ARV PRIORITY LIST FOR THE MEDICINES PATENT POOL

WORKING DRAFT

July 2011

Acronyms & Definitions

Acronym	
AIDS	Acquired Immune Deficiency Syndrome
ARIPO	African Regional Intellectual Property Organization
ART	Antiretroviral treatment
ARV	Antiretroviral drug
EAPO	Eurasian Patent Organization
EMEA	European Medicines Agency
FDA	United States Food and Drug Administration
FDC	Fixed Dose Combination
HIV	Human Immunodeficiency Virus
IP	Intellectual Property
LMIC	Low and Middle Income Countries
NIH	United States National Institutes of Health
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitor
OAPI	African Organization of Industrial Property
PMTCT	Prevention of Mother to Child Transmission of HIV
WHO	World Health Organization
WIPO	World Intellectual Property Organization

Antiretroviral Medicines	
3TC	Lamivudine
ABC	Abacavir
ATV	Atazanavir
AZT	Zidovudine
COB	Cobicistat
d4T	Stavudine
ddI	Didanosine
DLG	Dolutegravir
DRV	Darunavir
EFV	Efavirenz
ETR	Etravirine
EVG	Elvitegravir
FOS	Fosamprenavir
FTC	Emtricitabine
IDV	Indinavir
LPV	Lopinavir
NVP	Nevirapine
RAL	Raltegravir
RIL	Rilpivirine
RTV	Ritonavir

SQV	Saquinavir
TDF	Tenofovir

Country Codes	
AL	Algeria
AR	Argentina
AM	Armenia
BR	Brazil
CL	Chile
CN	China
CO	Colombia
DO	Dominican Republic
EG	Egypt
GT	Guatemala
IN	India
ID	Indonesia
KG	Kyrgyzstan
MY	Malaysia
MX	Mexico
MA	Morocco
PA	Panama
PE	Peru
PH	Philippines
RU	Russian Federation
ZA	South Africa
TJ	Tajikistan
TH	Thailand
UA	Ukraine
UY	Uruguay
UZ	Uzbekistan
VN	Vietnam

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Background

The Medicines Patent Pool (the "Pool") was established with the support of UNITAID in July 2010 with the aim of enhancing access to affordable HIV medicines in developing countries and promoting the development of adapted formulations, such as paediatric HIV medicines. It does so by negotiating voluntary licensing agreements with patent holders (e.g. companies, public research institutions, universities) and in turn licensing out on a non-exclusive basis to entities capable and willing to develop or manufacture products needed to treat HIV in developing countries. The Pool is a mechanism that could facilitate the development of optimal treatment options that could exist if intellectual property on HIV medicines is made available.

Since its inception, the Pool has collaborated with leading experts to identify urgently needed antiretrovirals (ARVs) that should be prioritised for inclusion in the Pool. The first prioritisation was done in October 2009 and submitted jointly by UNITAID and the WHO Secretariat to the WHO Expert Committee on the Selection and Use of Essential Medicines[1]. The document included lists of needed antiretroviral products and formulations for adults and children, based on the 2006 WHO treatment recommendations for HIV-infected adults, adolescents, infants and children [2, 3]. This document informed the selection of 19 priority ARVs identified in the UNITAID Patent Pool Initiative Implementation Plan, which was presented to the UNITAID Executive Board in December 2009. Selection criteria were: patent status; current availability of product (as originator or generic); registration status; adherence to international quality standards (e.g. WHO Pre-qualification); adequacy of formulations; timeline (for investigational drugs); clinical information on paediatric use; price; price of alternates; potential for co-formulation; clinical or practical advantages; and potential scope of use.

Since 2009, new clinical evidence has emerged on both existing and pipeline products. In 2010, the WHO issued a revision of the treatment guidelines for both children and adults [4, 5]. Simplified combinations using less toxic antiretrovirals are now recommended for 1st and 2nd line therapy. A new therapeutic class was also included and third line regimens were considered. In addition, some drugs are no longer recommended as preferred options, although they remain as alternative treatments in the guidelines.

Promising products have also progressed further in clinical development. New integrase inhibitors, second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) and pharmacokinetic enhancers, both as stand-alone drugs and as part of fixed dose combinations (FDCs), are in late stage development and are expected to be approved in their adult formulations shortly. Furthermore, a number of investigations are ongoing to optimize the dosage for some existing HIV medicines. Dose optimisation can have an important impact on decreasing side effects, improving dosing schedules, reducing the manufacturing costs of drugs, and making it easier to co-formulate ARVs as FDCs.

Finally, several patents on key ARVs have expired and these drugs are now widely available in generic form. Thus, while they may still be important from a clinical perspective, they may be less of a priority for the Pool.

In light of these developments, there is a need to update the priority list of ARV candidates for the Medicines Patent Pool.

A first step in updating the priorities for the Medicines Patent Pool was the revision of the list of missing formulations that had been prepared and submitted to the WHO Expert Committee in 2009. Thus, in February 2011, the Medicines Patent Pool, UNITAID and the WHO HIV/AIDS Department jointly submitted a proposed list of missing drug formulations for adults and children to the WHO Expert Committee based on the new WHO antiretroviral treatment guidelines[1]. The document identified formulations and combinations included in the 2010 WHO treatment guidelines, but were either not available, or there were limited suppliers and access remained a key concern. In addition, the document provided an overview of products in the last phases of development that may be approved before the next meeting of the Committee and may constitute important options for future treatment. The Expert Committee, which met in March 2011, recommended that the list be further prioritised, a process that is taking place, from a clinical perspective, through the WHO in the context of Treatment 2.0.

The objective of this working document is to prioritize compounds for the Medicines Patent Pool, based on clinical as well as market/intellectual property (IP) criteria. For the clinical prioritization it relies on the work undertaken by the WHO and on published information on the results of clinical trials for pipeline compounds.

Methodology

Categories for prioritisation

Compounds were categorised depending on whether they have already obtained regulatory approval and their stage of clinical development.

> Category 1: Compounds that have already received regulatory approval and are available today as single agents and/or in combinations[2].
>
> Category 2: These are pipeline compounds that are in phase III and are expected to be available shortly, as single agents and/or in combinations[3].
>
> Category 3: These are pipeline compounds that are in phase II and may be available sometime in the future.

[1] Submission endorsed by the following core partners of UNAIDS and WHO's Treatment 2.0 Initiative: Agence Nationale de Recherche sur le SIDA (ANRS), AIDS and Rights Alliance for Southern Africa (ARASA), The Global Fund to Fight AIDS, Tuberculosis and Malaria, HealthGap, International AIDS Society (IAS), International Treatment Preparedness Coalition (ITPS), Médecins Sans Frontières (MSF), Pangaea Global AIDS Foundation, the United States President's Emergency Plan for AIDS Relief (PEPFAR) and the Joint United Nations Programme on HIV/AIDS (UNAIDS)

[2] Category 1 does not include rilpivirine, which recently received FDA regulatory approval in May 2011.

[3] Category 2 includes rilpivirine, which recently received FDA regulatory approval in May 2011.

Criteria for prioritization

Compounds were prioritized based on a set of clinical and market/IP criteria, as described in further detail below.

Clinical criteria

For category 1 compounds, the Pool based its clinical prioritization on the 2010 WHO treatment guidelines [2, 3]. Products recommended in the guidelines for first-line and second-line treatment were considered to be high priority from a clinical perspective; products recommended for third-line were considered to be medium priority; and products not recommended in the 2010 guidelines were considered to be low priority[4].

For category 2 compounds, this document relied on the criteria included in the target product profile used by the WHO at its expert meeting on short-term treatment optimization priorities for antiretroviral drug regimens, which was held in April 2011. These are the following:

- **Safety/Efficacy**: Products must be equivalent or superior to currently available products and require minimal laboratory monitoring.
- **Tolerability:** Products must have minimal side effects and toxicities to improve adherence and reduce treatment failure.
- **Durability:** Products should present a high barrier to resistance and have a long half life to allow for flexibility in the dosing schedule and minimize the likelihood of resistance developing as a result of missed doses.
- **Stability:** Products should be heat-stable and simple to store over long periods of time with molecular stability.
- **Convenience:** Products should be suitable for once-daily dosing in fixed dose combinations - ideally one pill per day regimens - and simplified paediatric formulations or scored fixed dose combinations - once on one side, twice on the other - with no cumbersome testing requirements and the same dosing schedule for all drugs in a regimen.
- **Special Populations:** Products should be effective in all populations and in conjunction with treatment for other conditions: men and women of all ages, infants and children, people who inject drugs and patients with other co-infections, including tuberculosis, malaria and viral hepatitis.

The WHO criteria also include cost, highlighting the need for products to be available at the lowest sustainable price[5]. This factor was considered by the Pool when evaluating products from a market/IP perspective (see below).

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[4] An exception was rilpivirine, which obtained regulatory approval by the FDA in May 2011 and was not available at the time of the latest revision of the guidelines.

[5]Strategies to achieve this, as per the WHO definition, include negotiations with suppliers, interventions to influence market dynamics, use by countries as appropriate of TRIPS flexibilities and other trade agreements, as well as strategies that might include appropriate dose reduction and improvements in manufacturing and delivery processes.

Information on pipeline products is based on clinical trial data on the National Institutes of Health website (www.clinicaltrials.gov) [7] and the EU clinical trials register website [8]. In addition, a systematic search of abstracts was conducted from those presented at the XVIII International AIDS Conference (Vienna, July 2010), the 18th Conference on Retroviruses and Opportunistic Infections (Boston, March 2011), and published in PubMed. Other references such as the 2011 TAG Pipeline Report [9] have also been consulted.

For category 3 compounds, no detailed prioritisation was undertaken, as not enough information is available at this stage to assess the products. However, a general overview of some of the key characteristics of such products has been provided.

Market/IP criteria:

Once compounds had been evaluated according to their clinical significance, category 1 and 2 compounds were separately evaluated according to a set of market/IP criteria in order to determine to what extent patents posed a barrier to access in developing countries. The following criteria were used to evaluate compounds from a market/IP perspective:

- **Expected Compound Patent Expiry Date:** A single product may be protected by a number of different patents, relating to the compound, the process to manufacture it, and different formulations of that product. However, the patent on the drug compound or active ingredient is generally considered to be the most difficult to invent around. The expected expiry date of the compound patent was documented, based on a 20-year term from the filing date of the related international patent application (filed in accordance with the provisions of the Patent Cooperation Treaty or PCT)[6]. Compounds with a longer patent life were considered to be of higher priority than compounds for which the compound patent has expired or is close to expiry.
- **Compound Patent Status in India:** To the extent that Indian generic manufacturing accounts for more than 80% of annual purchase volumes of antiretrovirals in developing countries [10], compound patent status in India is particularly important in determining IP-related access issues. Thus, the existence of a product that had a compound patent in India was considered to be of higher priority from the market/IP perspective.
- **Compound Patent Status in Other Countries:** In addition to India, the extent to which the compound patents were in force in other low- and middle-income countries was evaluated based on available data. Illustrative examples of countries where compound patents were either granted or pending, as well as those designated in the international application filed under the PCT have been included in Table 2, below. The information provides a snapshot at a particular point in time based on the information that was available to the Medicines Patent Pool.
- **Other Relevant Patents (with expiry dates):** In addition to compound patents, patents may exist on specific forms of the compound (e.g. hydrate form of the drug salt), formulations (including combinations), and/or the manufacturing process for the drug. Such patents may represent less of a barrier to generic competition because generic companies can often develop non-infringing ways to make the same drug or successfully challenge the

[6] Actual expiry date may differ from country to country

validity of such patents. Nevertheless, in some cases they may represent an obstacle to the development of a generic version of specific formulations. As such, other important patents relevant to the drug have been noted, along with their expected expiry date, based on a 20-year term from the filing date of the related international patent application.

- **Geographical Coverage of Other Relevant Patents:** Similar to compound patent status in other countries, the geographical coverage of other patents relevant to the manufacturing of a drug was evaluated for all countries, including India.
- **Current Licences:** Even where a patent exists in a particular jurisdiction, generic supply may be possible where a licence to use that patent exists. This can happen either through government issued compulsory licences, or through voluntary programmes. In order to fully understand the access situation with respect to specific antiretrovirals, voluntary and compulsory licenses, non-assert declarations, and immunity-from-suit agreements were analysed to the extent that information about the terms and conditions of the agreements were publicly available. While such licences may allow lower-cost generic drugs to be made and sold, there are often several restrictions included in voluntary agreements. To the extent that such information was publicly available, they have been noted in Tables 2 and 4.
- **Number of WHO Prequalified or FDA Approved Generics:** The number of WHO prequalified or FDA tentatively approved generics has been noted as a proxy for the extent to which there is generic competition in the market. This information was obtained from the website of the WHO Prequalification Programme [11].

Information on patents status has been obtained from the Patent Status Database for Selected HIV Medicines, a resource publicly available on the Medicines Patent Pool website [12]. The database provides information on the patent status of selected antiretrovirals in a large number of low- and middle-income countries. The data was obtained from and cross-checked between a variety of sources, including many local patent offices that agreed to make this information available via the World Intellectual Property Organization (WIPO).

Summary of Results

Category 1 –Compounds with Regulatory Approval

Clinical and market/IP priorities of Category 1 compounds are presented in Tables 1 and 2 respectively[7]. Clinical prioritization for compounds in Category 1 is based on their position within the WHO Treatment guidelines (i.e. included or not, first-line, second-line, or third-line), as well as the extent to which formulations containing the compound have been included in the Updated List of Missing Drug Formulations for HIV Treatment presented to the 18th Expert Committee on the Selection and use of Essential Medicines. Formulations identified in the WHO Meeting Report on Short-Term Priorities for Antiretroviral Drug Optimization of April 2011 [13] are listed in bold.

[7] A number of approved ARVs have not been considered for this prioritization due to their very limited use in developing countries, despite having obtained regulatory approval many years ago.

Table 1: Clinical Prioritization of Category1 Compounds

Compound	WHO Guidelines		Missing Drug Formulation for HIV Treatment*		Clinical Priority
	Adult	Paediatric	Adult	Paediatric	
Abacavir (ABC)	-	Recommended for first-line	-	• ABC/3TC • ABC/3TC/NVP • ABC/3TC+EFV • ABC/3TC+LPV/r	**High** (paediatrics)
Atazanavir (ATV)	Recommended for second-line	Recommended for second line	• **ATV/r** • TDF/3TC/ATV/r • ATV/r under study for dose optimization	• ATV/r	**High** (priority for second line)
Darunavir (DRV)	Recommended for third-line	Key WHO research priority for second-line	• DRV/r • TDF/3TC+DRV/r • ETV+DRV/r • DRV/r+RAL	• DRV/r	**Medium** (priority for third line)
Didanosine (ddI)	-	-	-	-	**Low** (Not WHO recommended)
Efavirenz (EFV)	Recommended for first-line	Recommended for first-line for children > 3 years	• **TDF/3TC/EFV** • EFV under study for dose optimization	• ABC/3TC+EFV	**High** (priority for first line)
Emtricitabine (FTC)**	Recommended for first- and second line		• TDF/FTC+NVP • TDF/FTC/EFV • AZT/FTC/ETV • TDF/FTC+ETV • TDF/FTC/ATV/r • TDF/FTC+LPV/r • TDF/FTC+DRV/r • AZT/FTC+LPV/r • AZT/FTC+ATV/r • FTC under study for dose optimization	• ABC/FTC • TDF/FTC • ABC/FTC/NVP • ABC/FTC+EFV • AZT/FTC+LPV/r • ABC/FTC+LPV/r	**Medium** (used in first-line therapy, although 3TC generally preferred)
Etravirine (ETV)	Recommended for third-line	-	• AZT/3TC/ETV • TDF/3TC+ETV • ETV+DRV/r • ETV+RAL	• ETV	**Medium** (priority for third line)
Fosamprenavir (FPV)	-	-	-	-	**Low** (not recommended by WHO)
Indinavir (IDV)	-	-	-	-	**Low** (not recommended by WHO)

Compound	WHO Guidelines		Missing Drug Formulation for HIV Treatment*		Clinical Priority
	Adult	Paediatric	Adult	Paediatric	
Lamivudine (3TC)	Recommended for first- and second-line	Recommended for first-line	• **TDF/3TC+NVP** • **TDF/3TC/EFV** • AZT/3TC/ETV • TDF/3TC+ETV • TDF/3TC/ATV/r • TDF/3TC+LPV/r • TDF/3TC+DRV/r • AZT/3TC+LPV/r • AZT/3TC+ATV/r • 3TC under study for dose optimization	• ABC/3TC • TDF/3TC • ABC/3TC/NVP • ABC/3TC+EFV • **AZT/3TC+LPV/r** • ABC/3TC+LPV/r	**High** (priority for first-line)
Lopinavir (LPV)	Recommended for second-line	Recommended for first-line	• LPV/r • TDF/3TC+LPV/r • AZT/3TC+LPV/r • LPV/r under study for dose optimization	• **LPV/r** • **AZT/3TC+LPV/r** • ABC/3TC+LPV/r	**High** (priority for first- and second-line)
Maraviroc (MVC)	-	-	-	-	**Low** (not recommended by WHO)
Nevirapine (NVP)	Recommended for PMTCT		• **TDF/3TC+NVP**	• NVP • ABC/3TC/NVP	**High** (priority for PMTCT)
Raltegravir (RAL)	Recommended for third-line	-	• ETV+RAL • DRV/r+RAL • RAL under study for dose optimization	• RAL	**Medium** (priority for third-line)
Ritonavir (RTV)	Recommended for second- and third-line	Recommended for first-line	• RTV (heat stable tablet) • ATV/r • DRV/r • LPR/r • TDF/3TC/ATV/r • TDF/3TC+LPV/r • TDF/3TC+DRV/r • AZT/3TC+LPV/r • AZT/3TC+ATV/r • ETV+DRV/r • DRV/r+RAL • RTV, LPV/r, ATV/r under study for dose optimization	• **RTV (heat stable tablet, sprinkle)** • LPV/r • ATV/r • DRV/r • AZT/3TC+LPV/r • ABC/3TC+LPV/r	**High** (priority for second-, and third-line for adults and first-line for children)
Saquinavir (SQV)	-	-	-	-	**Low** (not recommended by WHO)
Stavudine (d4T)	-	-	-	-	**Low** (not recommended by WHO)

Compound	WHO Guidelines		Missing Drug Formulation for HIV Treatment*		Clinical Priority
	Adult	Paediatric	Adult	Paediatric	
Tenofovir (TDF)	Recommended for first- and second-line	Key WHO research priority for first-line	• **TDF/3TC+NVP** • **TDF/3TC/EFV** • **TDF/3TC+ETV***** • TDF/3TC/ATV/r • TDF/3TC+LPV/r • TDF/3TC+DRV/r	• TDF/3TC	**High** (priority for first-line)
Zidovudine (AZT)	Recommended for second-line	Recommended for first-line	• AZT/3TC/ETV • AZT/3TC+LPV/r • AZT/3TC+ATV/r • AZT under study for dose optimization	• AZT • **AZT/3TC**+LPV/r	**High** (priority for first- and second-line)

* Missing drugs and formulations for HIV treatment, as per the 'Updated List of Missing Drug Formulations for HIV Treatment to be Reviewed by the WHO 18th Expert Committee on the Selection and Use of Essential Medicines', February 2011. In some cases, the existing formulations have been developed but are produced by few manufacturers and access problems remain. Those cases have also been included in the table (e.g. TDF/3TC/EFV)

** Emtricitabine (FTC) is considered interchangeable with 3TC [4, 6]. Therefore, all combinations with 3TC could also be formulated with FTC and are equally important.

***Scored adult-strength dispersible formulation of TDF/3TC/EFV would become a priority for paediatrics first-line only if TDF is approved for use in younger children and appropriate dosing is established [13].

Table 2: Market/IP Prioritization of Category 1 Compounds

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licenses	# of WHO Prequal. or FDA Approved Generics	Market/IP Priority
Abacavir (ABC)	Expired in June/Dec. 2010	No	Mostly expired	New intermediates (2015); Hemisulfate salt (2018); Oral solution for paediatric use (2019)	Granted or pending in several LMICs. Paediatric solution granted in India and other LMICs	Yes, several licensees, but possible restrictions and limited geographical scope	5 or more for adult formulations but three approved for paediatric formulations	**Medium** (many suppliers; compound patent expired, but paediatric patent could be problematic)
Atazanavir (ATV)	2017	Initial application withdrawn but divisional application pending	Granted or pending in several LMICs, including e.g. AR, BR, CN, KG, MY, PH, TJ, TH	Bisulfate salt (2018); Use in HIV Therapy (2012); Process (2025)	Granted or pending in several LMICs.	Yes, limited number of licensees, possible restrictions and limited geographical scope	Two	**High** (few suppliers; compound patent pending in India and granted in other countries)
Darunavir (DRV)	Aug. 2013	No	No	Specific (2016); Method of Use (2019); Comb. w/ RTV (2022); Pseudopolymorph (2023); Prep. of key intermediates (2025); Comb. w/ RTV & TDF (2025)	Granted or pending in several LMICs	Yes, but only for packaging and distribution; limited number of licensees and limited geographical scope	None	**Medium** (no compound patents in most low and middle-income countries, but no generics currently on the market)
Didanosine (ddI)	2006	No	No	Improved oral formulation (July 2012) Enteric-coated (2018)	Granted or pending in several LMICs	Yes, several licensees. Commitment not to enforce its patent in SSA since 2001.	Three	**Low** (compound patent expired)
Efavirenz (EFV)	Aug. 2013	No	Granted or pending in some LMICs, including e.g. AL, BR*, CN, DO, MX, RU, ZA, TH*, UA	No	No	Yes, few licensees, possible restrictions and very limited geographical scope (only South Africa).	5 or more	**Medium** (no compound patent in India, many suppliers, but still compound patents in other countries)

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licenses	# of WHO Prequal. or FDA Approved Generics	Market/IP Priority
Emtricitabine (FTC)	Expired in 2010	No	Originally granted in several Low and LMICs, (including e.g. CN, MY, OAPI, PH, RU and ZA) but probably expired or due to expire shortly	No	No	Yes, immunity from suits issued in context of TDF license	Two	**Low** (compound patent expired)
Etravirine (ETV)	2019	Granted	Granted or pending in several LMICs, including e.g. ARIPO, AM, AR, BR, CL, CN, EAPO, ID, KG, MY, MX, OAPI, PH, RU, ZA, TJ, UA, VN	Novel series (2026) New forms (2026)	Granted or pending in several LMICs, including India	Only for packaging and distribution; limited number of companies and limited geographical scope	None	**High** (no generic suppliers; compound patent granted in India and other countries)
Fosamprenavir (FPV)	2018	Pending	Granted or pending in several LMICs, including e.g. ARIPO, AM, AR, CL, CN, Columbia, EAPO, ID, KG, MY, MX, OAPI, PE, PH, RU, ZA, TJ, TH, UA	Calcium salt (2019)	Granted or pending in several LMICs	Yes, several licensees, but possible restrictions and limited geographical scope (LDCs, LICs, SSA)	None	**High** (no generic suppliers; compound patent pending in India and granted in other countries)
Indinavir (IDV)	Nov. 2012	No	Granted or pending in some LMICs, including e.g. RU, ZA, UA	-	NA	None	Two	**Low** (due to expire shortly, no compound patent in India)
Lamivudine (3TC)	Feb. 2010	No	Originally granted in several LMICs, including e.g. MY, PH, RU, ZA but probably expired or due to expire shortly	Crystal form (June 2012) New formulation (2018)	Granted or pending in several LMICs, including India	Yes, several licensees, but possible restrictions and limited geographical scope (LDCs, LICs, SSA)	5 or more	**Low** (compound patent expired)
Lopinavir (LPV)	2016	No	Granted or pending in several LMICs, including e.g. AR, BR, CN, Colombia, MX, PH, ZA, TH	LPV/r Soft-gel caps (2017) LPV/r tablet formulation (2026) LPV/r tablet formulation (2024)	Granted or pending in several LMICs, including India	None	Three	**Medium** (few suppliers; compound patent in several countries;formulation patents pending in India and granted in other countries)

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licenses	# of WHO Prequal. or FDA Approved Generics	Market/IP Priority
Maraviroc (MVC)	2019	Granted	Granted or pending in several LMICs, including e.g. AL, ARIPO, AM, AR, BR, CL, EAPO, EG, GT, ID, KG, MY, MX, MA, OAPI, PA, PE, PH, RU, ZA, TJ, UA, UY, UZ, VN	Crystal form (2021)	Granted or pending in several LMICs, including India	None	None	**High** (no generic suppliers; compound patent granted in India and other countries)
Nevirapine (NVP)	Nov. 2010	No	Granted or pending in several LMICs, including e.g. OAPI, PH, RU, ZA	Hemihydrate formulation (2018) Extended release formulation (2028)	Granted or pending in several LMICs, including India	Yes, BI has policy of non-assert declarations, but potential restrictions for manufacturing in countries with patents and limited geographical scope	5 or more	**Low** (compound patent expired)
Raltegravir (RAL)	2022	Granted	Granted or pending in several LMICs, including e.g. BR, CL, CN, Columbia, MX, PH, ZA, UA, UZ, VN	Potassium salt (2025)	Granted or pending in several LMICs, including India	Yes, only two licensees. Also, possible restrictions and limited geographical scope	None	**High** (compound patent granted in India and other LMICs)
Ritonavir (RTV)	Dec. 2013/2014	No	Granted in few LMICs, including e.g. MX, PH	Crystalline polymorph (2019)	Granted or pending in several LMICs; opposed in India	None	One	**Medium** (few suppliers; no compound patent in India but in force in some LMICs, formulation patent pending in India and granted in other countries)
Saquinavir (SQV)	Dec. 2010	Expired	Originally granted in many LMICs, expired in many countries, but patent still in force in a few jurisdictions	Improved composition (2016) Oral dosage form (2024)	Granted or pending in several LMICs, including India	Several licenses and technology transfer agreements signed	None	**Medium** (no generic suppliers; compound patent expired but not in all jurisdictions)
Stavudine (d4T)	Dec. 2007 (expired)	No	No	No	-	Yes, several licensees. Commitment not to enforce its patents in SSA since 2001.	5 or more	**Low** (many suppliers; compound patent expired)

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licenses	# of WHO Prequal. or FDA Approved Generics	Market/IP Priority
Tenofovir (TDF)	2018	No	Granted or pending in several LMICs, including e.g. BR, CN, ID, MX	Ester prodrug (2017) Comb. w/ LPV, FTC, EFV (2024) Comb w/ EFV + FTC (2026)	Granted or pending in several LMICs, including India	Yes, several licensees but possible restrictions and limited geographical scope	5 or more	**Medium** (many suppliers; compound patent in some LLMICs process patent in India)
Zidovudine (AZT)	2006 (expired)	No	No	No	-	Yes, several, but limited geographical scope	5 or more	**Low** (many suppliers; compound patent expired)

Category 2 – Phase III Compounds

Category 2 (*Table 3 and 4*) presents compounds that are close to regulatory approval (Cobicistat, Dolutegravir and Elvitegravir) or have recently received approval (Rilpivirine). Several promising combinations that include these compounds and are under development have also been noted.

Table 3: Clinical Prioritization of Category 2 Compounds

Compound	Therapeutic Class	Combinations	Safety / Efficacy	Tolerability	Durability	Stability	Convenience	Special pop'ns	Cost	Clinical Priority*
Cobicistat (COB)	Pharmaco-kinetic booster	Already in phase III (study 236-0102) together with TDF/FTC** and ELVITEGRAVIR vs TDF/FTC/EFV. No results published yet. An agreement to produce DRV/COB FDC announced in July 2011[14]	Phase II study 236-0105 comparing cobicistat and ritonavir showed similar efficacy in both groups [15]	In phase II study 236-0102, cobicistat showed reduction of estimated glomerular filtration rate. Data at 24 weeks show no significant renal toxicity compared with ritonavir (study NCT01363011 [15])	No antiviral activity, so does not induce resistances.	Does not need refrigeration	One pill once daily	PAED: No clinical trials in children yet. TB: Cobicistat inhibits CYP450 [16], so may need dose adjustments with rifampicin Not yet approved for use in pregnant women and no ongoing studies.	May not be developed as stand-alone drug	**High**
Dolutegravir (DLG)	Integrase inhibitor	ABC/3TC/DLG entered phase III trial comparing with TDF/FTC/EFV [17]	Results of phase IIb study on naïve treatment patients (SPRING-1[17]) showed rapid viral load reductions ("after 4 weeks of therapy 66% taking the integrase inhibitor and 18% taking efavirenz had a viral load under 50 copies") 50mg dose BID is effective in treatment experienced patients with mild and heavy integrase resistance [18]. A phase III trial with twice daily dose in treatment experienced and naïve patients has already started[7])	SPRING-1 study results on naïve treatment patients presented in Vienna Conference showed less drug-related adverse events in DLG group compared with EFV (6% vs. 18%), and no serious adverse event was considered related to DLG [17] Recent results at 96 weeks confirm only 17% patients (n=24) presented grade 3 adverse events. No grade 4 events were observed [18]	Integrase inhibitor class does not have lower genetic barrier to resistance than EFV [19] but no comparison with boosted PIs Preliminary results on SPING-1 trial presented in Vienna showed that only 1 patient in the DLG group (n=155) experienced virologic failure.	Does not need refrigeration	One pill once daily	PAED: Phase II trial ongoing, but not enough data yet [7] TB: No information yet, although other integrase inhibitors are not TB friendly (RAL) Not yet approved for use in pregnant women and no ongoing studies.	Eligible for dose/cost reduction	**High**

Compound	Therapeutic Class	Combinations	Safety / Efficacy	Tolerability	Durability	Stability	Convenience	Special pop'ns	Cost	Clinical Priority*
Elvitegravir (EVG)	Integrase inhibitor	Already in phase III (study 236-0102) together with TDF/FTC** and COB vs. TDF/FTC/EFV. No results published yet.	In phase II 236-0102 study comparing EVG in combination with TDF/FTC/COB vs. TDF/FTC/EFV 90% vs. 83% had <50 copies/ml at 24 weeks and 48 weeks [15]	In phase II study 236-0102 study showed less efavirenz-related side effects. ("lower rate of drug-related central nervous system (17%) and psychiatric (10%) adverse events versus EFV/FTC/TDF (26 and 44%, respectively) [15]	Integrase inhibitor class does not have lower genetic barrier to resistance than EFV [19] but no comparison with boosted PIs	Does not need refrigeration	One pill once daily (only if boosted)	PAED: A phase II study for children over 12 years. No study yet for under 12. TB: Drug interactions with Rifampicin [20] Not yet approved for use in pregnant women and no ongoing studies.	Low dose of EVG would reduce cost	**High**
Rilpivirine (RIL)	NNRTI	TDF/FTC/RIL has already been studied vs. TDF/FTC/EFV [21] Another possible combination would be using 3TC instead of FTC. 3TC is cheaper and eligible for dose reductions (study ENCORE-3). This combination may require a single phase III pivotal trial for approval.	RIL vs. EFV comparative studies showed non-inferiority in the proportion of patients that reached undetectable viral load in both groups at 48 weeks (84.3% vs. 82.3%) (pooled results of studies THRIVE and ECHO [21])	Improved tolerability profile compared with EFV (at 96 weeks, RIL group showed reduced rash, less sleep disturbance and lower CNS toxicity compared with EFV, being serious adverse events similar in both groups as reported in TMC278-C204 study [22]	Pre-clinical and phase I studies support long acting injectable formulation [23]. Higher virological failure was found in the RIL group (9% vs. 4.8%) (pooled results of studies THRIVE and ECHO EFV [21])	Does not need refrigeration	One pill once daily (potential for long acting injectable formulation)	PAED: Still in phase II studies (NCT00799864 trial) but only in adolescents. TB: drug interactions with rifampicin. Not yet approved for use in pregnant women and no ongoing studies.	Potentially very cheap due to low dose used.	**High**

* Assessment of level of priority is preliminary and may be reviewed once compounds have obtained regulatory approval and further clinical evidence becomes available

** Another possible combination would be using 3TC instead of FTC. 3TC is cheaper and eligible for dose reductions (study ENCORE-3).

Table 4: Market/IP Prioritization of Category 2 Compounds

Compound	Expected Compound Patent Expiry Date	Compound Patent Status in India	Compound Patent Status in Other Countries	Other Relevant Patents (expiry date)	Geographical Coverage of Relevant Patents	Current Voluntary Licenses	# of WHO Prequal. or FDA Approved Generics	Market/IP Priority
Cobicistat (COB)	2028	Pending	Pending in several LMICs, including e.g. AL, ARIPO, AM, AR, BR, CN, EAPO, EG, ID, KG, MX, MA, OAPI, RU, ZA, TJ, VN	None have been identified at this stage	NA	No	NA	**High** (compound patent pending in India and other countries)
Dolutegravir (DLG)	2026	Pending	Granted or pending in several LMICs, including e.g. AM, CN, EAPO, KG, MX, PH, RU, ZA, TJ, UZ	Synthesis processes (2029) Intermediates (2029)	Granted or pending in several LMICs, including India	No	NA	**High** (compound patent pending in India and other countries)
Elvitegravir (EVG)	2023	Pending	Granted or pending in several LMICs, including e.g. AR, BR, CL, CN, Colombia, MY, MX, PE, PH, RU, ZA, VN	Crystal form (2025) Improved pharmacokinetics w/ RTV (2026)	Granted or pending in several LMICs, including India	No	NA	**High** (compound patent pending in India and other countries)
Rilpivirine (RIL)	2022	Granted	Granted or pending in several LMICs, including e.g. AR, ARIPO, BR, CL, CN, EG, Jordan, MY, MX, OAPI, PA, PH, ZA, UA, VN	None have been identified at this stage	NA	Yes, voluntary licenses with 3 companies but possible restrictions and limited geographical scope.	NA	**High** (compound patent granted in India and granted or pending in other countries)

Long Term – Category 3

In category3 (Table 5) presents promising compounds that have entered phase II of development.

Table 5: Clinical Review of Category 3 Compounds*

Adult	Therapeutic class	Development phase	Comments
BMS-663068	Attachment inhibitor	Phase II	New therapeutic class
CENICRIVIROC	CCR5 inhibitor	Phase II	Recently entered phase II (study NCT01338883) [7]
CMX-157	NRTI	Phase II	Recently entered phase II [9]
ELVUCITABINE	NRTI	Phase II finished, but development interrupted according to Achillion	Potential to be QD, weekly, monthly Potentially very cheap
FESTINAVIR	NRTI	Phase II [24]	Similar to d4T but less toxic Long-acting properties
FOZIVUDINE	NRTI	Finished phase II but development interrupted	New lipid conjugate of AZT that reduces toxicity and increases activity [25]
GSK-744	Integrase inhibitor	Phase II	Phase II study showed safety and efficacy [8] A phase I study investigates its use as long-acting IV or IM injection [8]
GSK-761	NNRTI	Phase II	Development on hold due to toxicity issues [9].
IBALUZIMAB	CD4 monoclonal antibody	Phase II	New therapeutic class
LERSIVIRINE	NNRTI	Phase II	No data available yet.
PRO-140	Monoclonal CCR5 antibody	Already entered phase II (NCT01272258 trial[8])	Long-acting properties
SPI-452	Pharmacokinetic enhancer	Phase II	Together with COB, only booster in advanced development
TDF vaginal gel	NRTI	Phase II	It has shown effective reduction of HIV acquisition (CAPRISA 004 study [26])

* Products included in this table are in early stage of development and may not reach approval. The list is not exhaustive.

Conclusions

By considering both the clinical and market/IP criteria for each compound, priority compounds for the Medicines Patent Pool have been identified. Compounds that were considered medium or high priority according to both sets of criteria are first-tier priorities for the Pool; products that were considered to be a low priority under one set of criteria (but not under the other) are second tier priorities; and products that were considered to be a low priority under both sets of criteria have been considered not to be a priority for the Medicines Patent Pool, as they are of limited interest from a clinical perspective in light of current WHO recommendations, and patents represent a limited barrier to generic competition. Compounds in Phase II have not been included in the list of priorities yet provided below, as not enough information is available. As compounds move to Phase III, and further clinical information becomes available, the Pool will assess those compounds according to the same criteria as the others.

Table 6: Summary of Priorities for the Medicines Patent Pool

Compound	Clinical Priority	Market/IP Priority
First Tier Priorities		
Atazanavir (ATV)	High	High
Cobicistat (COB)*	High	High
Dolutegravir (DLG)*	High	High
Elvitegravir (EVG)*	High	High
Rilpivirine (RIL)	High	High
Abacavir (ABC)	High	Medium
Efavirenz (EFV)	High	Medium
Lopinavir (LPV)	High	Medium
Ritonavir (RTV)	High	Medium
Tenofovir (TDF)	High	Medium
Etravirine (ETV)	Medium	High
Raltegravir (RAL)	Medium	High
Darunavir (DRV)	Medium	Medium
Second Tier Priorities		
Lamivudine (3TC)	High	Low
Nevirapine (NVP)	High	Low
Zidovudine (AZT)	High	Low
Emtricitabine (FTC)	Medium	Low
Fosamprenavir (FPV)	Low	High
Maraviroc (MVC)	Low	High
Saquinavir (SQV)	Low	Medium

* Compounds under development (Phase III)

Table 7: Compounds not considered to be a priority for the Pool

Not Priorities		
Didanosine (ddI)	Low	Low
Indinavir (IDV)	Low	Low
Stavudine (d4T)	Low	Low

The above list of 20 compounds will replace the earlier list of 19 products as the priority targets for inclusion for the Medicines Patent Pool. The list will be periodically updated, as new clinical information on the different compounds becomes available, WHO treatment guidelines are revised, and the patent status of the compounds changes.

References

1. Perez, C., *Annex 7: Missing ARVs for treatment or prevention of HIV in Adults and Children*. 2009, UNITAID: Geneva.
2. WHO, *Antiretroviral therapy of HIV infection in infants and children: Recommendations for a public health approach (2006 revision)*. 2006: Geveva.
3. WHO, *Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach (2006 revision)*. 2006: Geneva.
4. WHO, *Antiretroviral therapy for HIV infections in adults and adolescents: recommendations for a public health approach - 2010 revision*. 2010: Geneva.
5. WHO, *Antiretroviral therapy for HIV infection in infants and children: Towards universal access. Recommendations for a public health approach - 2010 revision*. 2010: Geneva.
6. NIH, *Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* 2011, Department of Health and Human Services.
7. http://www.aidsinfo.nih.gov/ClinicalTrials/Default.aspx. 2011.
8. *https://*www.clinicaltrialsregister.eu/. 2011.
9. Clayden, P., Collins, S., Harrington, M., Jefferys, R., Swan, T., Syed, J., Wingfield, C., *TAG 2011 Pipeline Report*. 2011, Treatment Action Group: New York.
10. Waning, B., E. Diedrichsen, and S. Moon, *A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries.* J Int AIDS Soc, 2010. **13**: p. 35.
11. http://apps.who.int/prequal/query/ProductRegistry.aspx.
12. http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs. 2011.
13. WHO, *WHO Meeting on Prioritization of ARV Drigs & Formulations for Treatment Optimization.* . 2010: London.
14. http://www.gilead.com/pr_1580287. 2011.
15. Cohen, C., et al., *Randomized, phase 2 evaluation of two single-tablet regimens elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for the initial treatment of HIV infection.* AIDS, 2011. **25**(6): p. F7-12.
16. German, P.e.a., *The effect of cobicistat on cytochromr P450 2D6, 2B6 and P-glycoprotein using phenotypic probes*, in *12th International Workshop on Clinical Pharmacology of HIV Therapy*. 2011: Miami.
17. Arribas, J., Lazzarin, A., Raffi, F., et al., *Once-daily S/GSK1349572 as part of combination therapy in antiretroviral-naive adults: rapid and potent antiviral responses in the interim 16-week analysis from SPRING-1 (ING112276).* . Program and abstracts of the XVIII International AIDS Conference, 2010.
18. Eron, J., Kumar, P., Lazzarin, A, Richmond, G., Soriano, V., Huang, J., Vavro, C., Ait-Khaled, M., Min, S., Yeo, J., *DTG in Subjects with HIV Exhibiting RAL Resistance: Functional Monotherapy Results of VIKING Study Cohort II*, in *18th Conference on Retroviruses and Opportunistic Infections*. 2011: Boston.
19. Lennox, J.L., et al., *Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses.* J Acquir Immune Defic Syndr, 2010. **55**(1): p. 39-48.

20. Ramanathan, S., et al., *Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir.* Clin Pharmacokinet, 2011. **50**(4): p. 229-44.
21. Cohen, C., Molina, JM., Cahn, P., et al, *Pooled week 48 efficacy and safety results from ECHO and THRIVE, two double-blind, randomised, phase III trials comparing TMC278 versus efavirenz in treatment-naive, HIV-1-infected patients.* , in *XVIII International AIDS Conference*. 2010: Vienna.
22. Pozniak, A.L., et al., *Efficacy and safety of TMC278 in antiretroviral-naive HIV-1 patients: week 96 results of a phase IIb randomized trial.* AIDS, 2010. **24**(1): p. 55-65.
23. van 't Klooster, G., et al., *Pharmacokinetics and disposition of rilpivirine (TMC278) nanosuspension as a long-acting injectable antiretroviral formulation.* Antimicrob Agents Chemother, 2010. **54**(5): p. 2042-50.
24. Cotte, L., Dellamonica, P., Raffi, F., et al, *A Phase-Ib/IIa Dose-Escalation Study of OBP-601 (4'-ethynyl-d4T, Festinavir) in Treatment-Experienced, HIV-1-Infected Patients*, in *50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2010)*. 2010: Boston.
25. *Fozivudine: BM 211290, fozivudine tidoxil, FZT, HDP 990002, W 09726867.* Drugs R D, 2004. **5**(1): p. 41-3.
26. Abdool Karim, Q., et al., *Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women.* Science, 2010. **329**(5996): p. 1168-74.