

AGENDA ITEM FOR DISCUSSION

UNITAID and WHO Secretariat proposal: the priority missing essential medicines for HIV

The WHO treatment guidelines for treatment of HIV in adults were last updated in 2006 and the WHO treatment guidelines for infants and children, in 2008. The guidelines for adult treatment and prevention of mother to child transmission of HIV will be reviewed this year, with a particular focus on when to start antiretroviral therapy, reviewing first line options and on optimizing second line treatments. Newer products, such as the integrase inhibitors (e.g. raltegravir, elvitegravir), or alternatives to ritonavir as 'booster' protease inhibitors (PIs) (e.g. SPD-452, GS-9350, currently in development) and second generation nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (e.g. rilpivirine), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g. etravirine) and PIs (e.g. darunavir) will be considered in the guideline revision process.

In the process of developing the treatment guidelines for children with HIV, not only were treatment options assessed, but ideal, missing essential products, were specified.¹ However in the light of revised criteria on initiation of ART in infants that were developed earlier this year, this list needs to be urgently reviewed with attention to second line and once daily options for children.

In July of 2008 the UNITAID board decided to take the necessary steps to set up a medicines patent pool. The initial focus of the UNITAID development of the patent pool will be on medicines for HIV/AIDS. The aim of the initiative is to improve access to patents and other relevant intellectual property (IP) to boost the availability of more affordable versions of AIDS medicines and to encourage the development and availability of better adapted formulations such as once daily, heat stable, fixed dose formulations and pediatric formulations of essential antiretroviral drugs (ARVs).

A Patent Pool is a portfolio of assets consisting of the entire set of patents and other relevant IP held by various actors (companies, universities, government institutions) related to a particular technology that are made available on a non-exclusive basis to third party actors, (e.g. generic manufacturers) against the payment of royalties. Although patent pools exist in many areas of technology, such as information, communication, environmental and nutrition technology, a medicines patent pool has not been developed before. The UNITAID initiative will initially focus on HIV/AIDS medicines: first and second line ARVs including pediatric formulations for use in lower and middle income countries. The Patent Pool will be a voluntary pool and its success will depend on the willingness of the patent holders to collaborate.

Patent pools can facilitate the availability of new technologies by making patents and other forms of intellectual property (IP) more readily available to third parties against the payment of a royalty. For instance, a medicines patent pool could promote the development and the production of new essential medicines combining several pharmaceutical ingredients which are patented by different companies. A patent pool can also facilitate additional research to assess the usefulness of the products in particular patient groups. In addition, the patent pool could make new medicines more affordable for populations in developing countries by increasing the competition in the market.

A first step towards the patent pool is to determine which products and formulations are needed. This exercise should go beyond listing the products currently recommended in

¹ Preferred antiretroviral medicines for treating and preventing HIV infection in younger children. http://www.who.int/hiv/pub/paediatric/ARV_WG_meeting_report_may2008.pdf

treatment guidelines as they are limited to what actually exists and not what would be desirable. The 'wish list' for the patent pool needs to include products that should be available if, for example, there were no patent barriers to developing and producing them. The patent pool should also facilitate additional research if required, such as identifying appropriate dosage forms of products previously not approved for children.

Based on the existing WHO Model List of Essential Medicines and the current treatment guidelines, the following two lists (Table 1 and Table 2) are the proposed priority missing essential medicines. Inclusion in this list indicates the medical need for the products. It does not necessarily mean that the listed products are patented in all relevant territories. Whether patent or other IP barriers to their development, production and marketing exist will need to be further assessed as the patent pool initiative develops.

The Committee is asked to review both lists and

- (1) identify the priority missing essential medicines, on the basis of clinical need and potential feasibility, based on existing products or technologies and those likely to become available.
- (2) amend or modify the Tables as appropriate.

Table 1. Adults: missing essential medicines

Medicine/form	Rationale from current treatment guidelines or EML
Stand-alone thermostable formulations of ritonavir or in combination with other PIs e.g. atazanavir/ritonavir (ATV/r) indinavir /ritonavir (IDV/r) saquinavir/ritonavir (SQV/r) fosamprenavir/ritonavir (FPV/r)	Thermostability critical for use in resource limited settings PIs 'boosted'; with ritonavir are recommended for use in second line treatment regimens.
Triple drug 1 st line combinations: <ul style="list-style-type: none"> ▪ Tenofovir(TDF) based triple combinations plus efavirenz (EFV) or nevirapine (NVP) plus lamivudine (3TC) or emtricitabine (FTC) e.g. TDF/FTC/NVP TDF/3TC/NVP TDF/FTC/EFV TDF/3TC/EFV ▪ Zidovudine(AZT) based triple combinations plus lamivudine or emtricitabine plus abacavir (ABC) or tenofovir e.g. AZT/3TC/ABC AZT/FTC/ABC AZT/3TC/TDF AZT/FTC/TDF 	These are all recommended combination regimens for first line ART; all are on the EML as individual components, 2 drugs as fixed dose combinations (FDCs) also exist but with limited availability
Alternative dual combinations based on lamivudine or emtricitabine plus tenofovir TDF/FTC TDF/3TC	Possible combinations based on current EML listing; limited availability at present.
Possible valuable second line triple combinations based on lamivudine or emtricitabine plus tenofovir and a once daily boosted PI (e.g. ATV/r, LPVr) LPVr/TDF 3TC LPVr/TDF/FTC ATV/r/TDF/FTC ATV/r/TDF /3TC	Components are all on EML and or treatment guidelines; second line regimens need further evaluation ideally as once daily FDCs.
Possible valuable second line dual and triple combinations: Alternative dual combinations based on lamivudine or emtricitabine plus didanosine enteric coated (ddI) ddi/3TC ddi/FTC Triple combinations based on lamivudine or emtricitabine plus didanosine EC and a once daily boosted PI (e.g. ATV/r, LPVr) LPVr/ddi/3TC LPVr/ddi/FTC ATV/r/ddi/FTC ATV/r/ddi/3TC	

NOTE: The WHO adult treatment guidelines will be revised in 2009. The revision will consider the potential use of newer products, such as the integrase inhibitors (e.g. raltegravir, elvitegravir), or alternatives to ritonavir as 'booster' PIs (e.g. SPD-452, GS-9350, currently in early development phase) and second generation NRTIs (e.g. rilpivirine), NNRTIs (e.g. etravirine) and PIs (e.g. darunavir).

Table 2. Children: missing essential medicines identified in 2007 based on 2006 guidelines. This list needs to be updated

Priority	Product	Recommended Ideal Dosing strengths
Recommended priority Antiretroviral products for infant MTCT prevention		
Urgent	Zidovudine	12 mg sachet granules
	Nevirapine	6 mg sachet granules
Recommended priority antiretroviral products required for treatment		
Urgent	Zidovudine/Lamivudine/Nevirapine	60/30/50 mg tablet*
	Zidovudine/Lamivudine	60/30 mg tablet
	Stavudine/Lamivudine	6/30 mg tablet*
	Stavudine/Lamivudine/Nevirapine	6/30/50 mg tablet*
	Abacavir/Zidovudine/Nevirapine	60/60/50 mg tablet*
	Nevirapine	50 mg tablet*
	Lopinavir/ritonavir	100/25mg tablet*
High	Abacavir	60 mg tablet
	Efavirenz	100 mg tablet
	Abacavir/Lamivudine	60/30 mg tablet
	Zidovudine	60 mg tablet
	Zidovudine/Lamivudine/Abacavir	60/30/60mg tablet
Important	Stavudine	6 mg tablet*
	Lamivudine	30 mg tablet
	Efavirenz/Emtricitabine	100/35mg tablet
	Emtricitabine	35 mg tablet
	Ritonavir	25 mg tablet
	Fosamprenavir	Not examined
	Atazanavir	Not examined

(All tablets should be scored wherever possible)

NOTE: 2008 recommendations now include boosted lopinavir/ritonavir for infants exposed to nevirapine, and so co-formulated preparations of lopinavir/ritonavir plus AZT or ABC plus 3TC are desired. The current solid forms of lopinavir /ritonavir are very large in size and difficult for young babies despite offering appropriate dosing, so sprinkles or alternative non liquid forms would be very useful. Second line options for children starting on lopinavir based regimens need to be considered and newer antiretroviral agents (classes and agents) need to be considered, as these will increasingly be needed for treatment experienced children.

It is also likely that recommendations on infant prophylaxis with ARVs will be revised in 2009-2010 and a range of new infant preparations required may need to be considered.