PRIORITY ANTIRETROVIRALS FOR THE MEDICINES PATENT POOL

WORKING PAPER

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2nd Edition

Acronyms & Definitions

Acronym	
AIDS	Acquired Immunodeficiency Syndrome
ARIPO	African Regional Intellectual Property Organization
ART	Antiretroviral treatment
ARV	Antiretroviral drug
AV-HALTS	AntiViral- HyperActivation Limiting Therapeutics
EAPO	Eurasian Patent Organization
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FDC	Fixed Dose Combination
HIV	Human Immunodeficiency Virus
IP	Intellectual Property
LDC	Least Developed Countries
LIC	Low Income Countries
MIC	Middle Income Countries
NIH	United States National Institutes of Health
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitor
OAPI	Organisation Africaine de la Proprieté Intellectuelle/African Organization of Industrial Property
PMTCT	Prevention of Mother to Child Transmission of HIV
PrEP	Pre-exposure prophylaxis
SSA	Sub-Saharan Africa
WHO	World Health Organization
WIPO	World Intellectual Property Organization

Antiretroviral Medicines	
3TC	Lamivudine
ABC	Abacavir
ATV	Atazanavir
AZT	Zidovudine
COBI	Cobicistat
d4T	Stavudine
ddI	Didanosine
DTG	Dolutegravir
DRV	Darunavir
EFV	Efavirenz
ETR	Etravirine
EVG	Elvitegravir
FOS	Fosamprenavir
FTC	Emtricitabine
IDV	Indinavir
LPV	Lopinavir
NVP	Nevirapine

RAL	Raltegravir
RPV	Rilpivirine
RTV	Ritonavir
r	Ritonavir used as booster
SQV	Saquinavir
TDF	Tenofovir Disoproxil Fumarate

Country Codes	
AL	Algeria
AR	Argentina
AM	Armenia
AZ	Azerbaijan
BO	Bolivia
BR	Brazil
CL	Chile
CN	China
CO	Colombia
CR	Costa Rica
DO	Dominican Republic
EG	Egypt
GE	Georgia
GT	Guatemala
IN	India
ID	Indonesia
KG	Kyrgyzstan
MA	Morocco
ME	Montenegro
MN	Mongolia
MX	Mexico
MY	Malaysia
PA	Panama
PE	Peru
PH	Philippines
RU	Russian Federation
ZA	South Africa
TJ	Tajikistan
TH	Thailand
TR	Turkey
UA	Ukraine
UY	Uruguay
UZ	Uzbekistan
VN	Vietnam

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EXECUTIVE SUMMARY

This Working Paper identifies antiretrovirals (ARVs) that are prioritised for inclusion in the Medicines Patent Pool (the Pool). Revised on an annual basis, the paper reviews the latest clinical data and market/intellectual property (IP) information on ARVs to determine different levels of priorities for the Pool.

Medicines are analysed based on two sets of criteria: medical and market/IP. This analysis allows the Pool to gauge the potential impact that its work could have by obtaining open, transparent and public-health oriented licences on targeted ARVs.

The clinical criteria are used to evaluate the medical importance, or potential importance, of each ARV for the treatment of HIV in low- and middle-income countries (LIC/MICs). The clinical assessment relies on World Health Organization (WHO) treatment guidelines, WHO technical updates and information from clinical trials.

The market/IP criteria are used to evaluate the extent to which there are IP barriers to robust market competition for each ARV. The assessment is based upon the patent status of each ARV in LIC/MICs, current licences (if any) and the number of quality-assured suppliers on the market.

Based on the above criteria, this paper identifies three levels of priority for the Pool. Six ARVs are Level 1 priorities, as they are considered to be high priority according to both clinical and market/IP criteria. They are: atazanavir, cobicistat, dolutegravir, elvitegravir, lopinavir and ritonavir.

Nine ARVs are Level 2 priorities, as they are considered to be at least a medium priority from both the clinical and market/IP perspective. They are: abacavir, darunavir, efavirenz, emtricitabine, etravirine, nevirapine, raltegravir, riplivirine and tenofovir.

Level 3 priorities comprise four products of limited clinical importance in light of current WHO treatment guidelines, but of medium to high priority from a market/IP perspective. They are: didanosine, fosamprenavir, maraviroc and saquinavir.

Background

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 formulations and Fixed Dose Combinations (FDCs). It does so by negotiating voluntary licensing agreements on patented ARVs with patent holders (e.g. companies, public research institutions, and universities) and in turn licensing these patents out to entities willing and able to develop or manufacture products needed to treat HIV in developing countries.

Since its inception, the Pool has collaborated with leading experts to identify needed antiretrovirals (ARVs) that should be prioritised for inclusion in the Pool. The first prioritisation was conducted in October 2009, and elements of it were submitted jointly by UNITAID and the WHO Secretariat to the 17th WHO Expert Committee on the Selection and Use of Essential Medicines [1]. The document submitted to the Committee 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 helped to inform the selection of 19 priority ARVs identified in the UNITAID Patent Pool Initiative Implementation Plan of 2009.

In February 2011, the Pool, UNITAID and the WHO HIV/AIDS Department jointly submitted an update to the previous list, based on the new 2010 WHO antiretroviral treatment guidelines, to the 18th WHO Expert Committee on the Selection and Use of Essential Medicines[a] The document identified several key formulations and combinations that were either not available or for which there were limited suppliers. The Expert Committee, which met in March 2011, recommended that the list be further prioritised.

In September 2011, the Pool published the first edition of this Working Paper, which included a clear description of the methodology for prioritisation and the identification of three levels of priority for the Medicines Patent Pool. This second edition of the Working Paper incorporates the latest clinical evidence on approved and pipeline ARVs, as well as new data on the patent status of ARVs in LIC/MICs.

Methodology

ARV Categories

ARVs were divided into categories before prioritisation, based on their regulatory status and on whether they had been reviewed by the WHO ART guidelines committee.

Category A ARVs are compounds that have received regulatory approval and have been considered by the WHO ART guidelines committee. ARVs in this category are: abacavir

[a] The submission was endorsed by the following core partners of the Joint United Nations Programme on HIV/AIDS (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 (ITPC), Médecins Sans Frontières (MSF), Pangaea Global AIDS Foundation, the United States President's Emergency Plan for AIDS Relief (PEPFAR) and UNAIDS.

(ABC), atazanavir (ATV), darunavir (DRV), didanosine (ddI), efavirenz (EFV), emtricitabine (FTC), enfuvirtide (T-20), etravirine (ETV), fosamprenavir (FPV), indinavir (IDV), lamivudine (3TC), lopinavir (LPV), maraviroc (MVC), nelfinavir (NFV), nevirapine (NVP), raltegravir (RAL), ritonavir (r), saquinavir (SQV), stavudine (d4T), tenofovir (TDF), zidovudine (AZT).

Category B ARVs are compounds that are currently in late-stage development (Phase III clinical trials) or have recently received regulatory approval but have not yet been reviewed by the WHO ART guidelines committee. ARVs in this category are: cobicistat (COBI), dolutegravir (DTG), elvitegravir (EVG), rilpivirine (RPV).

Category C ARVs are selected pipeline compounds that are in Phase II clinical trials.

Criteria for Prioritisation

ARVs in Categories A and B were prioritised based on a set of clinical and market/IP criteria, as described in further detail below. Category C ARVs have not been included in the priority list, but limited information on them is provided in Table 7 below.

Clinical Criteria

For Category A ARVs, the Pool based its clinical prioritisation on the 2010 WHO treatment guidelines for adults and children [4, 5], the technical updates issued by the WHO in 2012 [6-8] and the WHO priorities for treatment optimisation [9]. As a general rule, products recommended as preferred treatment options for first-line and second-line treatment in the guidelines were considered to be of high priority from a clinical perspective; products currently considered for third-line or as alternatives for first and second line were considered to be of medium priority[b]; and products which were only recommended in very specific circumstances, were being phased out or were not recommended were considered to be of low priority.

In addition, information on missing formulations or fixed-dose combinations was included for each ARV. Formulations or combinations are defined as "missing" if they could facilitate administration of WHO recommended regimens and if there are limited or no quality-assured suppliers for them, or if they are new combinations that are known to be under development.

[b] This decision was motivated by the fact that the WHO has not yet issued firm recommendations on a third-line regimen for resource-limited settings, given the limited evidence currently available to guide third-line strategies [4].

For Category B ARVs, the assessment was based on information available from clinical trials. ARVs were assessed based on the criteria included in the WHO's target product profile available in the report *Short-Term Treatment Optimization Priorities for Antiretroviral Drug Regimens* [9]. The criteria in the target product profile are:

- **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 minimise the likelihood of resistance developing as a result of missed doses.
- **Specific Populations:** Products should be effective in all populations and in conjunction with treatment for other conditions: men and women of all ages, pregnant women, infants and children, people who inject drugs, and patients with other co-infections, including tuberculosis, malaria and viral hepatitis.
- **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.
- **Cost[c]:** Products should be available at the lowest sustainable price.

The main source of information for data on clinical trials was the US National Institutes of Health ClinicalTrials.gov website [11]. In addition, a systematic search of abstracts was conducted from those presented at recent International AIDS Conferences, Conferences on Retroviruses and Opportunistic Infections and IAS Conferences on HIV Pathogenesis, Treatment and Prevention as well as those published in PubMed [12]. Other references, including the The TAG/i-Base *2012 Pipeline Report* [13], have also been consulted.

For Category C ARVs, no detailed prioritisation was undertaken, as not enough information was available to assess the products. However, a general overview of some of the key characteristics of these compounds, including preliminary information on safety and efficacy, is provided in Table 5.

Market/IP Criteria:

Category A and B ARVs were separately evaluated according to a set of market/IP criteria. The goal of the market/IP assessment was to determine to what extent patents in developing countries represent a potential barrier to accessing generic versions of these ARVs. The following criteria were used to evaluate ARVs from a market/IP perspective:

- **Expected Expiry Date of Compound Patent:** The expected expiry date of the compound patent relating to each ARV was estimated, based on a 20-year term from the filing date of the related international patent application.[d] ARVs with a longer

[c] Some of the factors influencing cost (e.g. availability of generics, degree of competition in the market, IP protection) were also considered by the Pool when evaluating products from a market/IP perspective.
[d] Actual expiry date may differ from country to country in accordance with national patent laws.

patent term left were considered to be of higher priority than ARVs for which the compound patent has expired or is close to expiry.

- **Compound Patent Status in India:** Given the leading role of Indian generic manufacturers in supplying ARVs to other developing countries,[e] the existence of a compound patent or patent application in India was considered to increase the level of priority of a given ARV from a market/IP perspective.
- **Compound Patent Status in Other Countries:** The extent to which compound patents were pending or granted in other LIC/MICs, including other countries where generic ARVs are commonly manufactured, were reviewed. Illustrative examples of countries where compound patents were either granted or pending, based on available information, are included in the tables below.
- **Other Relevant Patents:** In addition to compound patents, patents often exist on specific chemical forms of the compound (e.g. hydrate form of the drug salt), formulations, combinations, new indications and/or the manufacturing process for the drug. Such secondary 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 the validity of such patents may be challenged[f] [15]. Such "secondary patents" may also not be patentable in some jurisdictions. Nevertheless, in some cases, they may represent an obstacle to the development or sale of a generic version of the ARV or of specific formulations. Therefore, information on secondary patents, their patent status in LICs/MICs, and their date of expected expiry was considered, where such information was available.
- **Current Licences:** Even where a patent exists in a particular jurisdiction, generic supply may be possible where licences to use the relevant patents exist. Voluntary and compulsory licences, non-assert declarations, and immunity-from-suit agreements were analysed to the extent that information about their terms and conditions 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 United States Food and Drug Administration (FDA) tentatively approved generic suppliers making at least one formulation of an ARV or making it in combination with other ARVs has been noted as a proxy for the extent to which there is generic competition in the adult and paediatric market.

Information on patent status was obtained from the Patent Status Database for Selected HIV Medicines, a resource publicly available on the Pool's website [16]. The database provides information on the patent status of selected ARVs in 78 LIC/MICs and is regularly updated and expanded to include more countries. Wherever patent information was not available from the database (e.g. enfuvirtide, nelfinavir and tipranavir), this document relies on the limited information gathered from other sources, in particular, Médecins Sans Frontières' publication *Untangling the Web of Antiretroviral Price Reductions* (2011) [17].

[e] In 2006-2008, Indian generic manufacturers accounted for more than 80% of annual purchase volumes of donor-funded ARVs in developing countries [14]

[f] Even where some secondary patents are vulnerable to challenge, the legal process to invalidate them is often long and costly. For example, the European Commission estimates that it takes an average of almost three years for invalidation proceedings to be completed. During the pendency of such proceedings, interim injunctive measures may prevent the entry of a generic alternative.

Information on the number of WHO prequalified or FDA approved generics was obtained from the website of the WHO Prequalification Programme [18].

Summary of Results

Category A – ARVs with regulatory approval that have been reviewed by the WHO ART Guidelines Committee

Clinical and market/IP priorities of Category A ARVs are presented in Tables 1 and 2 respectively. As explained above, clinical prioritisation for ARVs in Category A is based on their position within the 2010 WHO Treatment guidelines (i.e. included or not, preferred option or alternative, first-line, second-line, or third-line).

Table 1: Clinical Prioritisation of Category A ARVs

† FDC or co-pack already produced but not enough sources available (≤ 3 sources prequalified by WHO available) (WHO PQ list consulted on 05/09/2012)
‡ Drug, regimen or combination under development (Phase II or Phase III)

ARV	WHO Guidelines		Missing Drug Formulation for HIV Treatment[g]		Clinical Priority
	Adult	Paediatric	Adult	Paediatric	
Abacavir (ABC)		Recommended for 1st and 2nd line	•ABC/3TC/DTG‡	•ABC/3TC† •ABC/3TC/NVP •ABC/3TC+EFV •ABC/3TC+LPV/r •ABC/3TC+ATV/r	**Medium** (priority primarily for paediatrics)
Atazanavir (ATV)	Recommended for 2nd line (preferred option)		**•ATV/r†** **•TDF/3TC+ATV/r†** **•AZT/3TC+ATV/r** •ATV/r+RAL‡ •ATV/COBI‡	•ATV/r‡ •ABC/3TC+ATV/r •TDF/FTC+ATV/r	**High** (priority for 2nd line)
Darunavir (DRV)[h]	Tentative recommendation for 3rd line		•DRV/r‡ •TDF/3TC+DRV/r •ETV+DRV/r •DRV/r+RAL •DRV/r+ETV+RAL •DRV/COBI‡	•DRV/r‡ •TDF/3TC+DRV/r	**Medium** (priority for 3rd line)
Didanosine (ddI)		Restricted to 2nd line as an alternative	-	-	**Low** (no longer recommended for adults, and only as an alternative 2nd line in paediatrics)
Efavirenz (EFV)	Recommended for 1st line (preferred option also in early pregnancy or women with potential for pregnancy [6])	Recommended for 1st line for children > 3 years	**•TDF/3TC/EFV†** •AZT/3TC+EFV†	•ABC/3TC+EFV •TDF/FTC/EFV **•TDF/3TC/EFV**	**High** (priority for first line)
Emtricitabine (FTC)	Recommended for 1st and 2nd line (considered interchangeable with 3TC [8])	Recommended for 1st and 2nd line (considered interchangeable with 3TC [19])	FDCs included for 3TC also apply for FTC and vice-versa	FDCs included for 3TC also apply for FTC and vice-versa	**High** (priority for 1st and 2nd line; considered interchangeable with 3TC).

[g] Combinations that are identified in the WHO meeting report on Short-Term Priorities for Antiretroviral Drug Optimization [9] are highlighted in bold. Some combinations may be difficult to co-formulate due to, for example, the pill size or different dosing schedules. In these situations a co-blister pack would be desirable. Therefore, the sign "/" has been used only when co-formulation is possible or known to be possible. Otherwise, the sign "+" has been used.
[h] Darunavir (DRV) has the potential to be used in 2nd line but is currently only recommended by WHO for use in 3rd line.

ARV	WHO Guidelines		Missing Drug Formulation for HIV Treatment[g]		Clinical Priority
	Adult	Paediatric	Adult	Paediatric	
Enfuvirtide (T-20)	-	-	-	-	**Low** (not recommended by WHO)
Etravirine (ETV)	Tentative recommendation for 3rd line	-	•ETV+DRV/r •DRV/r+ETV+RAL	•ETV‡	**Medium** (priority for 3rd line)
Fosamprenavir (FPV)	-	-	-	•FPV/r‡	**Low** (not recommended by WHO)
Indinavir (IDV)	-	-	-	-	**Low** (not recommended by WHO)
Lamivudine (3TC)	Recommended for 1st and 2nd line (considered interchangeable with FTC [8])	Recommended for 1st and 2nd line (considered interchangeable with FTC [8])	•**TDF/3TC/EFV†** •TDF/3TC+NVP† •**TDF/3TC+ATV/r†** •TDF/3TC+LPV/r† •TDF/3TC+DRV/r •AZT/3TC+LPV/r •**AZT/3TC+ATV/r** •AZT/3TC+EFV† •3TC/LPV/r‡ •	•ABC/3TC† •**AZT/3TC (dispersible formulation) †** •**TDF/3TC** •ABC/3TC/NVP •AZT/3TC/NVP† •ABC/3TC+EFV •AZT/3TC+LPV/r •ABC/3TC+LPV/r •TDF/3TC+NVP •**TDF/3TC/EFV** •TDF/3TC+LPV/r •TDF/3TC+DRV/r	**High** (priority for 1st and 2nd line)
Lopinavir (LPV)	Recommended for 2nd line (preferred option)	Recommended for 1st line below 24 months if prior exposure to NVP, and otherwise for 2nd line	•TDF/3TC+LPV/r •AZT/3TC+LPV/r •3TC/LPV/r‡ •RAL+LPV/r‡	•**LPV/r (sprinkles)‡** •LPV/r† •AZT/3TC+LPV/r •TDF/3TC+LPV/r •ABC/3TC+LPV/r	**High** (priority for 2nd line in adults and 1st and 2nd line in children)
Maraviroc (MVC)[i]	-	-	-	•MVC‡	**Low** (not recommended by WHO)
Nelfinavir (NFV)	-	-	-	-	**Low** (not recommended by WHO)
Nevirapine (NVP)[j]	Recommended for the prevention of mother to child transmission (PMTCT) and alternative to EFV in 1st line	Recommended for 1st line (if no prior exposure to NVP)	•TDF/3TC+NVP†	•ABC/3TC/NVP •AZT/3TC/NVP† •TDF/3TC+NVP	**High** (priority for adult and paediatric 1st line and for PMTCT)

[i] MVC is also in Phase II clinical trials for use in pre-exposure prophylaxis (PrEP), in Phase I clinical trials as a vaginal ring and in preclinical testing as a rectal microbicide gel.
[j] Nevirapine (NVP) extended release was approved by the FDA in March 2011.

ARV	WHO Guidelines		Missing Drug Formulation for HIV Treatment[g]		Clinical Priority
	Adult	Paediatric	Adult	Paediatric	
Raltegravir (RAL) [k]	Tentative recommendation for 3rd line [19]	-	•ETV+RAL •DRV/r+RAL •ATV/r+RAL‡ •DRV/r+ETV+RAL •RAL+LPV/r‡	•RAL †,‡	**Medium** (priority for 3rd line)
Ritonavir (r)	Recommended for 2nd and 3rd line (as pharmacological booster)	Recommended for 1st line (as pharmacological booster) in children below 24 months with prior exposure to NVP and otherwise for 2nd line	•r (heat stable tablet) † •**ATV/r†** •DRV/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 •ATV/r+RAL‡ •DRV/r+ETV+RAL •RAL+LPV/r‡	•**r (heat stable tablet)** •**LPV/r (sprinkles)‡** •LPV/r† •ATV/r •DRV/r •AZT/3TC+LPV/r •ABC/3TC+LPV/r	**High** (priority for 2nd, and 3rd line for adults and 1st and 2nd line for paediatrics)
Saquinavir (SQV)	No longer a preferred protease inhibitor in WHO guidelines (except for TB co-infection if rifabutin is not available)	-	-	-	**Low** (not recommended by WHO except for TB co-infection if rifabutin is not available)
Stavudine (d4T)	No longer recommended	Recommended as alternative to AZT and ABC for first-line	-	-	**Low** (no longer recommended for adults, recommended as part of alternative regimen for children, global efforts to phase out due to toxicity)
Tenofovir (TDF)[l]	Recommended for 1st or 2nd line (if not used in first line)	Recently approved in children > 2 yrs [7] but not yet reviewed by WHO ART Guidelines Committee	•TDF/3TC+NVP† •**TDF/3TC/EFV†** •**TDF/3TC+ATV/r†** •TDF/3TC+LPV/r •TDF/3TC+DRV/r •TDF/FTC/EVG/COBI†	•**TDF/3TC** •**TDF/3TC/EFV** •TDF/3TC+NVP •TDF/3TC+LPV/r •TDF/3TC+DRV/r •TDF/3TC+ATV/r	**High** (priority for 1st and 2nd line)

[k] Raltegravir can also be used in treatment naïve patients and does not need a booster. However, it is currently recommended by WHO for use in third-line only.
[l] Tenofovir recently received regulatory approval for use as oral PrEP in combination with FTC.

ARV	WHO Guidelines		Missing Drug Formulation for HIV Treatment[g]		Clinical Priority
	Adult	Paediatric	Adult	Paediatric	
Zidovudine (AZT)	Recommended for 1st or 2nd line (if TDF-based first line)	Recommended for 1st line (preferred)	•AZT/3TC+LPV/r •**AZT/3TC+ATV/r** •AZT/3TC+DRV/r •AZT/3TC+EFV†	•AZT •**AZT/3TC (dispersible formulation)** † •AZT/3TC+LPV/r •AZT/3TC/NVP†	**High** (priority for 1st and 2nd line)

Table 2: Market/IP Prioritisation of Category A ARVs

ARV	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 Licences[m]	Number of WHO Prequalified or FDA Approved Generics[n]	Market/IP Priority
Abacavir (ABC)	Expired in June/Dec. 2010	Not patented	Probably expired in most jurisdictions in which it was originally granted	New intermediates (2015); Hemisulfate salt (2018); Oral solution for paediatric use (2019)	Granted or pending in several LIC/MICs. Paediatric solution granted in India and other LIC/MICs	Yes, several licensees, but possible restrictions and limited geographical scope (69 countries)	Over five manufacturers for adult formulations and four for paediatric formulations	**Medium** (many suppliers; compound patent expired, but paediatric formulation and salt patent can be a market barrier in some countries)
Atazanavir (ATV)	2017	Initial application withdrawn but divisional application pending	Granted or pending in several LIC/MICs, e.g. AR, BR, CN, GE, KG, MY, PH, PK, TJ, TH	Bisulfate salt (2018); Use in HIV therapy (2012); Process (2025)	Granted or pending in several LIC/MICs	Yes, three licensees, possible restrictions and very limited geographical scope (SSA and India; 48 countries)	Two manufacturers for adult formulations	**High** (few suppliers; compound patent pending in India and granted in some other countries)

[m] With the exception of the licences obtained by the Pool, detailed terms and conditions of the other voluntary licence agreements are confidential, and it is not possible to undertake a thorough analysis to identify the extent to which certain restrictive conditions have been included. Example restrictions in certain voluntary licences could include: restrictions on the manufacturing of the active pharmaceutical ingredients, restrictions on the development of FDCs, restrictions on the ability to supply countries issuing compulsory licences, prohibitions on patent challenges, limited geographical scope, etc. For more information, see: http://pag.aids2012.org/PAGMaterial/aids2012/PPT/1350_2588/final.pptx

[n] In case several formulations exist, the number of manufacturers refers to the total number of manufacturers of any formulation for adults or children.

ARV	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 Licences[m]	Number of WHO Prequalified or FDA Approved Generics[n]	Market/IP Priority
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 a few LIC/MICs	Yes, but one licensee only for packaging and distribution (for SSA and LDCs only); and one licensee for manufacturing and sale in India only	None	**Medium** (first compound patent is not filed in LIC/MICs for which information is available, but a patent covering the specific compound, patents on combinations and a number of other secondary patents are pending/granted in many countries and unclear to what extent may be blocking; no quality-assured generics currently on the market).
Didanosine (ddI)	Expired in 2006	No	No	Improved oral formulation (expired); Enteric-coated (2018)	Granted or pending in several LIC/MICs	Yes, several licensees, but possible restrictions and limited geographical scope	Two manufacturers for adult formulations and two for paediatric formulations	**Medium** (compound patent expired but patent on enteric-coated formulation may act as barrier for that formulation)
Efavirenz (EFV)	Aug. 2013	No	Granted or pending in some LIC/MICs, e.g. AR, BR*, CL, CN, DO, MX, RU, TH*, UA, ZA	Comb. w/ LPV, FTC, EFV (2024); Comb. w/ EFV + FTC (2026)	Granted or pending in several LIC/MICs	Yes, but few licensees, possible restrictions and very limited geographical scope (South Africa and 10 countries in SSA).	Over five manufacturers for adult formulations and three for paediatrics	**Medium** (no compound patent in India, many suppliers; compound patents in a few LIC/MICs expiring in 2013 and combination patents with TDF and FTC pending or granted in several LIC/MICs)
Emtricitabine (FTC)	Expired in 2010	No	Originally granted in several LIC/MICs, (e.g. CN, MY, OAPI, PH, RU and ZA) but probably expired or due to expire shortly	There are a number of secondary patents on FTC and patent on combination with TDF and with TDF and EFV	Filed or granted in several LIC/MICs	Yes, immunity from suit issued in context of TDF licence (112 countries)	Three manufacturers for adult formulation	**Medium** (compound patent expired, but various secondary patents and patents on combinations pending or granted)

ARV	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 Licences[m]	Number of WHO Prequalified or FDA Approved Generics[n]	Market/IP Priority
Enfuvirtide (T-20)	2014	No	Unknown	Method for synthesising enfuvirtide (2019)	Granted in CN. Limited information in other countries	No	None	**Low** (based on currently available information)
Etravirine (ETV)	2019	Granted	Granted or pending in several LIC/MICs, 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 LIC/MICs	Only for packaging and distribution; limited number of licensees (one) and limited geographical scope (SSA and LDCs)	None	**High** (no generic suppliers; compound patent granted in India and in many other countries)
Fosamprenavir (FPV)	2018	Granted	Granted or pending in several LIC/MICs, e.g. ARIPO, AM, AR, CL, CN, CO, EAPO, ID, KG, MY, MX, OAPI, PE, PH, RU, ZA, TJ, TH, UA	Calcium salt (2019)	Granted or pending in several LIC/MICs	Unclear. Several licensees for ViiV products, but possible restrictions and limited geographical scope (69 countries)	None	**High** (no generic suppliers; compound patent granted in India and in many other countries)
Indinavir (IDV)	Nov. 2012	No	Granted or pending in some LIC/MICs, e.g. RU, ZA, UA	-	-	None	Two manufacturers for adult formulations	**Low** (limited patent issues and due to expire shortly)
Lamivudine (3TC)	Expired in Feb. 2010	No	Originally granted in several LIC/MICs, but probably expired or due to expire shortly	Crystal form (expired); New formulation (2018)	Granted or pending in several LIC/MICs but generally not perceived to be a barrier	Yes, several licensees, but possible restrictions and limited geographical scope (69 countries)	Over five manufacturers for adult formulations and four for paediatric formulations	**Low** (compound patent expired; many suppliers; formulation patents generally not perceived to be a barrier; possible exception may be combination patents)

ARV	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 Licences[m]	Number of WHO Prequalified or FDA Approved Generics[n]	Market/IP Priority
Lopinavir (LPV)	2016	No	Granted or pending in several LIC/MICs, e.g. AR, BR, CN, CO, 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 LIC/MICs	None	Three manufacturers for adult formulations and two for paediatric formulations	**High** (compound patent in several countries; formulation and combination patents are pending or granted in several LIC/MICs and being enforced by patent holder; no voluntary licences).
Maraviroc (MVC)	2019	Granted	Granted or pending in many LIC/MICs, e.g. AL, ARIPO, AM, AR, BO, BR, CL, EAPO, EG, GE, 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 LIC/MICs	Unclear. Availability of licence announced in 2010, but limited geographical scope (69 countries)	None	**High** (no generic suppliers; compound patent granted in India and other countries)
Nelfinavir (NFV)	2014	No	Not known	Not known	-	-	One manufacturer for adult formulations and one for paediatric formulations	**Low** (based on currently available information)
Nevirapine (NVP)	Expired in Nov. 2010	No	Originally granted in several LIC/MICs, e.g. OAPI, PH, RU, ZA, but likely expired	Hemihydrate formulation (2018); Extended release formulation (2028)	Granted or pending in several LIC/MICs	BI has policy of non-assert declarations, but potential restrictions for manufacturing in countries with patents and limited geographical scope (78 countries)	Over five manufacturers for adult formulations and three for paediatric formulations	**Medium** (compound patent expired but formulation patents may be a barrier, i.e. for new extended release formulation and for paediatrics)

ARV	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 Licences[m]	Number of WHO Prequalified or FDA Approved Generics[n]	Market/IP Priority
Raltegravir (RAL)	2022	Granted	Granted or pending in several LIC/MICs, e.g. AL, BR, CL, CN, CO, GE, ME, MX, PH, TR, UA, UZ, VN, ZA	Potassium salt (2025)	Granted or pending in several LIC/MICs	Yes, only two licensees. Also, possible restrictions and limited geographical scope (SSAs and LICs)	None	**High** (compound patent granted in India and other LIC/MICs; patent on potassium salt also granted in many jurisdictions)
Ritonavir (RTV)	Dec. 2013/2014	No	Granted in few LIC/MICs, including e.g. MX, PH.	Crystalline polymorph (2019); LPV/r tablet formulation (2026); LPV/r tablet formulation (2024)	Granted or pending in several LIC/ MICs	None	One manufacturer for RTV adult on its own (three in combination) and none for paediatric RTV on its own (one in combination)	**High** (few suppliers; no compound patent in India but in force in some LIC/MICs; combination patents pending or granted in several countries block generic sale of RTV in combination with LPV and possibly with other protease inhibitors)
Saquinavir (SQV)	Expired in Dec. 2010	Expired	Originally granted in many LIC/MICs, expired in many countries, but patent may still be in force in a few jurisdictions	Improved composition (2016); Oral dosage form (2024)	Granted or pending in several LIC/ MICs	Several licences and technology transfer agreements signed	None	**Medium** (compound patent expired in most jurisdictions; secondary patents granted or pending in several jurisdictions)

ARV	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 Licences[m]	Number of WHO Prequalified or FDA Approved Generics[n]	Market/IP Priority
Stavudine (d4T)	Expired in Dec. 2007	No	No	None have been identified	-	-	Over five manufacturers for adult formulations and four for paediatric formulations	**Low** (Many suppliers; compound patent expired; other relevant patents have not been identified)
Tenofovir (TDF)	Expired	No	No[o]	Fumarate salt (2018); Ester prodrug (2017); Comb. w/ LPV, FTC, EFV (2024); Comb w/ EFV + FTC (2026)	Granted or pending in several LIC/MICs	Yes, several licensees but restrictions and limited geographical scope[p]	Over five manufacturers for adult formulations	**Medium** (many suppliers; patents on the fumarate salt in a few LIC/MICs, process patents in India and combination patents in many LIC/MICs; licensees now able to sell in more countries as a result of Pool licence)
Tipranavir (TPV)	2015	No	Patents appear to have been filed in some developing countries but detailed information not available [17]	Not known	Not known	None	None	**Low** (limited patent information available)
Zidovudine (AZT)	Expired in 2006	No	No	AZT/3TC tablet formulation (2017)	Withdrawn in most countries, appears to be in force in a few. However, generally not perceived to be a barrier.	Yes, several, but limited geographical scope (69 countries)	Over five manufacturers for adult and paediatric formulations.	**Low** (many suppliers; compound patent expired; patents on combinations in few jurisdictions, but barriers seem to be limited)

[o] The first patent claiming the tenofovir compound was filed by the Academy of Sciences of the former Czechoslovakia in 1986, mostly in developed countries.
[p] On July 12, 2011, Gilead Sciences granted a licence covering TDF to the Pool. While certain restrictions remain, the geographical scope of the licence was expanded to 112 countries. Pool licences include a number of key flexibilities that are contributing to opening up the market for TDF. Details and the text of the licence are available at www.medicinespatentpool.org.

Category B

Category B presents investigational compounds that are in Phase III clinical trials or have recently received regulatory approval but have not yet been reviewed by the WHO ART guidelines committee (Table 3 and 4).

Table 3: Clinical Prioritisation of Category B ARVs

ARV	1) Safety / Efficacy	2) Tolerability	3) Durability	4) Specific populations	5) Stability 6) Convenience 7) Cost	Combinations	Clinical Priority[q]
Cobicistat (COBI)[r] Pharmaco-kinetic booster	Results of a Phase III study comparing cobicistat with ritonavir as pharmacoenhancers of ATV showed non-inferiority of cobicistat at 48 weeks. Safety profiles were comparable [20].	In a Phase III study, patients treated with cobicistat showed some reduction of renal function. That aside, tolerability is comparable for both products (cobicistat and ritonavir) [20, 21].	No antiviral activity, so it does not induce resistance. Studies confirmed no development of protease inhibitor-related mutations [20].	PAEDIATRICS: Positive opinion from EMA on paediatric investigational plan. TB: Cobicistat may need dose adjustments with rifampicin or use with rifabutin [22]. PREGNANT WOMEN: Not yet approved for use in pregnant women and no ongoing studies.	Does not need refrigeration. One pill once daily. Has been submitted for regulatory approval as a stand-alone drug and has already been approved as part of a combination (Quad). No information on cost in LIC/MICs yet.	Cobicistat is part of the Quad (EVG/COBI/FTC/TDF), which received regulatory approval on 27 August 2012 [21, 23]. Agreements to develop DRV/COBI and ATV/COBI FDCs were announced in July and October 2011. Phase III trials for both combinations are recruiting patients [24, 25]. EVG/COBI/FTC/GS-7340 and GS-7340/FTC/DRV/COBI are being developed as FDCs and recently entered Phase II [26].	**High** (part of potentially important single tablet regimen, under study in combination with protease inhibitors (PIs) and only booster in addition to ritonavir. Has also been submitted for registration as a stand-alone drug)

[q] The level of priority of pipeline compounds will be re-considered once further clinical evidence is available, regulatory approval is obtained and/or the compound is reviewed by the WHO ART guidelines committee.

[r] TDF/FTC/EVG/COBI has been approved by the FDA on 27 August 2012 but was not approved at the time of the latest revision of the WHO guidelines. Thus, it has been included in Category B.

ARV	1) Safety / Efficacy	2) Tolerability	3) Durability	4) Specific populations	5) Stability 6) Convenience 7) Cost	Combinations	Clinical Priority[q]
Dolutegravir (DTG) Integrase inhibitor	In a Phase III study in naïve patients, DTG showed non-inferiority compared to EFV and a favourable safety profile [27]. Another Phase III study in naïve patients showed the non-inferiority of DTG compared to RAL at 48 weeks [28]. DTG also was shown to be effective in treatment experienced patients with mild and heavy integrase resistance in Phase III studies [29].	In two Phase III studies conducted in naïve patients, DTG showed fewer drug-related adverse events compared to EFV and no difference in tolerability compared to RAL [27, 28]. In a Phase III study in treatment experienced patients, DTG also showed a good tolerability profile [29].	The integrase inhibitor class does not have a lower genetic barrier to resistance than EFV [30]. A Phase III study showed no cases of virologic failure [27]. No resistance mutations were found in the DTG group in comparative study with RAL [28]. A Phase III study to assess DTG in patients with resistance to EVG and RAL, showed that DTG continues to be active and well tolerated [29].	PAEDIATRICS: Preliminary results of a Phase I/II trial in children 12 to 18 years old showed good tolerability and efficacy. The study will start children from 6 weeks using a granule formulation in Q1 2013 [31] [32]. TB: Preliminary results of a Phase I trial showed that concomitant treatment with DTG and rifampicin may be possible [33]. PREGNANT WOMEN: Not yet approved for use in pregnant women and no ongoing studies.	Does not need refrigeration. Can be used as one pill once daily. Used in low dose, which facilitates co-formulations. Under study for dose-optimised regimens [34].	ABC/3TC/DTG entered Phase III trial [26]. Other combinations not under development could consider the use of TDF or GS-7340 instead of ABC, as TDF is better tolerated and GS-7340 is expected to be better tolerated [35].	**High** (promising compound that has so far shown to be safe and effective, may be easy to combine and has potential for low cost)
Elvitegravir (EVG) [u] Integrase inhibitor	In two Phase III studies in naïve patients, EVG in combination with COBI/TDF/FTC demonstrated non-inferiority as compared to EFV and ATV/r at 48 weeks. [21, 23] Recent results of another Phase III study in treatment experienced patients showed non-inferiority of EVG compared to RAL at 48 weeks [36].	In both Phase III studies in naïve patients, EVG in combination with COBI/TDF/FTC showed similar rate of discontinuation due to adverse events when compared to EFV/TDF/FTC and ATV/r +TDF/FTC [21, 23].	The integrase inhibitor class does not have lower genetic barrier to resistance than EFV [30]. Results of a Phase III study in treatment experienced patients showed that development of resistance to integrase inhibitors was uncommon and similar in patients treated with EVG and RAL [37].	PAEDIATRICS: A Phase Ib study for children over 12 years completed. No study yet for under 12, but plans to produce more pharmacokinetic data. TB: Drug interactions with rifampicin [38]. Thus, requires the use of rifabutin. PREGNANT WOMEN: Not yet approved for use in pregnant women and no ongoing studies.	Does not need refrigeration. One pill once daily (only if boosted) Low dose of EVG could reduce cost (now dosed at 150 mg). Dose reduction needs to be explored [34].	Cobicistat is part of the Quad (EVG/COBI/FTC/TDF), which received regulatory approval on 27 August 2012 [21, 23]. EVG/COBI/FTC/GS-7340 is being developed as FDCs and recently entered Phase II [26].	**High** (part of the recently approved single tablet regimen Quad)

ARV	1) Safety / Efficacy	2) Tolerability	3) Durability	4) Specific populations	5) Stability 6) Convenience 7) Cost	Combinations	Clinical Priority[q]
Rilpivirine[s] (RPV) NNRTI	Comparative studies of RPV vs. EFV showed non-inferiority in the proportion of patients that reached undetectable viral load in both groups at 48 weeks, but higher incidence of virologic failure in the RPV group [39]) A Phase III study showed that switching from boosted PI regimen to FTC/TDF/RPV in virologically suppressed patients maintains virologic suppression [40].	Pooled results of two Phase III clinical trials showed improved tolerability profile and fewer discontinuations due to adverse events compared with EFV [39]. The same differences appeared in patients with low viral load at initiation (≤100,000 copies/mL) [41]	Higher incidence of virologic failure was found in patients treated with RPV group compared to those treated with EFV at 48 weeks [39]. This difference disappears when the analysis is done in the subgroup of patients with low viral load (≤100,000 copies/mL) [41].	PAED: Still in Phase II studies but only in adolescents. TB: Drug interactions with rifampicin. Thus, requires the use of rifabutin [42] PREGNANT WOMEN: Not yet approved for use in pregnant women and no ongoing studies.	Does not need refrigeration. One pill once daily Potentially low price due to low dose used. RPV long-acting properties are being tested in Phase I as PrEP [43, 44]. It is also in Phase I in combination with GSK-744, and will soon enter Phase II [45].	TDF/FTC/RPV has been approved by the FDA for use in first line Another possible combination would use 3TC instead of FTC. 3TC is cheaper and eligible for dose reductions.	**Medium** (good safety profile but not as effective as EFV and only recommended for patients with low viral load at initiation, which may be problematic in resource-limited settings. Not yet assessed by WHO ART guidelines)

[s]RPV and TDF/FTC/RPV obtained regulatory approval from the FDA in May and August 2011 respectively, but were not approved at the time of the latest revision of the WHO guidelines. Thus, RPV has been included in Category B.

Table 4: Market/IP Prioritisation of Category B ARVs

ARV	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 Licences	Number of WHO Prequalified or FDA Approved Generics	Market/IP Priority
Cobicistat (COBI)	2028	Pending	Granted or pending in several LIC/MICs, e.g. AL, ARIPO, AM, AR, BR, CN, EAPO, EG, ID, KG, MX, MA, OAPI, RU, ZA, TJ, VN	Two have been identified, which expire in 2028	Granted or pending in several LIC/MICs including India	Yes[t]	NA	**High** (compound patent pending in India and several other countries)
Dolutegravir (DTG)	2026	Pending	Granted or pending in several LIC/MICs, e.g. AM, AZ, CN, EAPO, KG, MX, PH, RU, TJ, UA, UZ, ZA	Synthesis processes (2029) Intermediates (2029)	Granted or pending in several LIC/MICs, including India	No	NA	**High** (compound patent pending in India and several other countries)
Elvitegravir (EVG)	2023	Granted	Granted or pending in several LIC/MICs, i e.g. AR, BR, CL, CN, CO, MY, MX, PE, PH, RU, VN, ZA	Crystal form (2025) Improved pharmacokinetics w/ RTV (2026)	Granted or pending in several LIC/MICs, including India	Yes[u]	NA	**High** (compound patent granted or pending in India and several other countries)
Rilpivirine (RPV)	2022	Granted	Granted or pending in several LIC/MICs, 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, four licensees. May include restrictions and covers 112 countries	NA	**High** (compound patent granted in India and granted or pending in other countries; licences may be restrictive and geographical scope could be further expanded)

[t]On July 12, 2011, Gilead Sciences granted a licence covering cobicistat to the Pool with a geographical scope of 103 countries. Details and the text of the licence are available at www.medicinespatentpool.org. In addition, Gilead has entered into semi-exclusive licences for 9 additional countries.
[u]On July 12, 2011, Gilead Sciences granted a licence covering elvitegravir and the Quad to the Pool with a geographical scope of 100 countries. Details and the text of the licence are available at www.medicinespatentpool.org. In addition, Gilead has entered into semi-exclusive licences for 9 additional countries.

Category C

Table 5 presents selected compounds that have entered Phase II clinical trials.

Table 5: Clinical Review of Category C ARVs*

* Products included in this table are in early stage of development and may not reach approval. The list is not exhaustive. A full analysis, including indication of level of priority from a clinical and market/IP perspective, will be undertaken once products enter Phase III.

** Based on information available through on-line databases of a few patent offices (information is incomplete and preliminary in nature).

Compound	Therapeutic Class	Development Phase	Company	Preliminary Clinical Information	Preliminary Information on Patent Status**
APRICITABINE	NRTI	Phase II	Avexa	Development resumed recently. No data yet. Projected to enter Phase III in Q1 2013 [46].	No information currently available
BMS-663068 (pro-drug of BMS-625529)	Attachment inhibitor	Phase II	Bristol-Myers Squibb	New therapeutic class. Phase IIb preliminary results expected for February 2013. Results on resistance at 8 days showed no selection of resistances against other entry inhibitors [47] [48].	International Patent Application: WO2005090367 Filed: BR, GE, IN, PE, RU, VN, ZA Granted: AR, CN, MY, PH
CENICRIVIROC (TBR-652)	CCR5 inhibitor	Phase II	Tobira Therapeutics	Recently entered Phase II [11, 49].	No information currently available
DAPIVIRINE	Vaginal microbicide	Phase II	Tibotec	Long-acting properties. Two Phase II studies (ASPIRE and IPM027) already started and results expected in 2014 and 2015 respectively [50].	No information currently available
BMS-986001 (previously FESTINAVIR, OBP-601)	NRTI	Phase II	Bristol-Myers Squibb	No news on Phase II study [51] but *in vitro* safety study showed no mitochondrial toxicity compared to other NRTIs and no evidence of in vitro renal or bone toxicity [52] [53].	International Patent Application: WO2005011709 Filed: MX, VN, ZA Granted: CN
GS-7340	NRTI	Phase II	Gilead	Oral pro-drug of TDF with potential to improve efficacy and safety compared with TDF [54, 55]. Two Phase II studies of the combinations GS-7430/FTC/DRV/COBI and GS-7340/FTC/EVG/COBI have already started. Potentially fewer side effects than TDF [56].	International Patent Application: WO2002008241 Filed: ARIPO, BR, MX, OAPI, TR, UA, VN, ZA Granted: CN
GSK-744	Integrase inhibitor	Phase II	ViiV	Phase II study showed safety and efficacy of the oral drug [57]. Results of a Phase I study that investigates its use as long-acting injection showed plasma levels known to be effective up to 50 days after subcutaneous or intramuscular administration and good safety profile [45]. Phase II with RPV long-acting formulation is planned.	International Patent Application: WO2011017395
IBALUZIMAB	CD4 monoclonal antibody	Phase II	TaiMed Biologics/Ambrillia Biopharma	New therapeutic class. Interesting as long-acting product with potential for weekly administration. Results of a Phase IIb study were published in 2011. [58].	No information currently available

Compound	Therapeutic Class	Development Phase	Company	Preliminary Clinical Information	Preliminary Information on Patent Status**
LERSIVIRINE	NNRTI	Phase II	ViiV	Results of a Phase II study in naïve patients showed similar efficacy to efavirenz over 48 weeks [59]. Another Phase II study in experienced patients is expected to be completed in May 2013.	International Patent Application: WO2002085860 Filed: ARIPO, BR, GE, ME, MX, MO, OAPI, PA, PE, UA, VN, ZA Granted: AR, CN, PH
MK-1439	NNRTI	Phase II	Merck	A Phase IIb study planned to start in September to compare MK-1439 with EFV. In the pre-clinical Phase it showed high activity against highly resistant HIV strains [26]	No information currently available
SB-728	Gene therapy	Phase I/IIa	Sangamo	New therapeutic class under evaluation (Phase I/II study estimated to be completed in Q4 2012).	No information currently available
VS411	AV-HALTs	Phase II	ViroStatics	New therapeutic class that aims to activate the immune system, increasing proliferation of CD4 cells. Promising results presented in 2011 [60]	No information currently available
NO RECENT NEWS ON DEVELOPMENT					
AMDOXOVIR (DAPD)	NRTI	Phase II	RFS Pharma	Several Phase II studies completed but not moving into Phase III. According to some sources development is discontinued.	No information currently available
CMX-157	NRTI	Phase II	Chimerix	Entered Phase II [61], but results published and no news since 2010.	International Patent Application: WO200139724 Filed: CN, MX, RU, ZA
CTP-518	PI	Phase I/II	Concert Pharmaceuticals/GSK	Slow hepatic elimination that may imply activity without boosting and longer half-life. According to 2012 TAG pipeline report, development is on hold [13].	No information currently available
AMD11070	CXCR4	Phase II	Genzyme	Initially developed by AnorMED and apparently discontinued [13], but recently presented positive results at 17th International Symposium on HIV and Emerging Infectious Diseases (ISHEID) [62]	No information currently available
ELVUCITABINE	NRTI	Phase II completed	Achillion	Potential to be once-daily, weekly or monthly. Potential for low price, but concerns with clinical trial results. No updated information since 2009.	No information currently available
FOZIVUDINE	NRTI	Phase II	Boehringer-Ingelheim	Lipid conjugate of AZT that reduces toxicity and increases activity [63]. Completed Phase II but development interrupted since 2005. No news if development will be resumed.	No information currently available
PRO-140	Monoclonal CCR5 antibody	Phase II	Progenics Pharmaceuticals	Entered Phase II in 2010. Long-acting properties. No results yet on the study, that is still recruiting according to clinicaltrials.gov [26] but discontinued according to 2012 TAG pipeline report [13].	No information currently available
RACIVIR	NRTI	Phase II (RCV-04-201) completed in 2006	Pharmasset/Gilead	Once daily, can be used in experienced patients. It was developed by Pharmasset, a company that is now owned by Gilead. Results on study RCV-04-201 not presented and not moving to Phase III. Unclear if discontinued or not.	No information currently available
RDEA-806	NNRTI	Phase IIa	Ardea Biosciences	No news since 2010 even though it showed high activity and safety in Phase IIa [64]	No information currently available

Compound	Therapeutic Class	Development Phase	Company	Preliminary Clinical Information	Preliminary Information on Patent Status**
KP-1461	Viral decay accelerator.	Phase II	Koronis Pharmaceuticals	New therapeutic class that provokes mutations in HIV. Phase II trial was terminated but not because of safety issues. Recently published results show good tolerability and safety *in vivo*, and confirms that expected mutations occurred in the viral RNA [65].	No information currently available
PRO-542	Monoclonal CCR5 antibody	Completed a Phase II in 2005	Progenics Pharmaceuticals	Not moving to Phase III, but no news about stopping development	No information currently available

Conclusions

The Pool has used clinical and market/IP criteria to sort ARVs into three priority levels.

ARVs considered high priority according to both sets of criteria are Level 1 priorities for the Pool as they are highly important from a medical perspective, and there appear to be significant barriers to market competition in low- and middle-income countries.

ARVs that have at least a medium ranking under both clinical and market/IP criteria are Level 2 priorities for the Pool.

ARVs that are a medium or high priority based on market/IP criteria, but which are considered to be of limited clinical importance appear in Level 3.

Other ARVs have been de-prioritised and appear in Table 7. These lists will be updated annually, in order to take into account new clinical data, revisions to WHO treatment guidelines and new information on the patent status of individual ARVs.

Table 6: Summary of Priorities for the Medicines Patent Pool

Compound	Clinical Priority	Market/IP Priority
Level 1 Priorities (high priority under both sets of criteria)		
Atazanavir (ATV)	High	High
Cobicistat (COBI)	High	High
Dolutegravir (DTG)*	High	High
Elvitegravir (EVG)	High	High
Lopinavir (LPV)	High	High
Ritonavir (r)	High	High
Level 2 Priorities (clinically important and market/IP barriers ranging from high to medium)		
Etravirine (ETV)	Medium	High
Raltegravir (RAL)	Medium	High
Rilpivirine (RPV)	Medium	High
Tenofovir (TDF)	High	Medium
Emtricitabine (FTC)	High	Medium
Efavirenz (EFV)	High	Medium
Nevirapine (NVP)	High	Medium
Abacavir (ABC)	Medium	Medium
Darunavir (DRV)	Medium	Medium
Level 3 Priorities (low clinical priority today, but patent barriers ranging from high to medium)		
Fosamprenavir (FPV)	Low	High
Maraviroc (MVC)	Low	High
Didanosine (ddI)	Low	Medium
Saquinavir (SQV)	Low	Medium

(*) Compounds in late stages of clinical trials (Phase III)

Products considered a low priority from a market/IP perspective are considered not to be a priority for Pool licensing (except to the extent that they may be included in important and patented combinations), as there are either limited or no patent barriers to generic sale and manufacture. These ARVs are included in Table 7.

Table 7: ARVs not considered to be a priority for Pool licensing at this stage

ARV	Clinical Priority	Market/IP Priority
Not Priorities		
Lamivudine (3TC)	High	Low
Zidovudine (AZT)	High	Low
Enfuvirtide (T-20)*	Low	Low
Indinavir (IDV)	Low	Low
Nelfinavir (NFV)*	Low	Low
Stavudine (d4T)	Low	Low
Tipranavir (TPV)*	Low	Low

* Very limited patent information was available on these compounds. They could become Level 3 priorities if additional patent information indicated that patent barriers are greater than currently known.

ARVs in Phase II clinical trials (Category C ARVs) have not been included in the list of priorities for the Pool, although some appear to be very promising based on available clinical evidence. As these compounds move to Phase III, and further clinical information becomes available, the Pool will assess those compounds according to the same criteria outlined in this document.

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Annex 1 - Summary of Changes to the 2nd Edition

The first edition of this Working Paper was issued in September 2011. The following summarises key changes introduced to this, the 2nd edition of this Working Paper.

1. Changes in methodology

Market/IP prioritisation criteria have been refined to make the methodology more systematic. Under the new methodology, ARVs for which there are compound patents pending or granted in several countries and limited competition or restrictive licences are considered high priority for the Pool. ARVs for which there are patents granted or pending on specific formulations or that are close to patent expiry, have been assigned a medium level of priority. Finally, those ARVs for which there do not appear to be patent barriers, or for which such barriers are perceived to be negligible, are a low priority from a market/IP perspective.

2. Changes relating to ARVs with regulatory approval (Category A ARVs)

The main criterion for assigning clinical priority to Category A ARVs is their inclusion in WHO treatment guidelines. Since no changes have been made to the guidelines since 2010, the clinical prioritisation has not changed compared to the previous edition of this Working Paper. An exception is stavudine (d4T), which is now considered of low clinical priority in light of global efforts to phase out its use due to toxicity.

The application of the new methodology for market/IP prioritisation resulted in slight changes to the level of priority of certain ARVs (e.g. nevirapine).

3. Changes relating to ARVs in late-stage development or that recently received regulatory approval (Category B ARVs)[v]

Recent findings from clinical trials were considered in the prioritisation of Category B ARVs. However, this resulted in limited changes in their level of priority. The exception is rilpivirine, which has been moved from high to medium priority because it received regulatory approval recommending initiation at low levels of viral load. This is likely to be a significant constraint in resource-limited settings.

The patent status of Category B ARVs was updated but did not result in any changes in their level of priority. Category B ARVs are all high priority for the Pool from a market/IP perspective, as they are widely patented in LIC/MICs and patents have been granted or are pending in key countries of manufacture, such as India.

4. Products in early stages of development (Category C ARVs)

None of the pipeline compounds included in Category C in the first edition of this Working Paper advanced to Phase III clinical trials during the past year. Nevertheless, some compounds have been discontinued, new ones have reached Phase II and new data are available for several others. In addition, for the first time, preliminary patent status data has been gathered and included for some Category C compounds. However, as was the case in the 2011 edition, no detailed prioritisation was undertaken for Category C ARVs.

5. Overall priorities for the Pool

[v] Category B includes compounds already approved by regulatory authorities but have not yet been reviewed by the WHO ART guidelines committee.

By combining clinical with market/IP priorities, three overall levels of priority have been identified. These replace the three priority levels identified for the 2011 edition. A key change with respect to the previous edition is that ARVs for which there appear to be no or very limited patent barriers are now "de-prioritised." This change affects products such as lamivudine and zidovudine, which appeared as Level 3 priorities in the 2011 edition.