- Avexa- Tibotec. He is not a shareholder nor does he have any commercial interest or investment in any pharmaceutical company.

The other participants did not declare any conflict of interest.

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