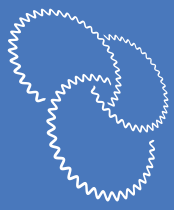

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ANTIRETROVIRAL PRIORITIES

OF THE MEDICINES PATENT POOL

4th Edition

ACKNOWLEDGEMENTS

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CONTENTS

INTRODUCTION

The purpose of this working paper is to revise and update the antiretroviral (ARV) priorities of the Medicines Patent Pool (MPP) taking into consideration recent developments in the clinical, market and intellectual property landscape for different ARVs. As part of its mandate, MPP assigns greater priority to in-licensing HIV medicines that are most important from a clinical perspective and for which there is significant intellectual property in low- and middle-income countries (LMICs). The focus is on ARVs that are already on the market as well as ARVs that are currently in late-stage clinical development, defined as those that are already in Phase III. MPP publishes its prioritization report on an annual basis. The present working paper is the fourth edition.

METHODOLOGY

As in previous editions of this working paper, MPP analysed ARVs on the basis of two sets of criteria (clinical and market/IP) as described in further detail in Annex I. Each ARV was assigned a level of priority (high, medium or low) according to each set of criteria. ARVs that are considered to be either medium or high under both sets of criteria are included in the list of priority ARVs for the MPP, while ARVs identified as low priority under at least one set of criteria are de-prioritized.

The clinical criteria MPP employed differed for ARVs currently recommended by the WHO (1) and new ARVs that may be important for treatment in the future. For currently recommended ARVs, clinical prioritization relied on the WHO treatment guidelines, with ARVs included in preferred regimens for first- and second-line treatment considered to be high priority. New ARVs were assessed on the basis of seven criteria namely: clinical trial data on safety/efficacy; tolerability; durability; suitability for specific populations (e.g. TB co-infected patients, pregnant women); stability; convenience; and likely cost ranges in LMICs.

The market/IP prioritization takes into consideration the patent expiry date of each ARV, the patent status in developing countries and the extent to which there is a competitive market for that ARV in LMICs already.

While the detailed analysis of each individual ARV is contained in the product cards included in the annexes, the core of this paper provides an overview of the clinical and market/IP landscape at the treatment regimen level. The focus on regimens (rather than stand-alone ARVs) in the core part of this document allows for better alignment with the WHO treatment recommendations. ARVs already licensed to the MPP were no longer assigned a level priority but have been included in the general analysis.

Section 1: Priority Regimens for Adults*

First-line regimens

TDF/3TC (or FTC)/EFV: Demand for the WHO preferred first-line regimens has continued to increase and currently both options (with 3TC or with FTC) are now the most widely used first-line regimens (2) with prices dropping to approximately USD130 per patient per year (3). As more countries shift to these regimens and implement the WHO recommendation to start treatment earlier, it is expected that demand will continue to rise.

Over the past year, four new manufacturers have received regulatory approval from the WHO Prequalification Programme or the United States Food and Drug Administration (US FDA), leading to a total of eight suppliers for the regimen containing FTC and five for the regimen containing 3TC (4). The recent amendment to the MPP-Gilead licences announced in July 2014 will enable the manufacturing of active pharmaceutical ingredient (API) and finished formulation of TDF in China (in addition to India), which should contribute to further reducing the price of the API and potentially expanding the manufacturing base for this key regimen (5).

Patents on EFV, 3TC and FTC have generally expired, and the voluntary licences on TDF negotiated by the MPP have helped open the market for TDF-based combinations† in most LMICs (6). However, patents pending or granted on TDF/FTC and TDF/FTC/EFV in countries not covered by the MPP licences may affect procurement choices for TDF/FTC/EFV (but likely do not apply to the regimen containing 3TC).

Other important regimens in first-line

While TDF/3TC (or FTC)/EFV is the WHO preferred first-line treatment for adults, regimens considered alternatives by the WHO continue to be widely used in many countries. These include **AZT/3TC/NVP** and **TDF/3TC+NVP**. The former is still widely used in first-line (2), although the procurement volume stagnated in 2013. In general, the importance of NVP-based formulations will likely decrease in light of WHO recommendations and evidence of poorer outcomes compared to EFV (1). In light of the above, NVP is considered a medium priority for the MPP from a clinical perspective.

Patents on NVP and AZT have generally expired and should therefore not impact on the competitive procurement of these regimens in developing countries. A patent on the extended release formulation of NVP has been granted or is pending in a number of LMICs (including countries outside of the present non-assert policy of the patent holder) but is only limited to that formulation, which has so far had limited uptake. As a result, NVP is now considered a low priority from a market/IP perspective and is therefore de-prioritized by the MPP.

* 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.

† Recent amendments to the MPP-Gilead licence included the patent on TDF/FTC in the scope of the licence.

Preferred second-line regimens for adults

The WHO treatment guidelines recommend AZT/3TC as the preferred backbone for second-line adult treatment combined with one of two boosted protease inhibitors: ATV/r or LPV/r.‡ At present, LPV/r-containing regimens have dominated the market, but regimens containing ATV/r are gaining market share.

AZT/3TC + LPV/r: Today, there are a significant number of quality-assured suppliers for AZT and 3TC as well as for the fixed-dose combination AZT/3TC. Patents on both ARVs have generally expired and the patent on the AZT/3TC tablet formulation has generally lapsed or was withdrawn from most low- and middle-income countries. With respect to LPV/r, there are five quality-assured suppliers but the patent situation is more complex. Patents on LPV, RTV or on the heat-stable tablet formulation of LPV/r are pending or have been granted in many developing countries, thus limiting the market for generic suppliers. While there are no voluntary licences on adult formulations of LPV/r today,§ public health-oriented licensing could enable competitive procurement of LPV/r in LMICs where LPV/r is patented and help reduce second-line prices.

AZT/3TC + ATV/r: There are two quality-assured manufacturers of ATV/r as a fixed-dose combination (both generic) and three generic manufacturers of ATV stand-alone formulations. While ATV/r's current price is similar to the lowest price for LPV/r, there is potential for significant price reductions in light of ATV/r's lower daily dose requirement if demand increases. The recent MPP licence on ATV will increase generic suppliers and enable them to sell in more countries, thus spurring additional competition in the second-line drug market (7). The lack of registration of ATV in some developing countries, however, continues to be a barrier to greater use of the medicine. Existing patents on RTV (or r) also will have an impact on the competitive procurement of this regimen in certain countries. A combination of ATV with COBI (recently approved by the US FDA) may represent an interesting alternative in the future.

Other important regimens in second-line

The choice of a second-line regimen depends on the regimens that were taken in first-line. As many adults took AZT or d4T-based regimens in first-line, TDF continues to be in high demand for second-line treatment. Important priorities for such cases are **TDF/3TC (or FTC)+ATV/r** and **TDF/3TC + LPV/r**. Information on the IP status of TDF/3TC (or FTC), ATV/r and LPV/r is available above.

‡ DRV is recommended as an alternative regimen by the WHO for second-line treatment in light of its unavailability in a heat-stable co-formulation with a booster and its current price (1).

§ Some countries have issued compulsory licences such as Ecuador, Indonesia and Thailand.

Preferred third-line medicines for adults

The WHO recommends the use of new ARV drugs or classes with minimal risk of cross-resistance to previously used regimens for third-line treatment, but does not provide a strong recommendation on which ARVs to use in which situation. However, available evidence relates primarily to DRV+r, RAL and ETV, and the WHO lists these ARVs as options for third-line treatment.

The market for third-line medicines remains very small, but may gradually increase with wider access to viral load monitoring and with growing drug resistance as people remain on treatment longer. Given the limited number of PLHIV on third-line medicines in LMICs, and the tentative nature of the relevant WHO recommendations, ARVs recommended as third-line medicines are considered medium priority by the MPP from a clinical perspective.

RAL: While integrase inhibitors like RAL are recommended and used for first-line in some countries (e.g. US (8)), WHO guidelines maintain RAL as an option for third-line treatment. RAL is patented in many developing countries, including in key countries of manufacture such as Brazil, China, India and South Africa. There is currently one quality-assured generic supplier on the market and two have received a licence. Details of the licences, however, are unavailable, although the geographical scope is Sub-Saharan Africa and low-income counties.* Licensing of adult formulations of raltegravir on public health friendly terms and with a wider geographical scope could lead to improved availability and competition.

DRV+r: DRV+r is recommended by the WHO for third-line treatment and also as an alternative for second-line. Given its advantageous clinical profile, it may become a preferred option for second-line in the future if heat-stable fixed-dose combinations are developed and become available at affordable prices (1). Current studies also suggest that reduced doses of DRV could be as effective as standard doses, which could facilitate the development of FDCs. Currently, there are no quality-assured suppliers for DRV/r as an FDC or as co-pack,†† and prices remain high as compared to other protease inhibitors. Patents on DRV have now generally expired or are no longer considered to be blocking generic manufacture or supply. Thus, DRV is a low priority for the MPP from an IP perspective. However, patents on RTV (or r) would likely impact the competitive procurement of this formulation in certain countries. Co-formulation with COBI (recently approved by the US FDA) could also represent an interesting alternative.

ETV: Uptake of ETV has been very slow as compared to other drugs the WHO recommends for third-line treatment (3). Nevertheless, it has shown antiviral activity against NNRTI-resistant HIV with a good safety profile (9). It also showed efficacy in highly experienced patients in combination with other third-line agents such as RAL and DRV/r (10). ETV is widely patented in developing countries including in key countries of manufacture. There are currently no voluntary licences for the manufacturing of generic ETV and no generic manufacturers. Voluntary licensing of this medicine would create competition for this ARV potentially leading to lower prices.

* There is also a bilateral technology transfer agreement with a Brazilian company.
†† One manufacturer has launched DRV/r but has not yet obtained approval by an SRA or WHO Prequalification (4).

New and pipeline combinations and regimens

This section focuses on regimens, FDCs and single tablet regimens recently approved, in late-stage testing as well as those proposed for future development. ‡‡

Since 2010, three ARVs and one pharmacokinetic booster have obtained regulatory approval and one other ARV is currently in Phase III clinical trials. These five products (DTG, EVG, RPV, COBI and TAF) have not yet been included in WHO treatment guidelines, but may become important components of treatment regimens in the future. Their inclusion in subsequent recommendations will likely depend on whether they are integrated into regimens that offer public health advantages over existing recommended treatments.§ §

The following analysis provides an assessment of these combinations from a clinical and market/IP perspective. More detailed analysis for each individual ARV is provided in the product cards in Annex IIb.

Approved new combinations

TDF/FTC/EVG/COBI: This FDC was approved for use in treatment-naïve adults in August 2012 by the US FDA. It is the first once-daily pill to include an integrase inhibitor and has shown comparable efficacy to TDF/FTC/EFV in clinical trials (12,13). However, concerns over renal toxicity and drug interactions, particularly with COBI, may be a limitation (8). Voluntary licences were granted to the MPP for this combination for 100 countries and bilateral semi-exclusive licences exist for a further nine countries.

TDF/FTC/RPV: Approved by the US FDA for use in adults in August 2011, this is a well-tolerated once-daily FDC that could be used as an option for patients that are intolerant or unable to adhere to NVP- or EFV-based regimens. However, the FDC is only recommended in treatment-naïve adult patients with low viral load at initiation*** (14), which may be a significant limitation in resource-limited settings where viral load monitoring is less widespread and where patients initiating ART often have higher viral loads. While RPV is patented in many developing countries, voluntary licences have been granted to some generic manufacturers with a geographical scope of 112 countries. The detailed terms and conditions are, however, not public.

‡‡ See in particular recommendations made by the Conference on ARV Drug Optimization (CADO) that took place in Cape Town in April 2013 (11).
§ § The WHO has indicated a clear preference for the use of "simplified, less toxic and more convenient regimens as FDCs" whenever possible (1).
*** HIV-1 RNA less than or equal to 100,000 copies/mL.

ABC/3TC/DTG: This combination was approved by the US FDA in August 2014, a year after the approval of DTG stand-alone. In clinical trials, regimens containing DTG were shown to be highly effective, well-tolerated and were less likely to lead to resistance in treatment-naïve and treatment-experienced patients (15-18). In addition, DTG has the potential to be very cost-effective in light of its low dose (50mg once daily). However, Conference on Antiretroviral Drug Optimization (CADO 2) experts have advocated studying DTG in alternative regimens, such as with TDF (or TAF) or DRV/r instead of ABC (11). The MPP's recent licensing agreement on DTG and ABC will likely help accelerate the availability of DTG and DTG-based combinations in the more than 125 countries that will be able to procure generics.

DRV/COBI: This combination is already approved in the US (23). The FDC could be used with two NRTIs or possibly in the future with DTG. Generic versions of this combination could become available given MPP licences for the generic manufacture of COBI. DRV is generally off patent.

ATV/COBI: This combination is already approved in the US. It could be a once-daily alternative to LPV/r or ATV/r for use in second-line (25).

Combinations under development

TAF/FTC: TAF is a new pro-drug of tenofovir. In a recent Phase III study, TAF achieved a level of virological suppression that matched TDF, despite the fact that the TAF dosage was substantially lower than the standard TDF dosage but with less risk of renal and bone toxicity at 48-weeks (19). These results suggest that TAF could eventually replace TDF in first-line treatment and have made the medicine a high priority for the MPP. The combination with FTC, currently under development (20), would allow its use as a backbone with several ARVs. TAF is patented in many developing countries including India. The MPP licence with Gilead for TAF will enable generic manufacturing of TAF in China and India for sale in 112 countries if and when the product receives FDA approval.

TAF/FTC/EVG/COBI: Phase III results were recently announced for this single tablet regimen and it was filed for approval in November 2014 (21). The combination also entered Phase II/III studies in adolescents (22). There are pending or granted patents on COBI, EVG and TAF in many developing countries including India. MPP licences would enable the manufacturing of generic versions for supply in 100 LMICs.

TAF/FTC/DRV/COBI: This is another potentially important combination that is currently under development (in Phase II studies)(24). The good clinical and safety profile of DRV, and its high genetic barrier to resistance, make it a potentially interesting formulation in experienced patients but also eventually for treatment-naïve patients.

DTG/RPV: This double FDC is being tested in Phase II/III clinical trials as maintenance therapy in people that are already virologically supressed and may contribute to simplifying treatment in NNRTI- and/or INSTI-naïve patients (26). Given MPP's licences for DTG and existing bilateral licences for RPV, the regimen could become available from generic manufacturers in approximately 101 countries.

TDF/3TC(or FTC)/EFV 400mg: EFV 400mg has demonstrated comparable efficacy to the standard dose of 600mg (27). However, limited information on its safety in pregnant women and TB patients has raised some concerns, and specific pK studies are ongoing. In light of these results, a triple FDC with a lower dose of EFV could become important given potential lower costs and side effects, and is a candidate for replacing current first-line recommendations. As for the combination with EFV 600mg, patents on the combination with FTC could limit competitive procurement for that formulation in countries outside the 112 included in the existing voluntary licences.

Other FDCs / regimens with strong potential

There are a number of other combinations that are currently not under development, but have been identified by clinical experts as having significant potential and may be important options for future treatment (11). Pending further studies and expert advice from WHO, these would likely represent key priorities for the MPP.

TAF/3TC(or FTC)/EFV: Given TAF's favourable side effect profile, it could potentially replace TDF in first-line regimens. This combination, however, is not currently being tested and should be studied (potentially also combined with EFV 400mg) (27). MPP licences would enable competitive procurement for this product in 112 countries.

TDF(or TAF)/3TC(or FTC)/DTG: Clinical trials for DTG have indicated better tolerability over EFV at standard dose in treatment-naïve patients (28) and in light of its low dosage may be possible to produce at a low cost. This would make DTG an interesting candidate for potentially replacing EFV as part of a preferred first-line treatment regimen. This combination was identified by experts at the Second Conference on Drug Optimization (CADO 2) and at the first and second Paediatric Conferences on Drug Optimization (PADO 1 and 2) as a promising option that should be studied in adults, adolescents and children (11, 29, 30).

DTG+DRV/r: This could represent a robust alternative for second-line treatment in adults, with or without an accompanying NRTI-backbone, in light of DTG's superiority as compared to RAL in treatment-experienced patients (17). It was also recommended by experts at CADO 2 as a promising option to be studied (11).

Section 2: Priority Regimens[†††] for Children and Adolescents

The market for paediatric formulations is relatively small and highly fragmented. Efforts to eliminate mother-to-child transmission have been very important in reducing the number of new infections every year and will result in lower treatment needs in the long-term. Nevertheless, 3.2 million children are living with HIV globally today, but only 24% has access to treatment. Thus, efforts to scale-up paediatric treatment will likely result in a market expansion in the short/medium term. Recent initiatives, such as the Accelerating Children's HIV/AIDS Treatment (ACT) Initiative launched by PEPFAR, in partnership with the Children's Investment Fund Foundation (CIFF), will contribute to increasing access to treatment and expanding the market (31).

More than one year after the publication of the WHO treatment guidelines (1), the lack of simple, child-friendly HIV formulations of preferred regimens continues to stall its full implementation, contributing to the slow phase out of less effective ARVs which are no longer preferred treatments (e.g. NVP-based regimens). Suitable formulations for young children, formulated as FDCs, palatable and heat-stable are needed. To address this issue, WHO convened the PADO expert group that first met in Dakar in October 2013, and recently convened in Geneva (December 2014), in order to identify which formulations need to be developed to address this problem (11, 29, 30).

In an effort to accelerate the development of the missing formulations, in May 2014, UNITAID, MPP and the Drugs for Neglected Diseases *initiative* (DND*i*) launched the Paediatric HIV Treatment Initiative (PHTI) (32), later also joined by the Clinton Health Access Initiative (CHAI). The objective of the PHTI is to bring together all stakeholders to facilitate cooperation in order to deliver the missing formulations identified by the WHO and PADO. The PHTI operates through formulation-specific working groups that seek to address the various challenges pertaining to each missing formulation.

Priority paediatric ARVs for first-, second- and third-line

The following provides an overview of the main formulations that are needed for paediatric treatment as identified by the PADO expert group. These are now the priority of the MPP and the PHTI.

ABC or AZT/3TC+LPV/r: These two regimens are the WHO preferred options for first-line treatment in children less than three years of age and for second-line in children who failed after an NNRTI-based regimen. Taste-masked and heat-stable FDCs containing the four ARVs are currently under development and are among the priority products identified by PADO experts. Additionally, LPV/r formulated as pellets has been submitted for approval to the US FDA (33). In the meantime, the only available formulations are low-dose tablets and syrup. The former is not suitable for toddlers and infants and the latter has palatability and toxicity issues and requires refrigeration. In terms of IP on this regimen, licences have been granted to the MPP on paediatric ABC/3TC, and on non-tablet formulations of LPV/r and RTV (as well as low dose tablets of LPV/r), which would enable the development and sale of this regimen for the 0 to three age group, including improved formulations, in at least 121 countries.

ABC/3TC+EFV: This is the preferred first-line regimen for children from three to 10 years of age, an age group that accounts for 65% of children living with HIV globally (1). PADO experts identified the need for a triple FDC. The PHTI has started coordinating the development of this FDC and is currently reviewing proposals to cover the recommended weight-bands for the three components. From an IP perspective, patents on EFV expired in 2013 and licences have been granted to the MPP on paediatric formulations containing ABC/3TC.

DRV/r containing combinations could be important in second-line treatment for children that received LPV/r in first-line and could also be a good option for third-line. DRV oral solution and a low strength tablet were approved for use in children more than three years of age. However, there is no FDC containing boosted DRV as of yet, and the use of separate formulations is difficult within the currently approved dosing range for DRV (34). For that reason, the PADO 2 conference identified this formulation as a top priority and the PHTI will coordinate its development.

Recent approval of **ATV** in children from three months of age (35) may also be an interesting option for paediatric treatment. There are currently no paediatric FDCs containing ATV boosted with RTV, which may be difficult to achieve in the absence of a fixed ratio across weight bands. An ATV/r formulation has been identified by PADO experts as a priority product. Second-line formulations with ATV/r would be: **ABC/3TC + ATV/r**, which could be administered once daily, and **AZT/3TC + ATV/r** (36).

RAL is currently recommended in third-line. Its recent approval in children from four weeks of age (37), and the possibility of extending its use to neonates, together with its favourable safety profile, may increase its importance in the near future. RAL is widely patented in developing countries (including India) and a recent licence negotiated with the MPP would enable the development and sale of generic versions in Sub-Saharan Africa as well as low-income and lower middle-income countries in other regions (92 countries).

New ARVs with potential for paediatric HIV treatment

COBI is under study in combination with TAF/FTC/EVG, DRV and ATV for paediatric treatment. It may become an alternative to RTV, and offer a child-friendly booster with potentially fewer palatability issues than RTV and, at least in principle, less heat stability challenges.

DTG is already approved for children between 12 to 18 years of age and is currently in Phase II clinical trials for infants from four weeks. Preliminary results show good tolerability and efficacy in younger groups (38,39). It has potential to become an important component of first- or second-line and has been identified by PADO experts as a long-term priority (29).

[†††] Some combinations may be difficult to co-formulate due to 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.

TAF is still under study in adolescents (22) and could become an important backbone for children and adolescents in the future. TDF-based formulations are no longer considered a priority by PADO experts who have recommended a focus shift to TAF. Ongoing studies, however, are needed to confirm TAF's lower bone and renal toxicity compared to TDF. TAF could also be helpful for future harmonization with adult regimens such as **TAF/3TC/DTG** or **EFV** (29).

Other important regimens for children

Regimens containing NVP are recommended as alternatives to the preferred regimens in current WHO treatment guidelines. However, they are still widely used today in paediatric populations (41% of children receiving first-line are estimated to be on **AZT/3TC/NVP** (2)) and will likely remain important in the near future until improved paediatric formulations of preferred regimens are developed. Regimens with NVP include **AZT/3TC/NVP** and **ABC/3TC+NVP**. The use of regimens containing d4T (e.g. **d4T/3TC/NVP**) is rapidly declining. Patents on these ARVs have expired and there do not seem to be IP-related challenges to the competitive procurement of these medicines in LMICs.

The preferred treatment for infant prophylaxis is stand-alone **NVP**. Currently, NVP 10mg/ml oral suspension and NVP 50mg tablet for oral suspension (i.e. similar to a dispersible tablet) are available and there do not appear to be any IP-related challenges to its procurement.

ARVs in Early-Stage Development

For the purposes of this paper, ARVs in early stage development are those that are currently in Phase I and II studies. While information on such ARVs is still limited, some appear to offer interesting opportunities for the medium to long term and, as a result, are being monitored closely by the MPP. These include **Fostemsavir** (BMS-663068), **Cabotegravir** (GSK-1265744), **Doravirine** (MK-1439) and **Rilpivirine long-acting** (brief descriptions of these and other ARVs under development can be found in Annex IIc).

Conclusions

In light of the above analysis and the more detailed information on each ARV included in the product cards in the annex, the following priorities have been identified for the Medicines Patent Pool for 2015. Two ARVs, namely darunavir and nevirapine, are no longer considered a focus of the MPP (except in the context of the development of suitable paediatric formulations of DRV/r) given their present low priority from an IP perspective.

It should be noted that as of this edition, ARVs that have already been licensed by the MPP are no longer assigned a level of priority.

PRODUCTS NOT YET LICENSED TO THE MPP		
ARV	**CLINICAL PRIORITY**	**MARKET/IP PRIORITY**
Lopinavir (LPV) *	High	High
Ritonavir (RTV) *	High	High
Efavirenz (comb. TDF/FTC/EFV) #	High	Medium (combination patents only)
Raltegravir (RAL) *	Medium	High
Rilpivirine (RPV)	Medium	High
Etravirine (ETV)	Medium	High

PRODUCTS ALREADY LICENSED TO THE MPP		
ARV	**DATE ADULT LICENCE**	**DATE PAED. LICENCE**
Abacavir (ABC)	July 2014	February 2013
Atazanavir (ATV)	December 2013	December 2013
Cobicistat (COBI)	July 2011	July 2011
Darunavir (DRV) ‡‡‡	September 2010	September 2010
Dolutegravir (DTG)	April 2014	April 2014
Elvitegravir (EVG)	July 2011	July 2011
Emtricitabine (FTC)	July 2011	July 2011
Lopinavir (LPV)	-	December 2014
Raltegravir (RAL)	-	February 2015
Ritonavir (RTV)	-	December 2014
Tenofovir alafenamide (TAF)	July 2014	July 2014
Tenofovir disoproxil fumarate (TDF)	July 2014	July 2014

* Licensed to the MPP for paediatric use
\# Discussion ongoing for inclusion in current MPP licences

‡‡‡ In September 2010, the MPP obtained a licence on darunavir-related patents from the US National Institutes of Health. At the time, however, there were other patents on DRV held by other patent holders.

Annex I - Methodology

ARVs that have not already been licensed to the MPP were prioritised based on a set of clinical and market/IP criteria as described in further detail below. Each ARV was assigned a level of priority (high, medium or low) according to each set of criteria. ARVs that are considered to be either medium or high under both sets of criteria are selected as a priority for the MPP and any ARV identified as a low priority under at least one set of criteria is no longer considered a priority for the MPP.

For selected pipeline compounds that are in Phase I or II clinical trials, no detailed prioritization was undertaken as not enough information was currently available to assess them. However, a general overview of some of the key characteristics of these compounds, including preliminary information on safety and efficacy, is provided in Annex IIc.

Criteria for Prioritisation

1) Clinical Criteria

Clinical criteria used differed between ARVs that have been included in the WHO treatment guidelines (2013 edition) (1), and new ARVs that have received regulatory approval since 2010 or are in late stages of development.

For ARVs included in WHO treatment guidelines, the MPP based its clinical prioritization as follows: as a general rule, ARVs recommended as part of preferred treatment regimens for first- and second-line were considered to be of high priority from a clinical perspective; ARVs currently considered for third-line or as alternatives for first- and second-line were considered to be of medium priority; and ARVs which were only recommended in very special circumstances, were not recommended and/or were being phased out, were considered to be of low priority.

In addition, information on missing formulations or combinations was included for each ARV and was considered in the prioritization. These are defined as combinations that could facilitate administration of WHO-recommended regimens and for which there are limited or no quality-assured suppliers or new combinations that are known to be under development.

For ARVs in late stages of development or that have been recently approved but not yet included in the guidelines, the assessment was based on information available from clinical trials. The assessment criteria used were those identified in the WHO's target product profile available in the report *Short-Term Treatment Optimization Priorities for ARV Drug Regimens* (40), which are as follows:

Safety/Efficacy: ARVs must be equivalent or superior to currently available products and require minimal laboratory monitoring.

Tolerability: ARVs must have minimal side effects and toxicities to improve adherence and reduce treatment failure.

Durability: ARVs 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: ARVs 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 FDCs - ideally one pill per day regimens - and simplified paediatric formulations or scored FDCs - 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: Products should be available at the lowest sustainable price.

The main source of information for data on clinical trials on new ARVs or ARVs under development was the National Institutes of Health ClinicalTrials.gov website (41). In addition, a systematic search of abstracts was conducted from those presented at recent International AIDS Conferences, Conferences on Retroviruses and Opportunistic Infections (CROI) and IAS Conferences on HIV Pathogenesis, Treatment and Prevention as well as those published in PubMed (42). Other important references include the reports of the CADO and PADO conferences and the TAG/i-Base *2014 Pipeline Report* (43).

2) Market/IP Criteria:

Once ARVs were evaluated according to their clinical significance, they were separately evaluated according to a set of market/IP criteria. The goal of the market/IP assessment was to determine the extent to which there was competition on the market for a given ARV, whether there were patents that could impact procurement options in developing countries and their date of expiry.

As a general rule, ARVs were considered to be high priority from a market/IP perspective when there were blocking patents pending or in force with at least three years left to expiry in countries accounting for over 15% of people living with HIV in LMICs. Due to the present role of Indian manufacturers, ARVs for which a patent (or patent application) could block generic production in India automatically resulted in a high priority classification.

ARVs with either a shorter time to patent expiry or with blocking patents pending or in force in countries accounting for between 1% and 15% of people living with HIV in LMICs were considered medium priority. Cases in which patents were only on specific combinations/ formulations of the ARVs but not on the ARV itself or not on the most important formulation are also considered medium priority. ARVs that were neither high nor medium priority as per the above criteria were classified as low priority.

The following provides further details on some of the data that was considered to evaluate ARVs from a market/IP perspective and the sources:

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.[§§§] Data was collected from the MPP Patent Status Database.

Compound Patent Status in India: Given the leading role of Indian generic manufacturers in supplying ARVs to other developing countries, the existence of a compound patent or patent application in India was reviewed in detail. Information was obtained from the national patent office of India.

Compound Patent Status in Other Countries: Collected from the MPP Patent Status Database.

Other Relevant Patents: Information on other patents relating to each ARV taken from the MPP Patent Status Database and based on the patents appearing in the database. Note that there may be other patents on each ARV that are not included in the MPP database and are therefore not included in this analysis.

Number of WHO Prequalified or FDA Approved (and tentatively approved) products: The number of different manufacturers having a WHO prequalified or US FDA-tentatively approved formulation containing the ARV has been used to understand the extent to which there is competition for a given ARV and the extent to which there are blocking patents in force. Information was obtained from the website of the WHO Prequalification Programme (4) and Drugs@FDA.

[§§§] Actual expiry date may differ from country to country in accordance with national patent laws.

Annex II - Product Cards

The product cards include details on the clinical and market/IP assessment for each ARV. For ARVs included in the WHO treatment guidelines, clinical information summarizes their position in such guidelines. Only products recommended as part of preferred or alternative regimens have been considered. Thus, those that are not recommended in the guidelines or only recommended as alternatives in very few instances or as ARVs that are to be phased out (d4T, ddI, T-20, FPV, IDV, MVC, NFV and SQV) are not considered.

Potentially important combinations are also listed in the cards. Some of these combinations are highlighted (**in bold**) when:

- They were identified as needed formulations in the WHO meeting report on Short-Term Priorities for ARV Drug Optimization (40), at the Second Conference on Paediatric ARV Drug Optimization (PADO 2) meeting (29), and/or in the report of the Second Conference on ARV Drug Optimization (CADO) (11)
- They could simplify administration of preferred treatment regimens for first-, second- and third-line according to the latest WHO guidelines

Some combinations may be difficult to co-formulate due to, for example, the required dose of the ARVs and hence the potential pill size when co-formulated, or because they are only approved with 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.

(†) Indicates combinations that already exist, but for which not enough sources are available (i.e. ≤ 3 sources for adult formulations and ≤ 1 source for paediatric formulations).
(‡) Indicates, regimens or combinations are not yet marketed but are under development (Phase II or Phase III).

Annex IIa: Product Cards for WHO-Recommended ARVs

ABACAVIR (ABC)

GENERAL INFORMATION:	
First FDA approval: December 1998 Adult formulations: • ABC 300mg tablet • ABC/3TC 600/300mg tablet • ABC/3TC/AZT 300/150/300mg tablet • ABC/3TC/DTG 300/150/50mg tablet	Therapeutic class: NRTI Paediatric formulations: • ABC 20 mg/ml oral solution • ABC/3TC 60/30mg tablet • ABC/3TC 120/60mg tablet
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Only in special circumstances (e.g. HIV-2 infection)
	Paediatric: Recommended for first- and second-line
Main missing formulations:	***Adult:*** N/A
	Paediatric: ABC/3TC†; ABC/3TC/NVP; **ABC/3TC+EFV; ABC/3TC/LPV/r‡; ABC/3TC+ATV/r; ABC/3TC+RAL**
Clinical priority:	**Already licensed to the MPP**
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	Expired in June/Dec. 2010
Compound Patent Status in India:	Not patented
Compound Patent Status in Other Countries:	Expired in most jurisdictions in which it was originally granted
Other Relevant Patents (expiry date):	New intermediates (2015); Hemisulfate salt (2018); Oral solution for paediatric use (2019); Combination with 3TC (2016)
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs. Paediatric solution granted in India and other LMICs
Current Voluntary Licences	Paediatric formulations: licence to the MPP covering at least 99% of children living with HIV in developing countries Adult formulations: geographical scope of SSA, LICs and LDCs (approximately 69 countries)
Number of suppliers with WHO Prequalified or FDA Approved products*:	Over five manufacturers for adult formulations and three for paediatric formulations
Market/IP priority:	**Already licensed to the MPP**

* For paediatrics, only formulations as included in the list of formulations identified by the Interagency Task Team (IATT) Paediatric Working Group as optimal have been considered (last update presented at the Paediatric ARV Procurement Working Group (PAPWG) meeting, 11 December 2014, The Global Fund Secretariat).

ATAZANAVIR (ATV)

GENERAL INFORMATION:	
First FDA approval: June 2003 Adult formulations: • ATV 300mg capsule • ATV/r 300/100mg tablet	Therapeutic class: PI Paediatric formulations: • ATV 100mg capsule • ATV 150mg capsule • ATV 200mg capsule
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** One of two preferred protease inhibitors in second-line
	Paediatric: Alternative second-line in children >6 years
Main missing formulations:	***Adult:*** **ATV/r†**; TDF/3TC/ATV/r; TDF/3TC+ATV/r†; **AZT/3TC+ATV/r**; ATV/r+RAL‡; ATV/COBI‡
	Paediatric: **ATV/r‡**; ABC/3TC+ATV/r;
Clinical priority:	**Already licensed to the MPP**
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	2017
Compound Patent Status in India:	Initial application withdrawn but divisional application pending
Compound Patent Status in Other Countries:	Granted or pending in several LMICs, e.g. granted in AR, BR, CL, CN, MX, MY, PH, TH, ZA
Other Relevant Patents (expiry date):	Bisulfate salt (2018); Use in HIV therapy (2022); Process (2025)
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs
Current Voluntary Licences	Yes, licensed to the MPP with a geographical scope of 110 countries. Provisions allowing for sale in additional countries.
Number of suppliers with WHO Prequalified or FDA Approved products:	Three manufacturers for adult formulations
Market/IP priority:	**Already licensed to the MPP**

DARUNAVIR (DRV)

GENERAL INFORMATION:	
First FDA approval: June 2006 Adult formulations: • DRV 400mg tablet • DRV 600mg tablet • DRV 800mg tablet	Therapeutic class: PI Paediatric formulations: • DRV 75mg tablet • DRV 150mg tablet • DRV 100mg/ml oral suspension
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Recommended in third-line and as an alternative in second-line
	Paediatric: Recommended in third-line in older children
Main missing formulations:	***Adult:*** **DRV/r‡**; TDF/3TC+DRV/r; ETV+DRV/r; DRV/r+RAL; **DRV/r+ETV+RAL; DRV/r+DTG**; DRV/COBI‡; DRV/r+RPV‡, TDF/FTC/EVG/COBI+DRV
	Paediatric: **DRV/r‡;** DRV/COBI‡
Clinical priority:	**MEDIUM/HIGH** (priority for third-line but likely to become important as part of second-line in the future if combination with RTV is developed and if costs decrease; also being tested in new combination)
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	Aug. 2013
Compound Patent Status in India:	Not patented
Compound Patent Status in Other Countries:	Expired in most jurisdictions in 2013
Other Relevant Patents (expiry date):	Method of Use (2019); Comb. w/ RTV (2022); Pseudopolymorph (2023); Prep. of key intermediates (2025); Comb. w/ RTV & TDF (2025)
Geographical Coverage of Relevant Patents	Granted or pending in a few LMICs.
Current Voluntary Licences	Yes, one bilateral licensee for manufacturing and sale in India and a commitment not to enforce for SSA and LDCs.
Number of suppliers with WHO Prequalified or FDA Approved products:	One manufacturer for adult formulations
Market/IP priority:	**LOW** (compound patent expired or not filed in LMICs for which information is available, secondary patents do not appear to be blocking)

EMTRICITABINE (FTC)

GENERAL INFORMATION:	
First FDA approval: June 2006 Adult formulations: • FTC 200mg tablet • TDF/FTC 300/200mg tablet • TDF/FTC/EFV 300/200/300mg tablet • TDF/FTC/RPV 300/200/25mg tablet • TDF/FTC/EVG/COBI 300/150/150mg tablet	Therapeutic class: NRTI Paediatric formulations: • FTC 10mg/ml oral solution
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Recommended as part of the preferred first-line and second-line
	Paediatric: Recommended as part of the alternative regimen in first-and second-line
Main missing formulations:	***Adult:*** FDCs included for 3TC also apply for FTC and vice-versa
	Paediatric: FDCs included for 3TC also apply for FTC and vice-versa
Clinical priority:	**Already licensed to the MPP**
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	Expired in 2010
Compound Patent Status in India:	Not patented
Compound Patent Status in Other Countries:	Originally granted in several LMICs, (e.g. CN, MY, OAPI, PH, RU and ZA) but probably expired in most if not all LMICs.
Other Relevant Patents (expiry date):	Combination with TDF (exp.2024) Combination with TDF & EFV (exp.2026) Combination with TDF & RPV (exp.2024)
Geographical Coverage of Relevant Patents	Filed or granted in several LMICs
Current Voluntary Licences	Yes, immunity from suit issued in context of MPP's TDF licence (112 countries)
Number of suppliers with WHO Prequalified or FDA Approved products:	Three manufacturers for adult formulation
Market/IP priority:	**Already licensed to the MPP**

EFAVIRENZ (EFV)

GENERAL INFORMATION:	
First FDA approval: June 2006 Adult formulations: • EFV 600mg tablet • EFV 200mg tablet • TDF/3TC/EFV 300/300/300 mg tablet • TDF/FTC/EFV 300/200/300 mg tablet • AZT/3TC+EFV 300/150+600mg tablets	Therapeutic class: NNRTI Paediatric formulations: • EFV 50mg capsule or tablet • EFV 100mg capsule • EFV 30mg/ml oral suspension
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Recommended as part of the preferred first-line
	Paediatric: Recommended as part of the preferred first-line in three to ten year olds and adolescents and in second-line for >3y that were on LPV/r in first-line.
Main missing formulations:	***Adult:*** **TDF/3TC/EFV (400mg tablet)‡**
	Paediatric: **ABC/3TC+EFV; TDF/FTC/EFV; TDF/3TC/EFV; EFV (200mg)†**
Clinical priority:	**HIGH** (priority for first-line in children, adolescents and adults)
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	Aug. 2013
Compound Patent Status in India:	Not patented
Compound Patent Status in Other Countries:	Granted or pending in some LMICs, e.g. AR, BR*, CL, CN, DO, MX, RU, TH*, UA (exp. 2018), ZA but likely to have expired in these countries in 2013
Other Relevant Patents (expiry date):	Comb. w/ TDF + FTC (2026)
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs
Current Voluntary Licences	Given expiry of main patent in most jurisdictions, licences no longer seem to be required
Number of suppliers with WHO Prequalified or FDA Approved products*:	Over five manufacturers for adult formulations and one for paediatrics
Market/IP priority:	**MEDIUM** (many suppliers; market demand likely to increase; compound patents generally expired in 2013 (except Ukraine) and combination patents with TDF and FTC pending or granted in several LMICs)

* For paediatrics, only formulations as included in the list of formulations identified by the Interagency Task Team (IATT) Paediatric Working Group as optimal have been considered (last update presented at the Paediatric ARV Procurement Working Group (PAPWG) meeting, 11 December 2014, The Global Fund Secretariat).

ETRAVIRINE (ETV)

GENERAL INFORMATION:	
First FDA approval: January 2008 Adult formulations: • ETV 100mg tablets • ETV 200mg tablets	Therapeutic class: NNRTI Paediatric formulations: • ETV 25mg tablets
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Recommended in third-line
	Paediatric: Recommended in third- line in older children
Main missing formulations:	***Adult:*** ETV+DRV/r; **DRV/r+ETV+RAL**
	Paediatric: ETV†
Clinical priority:	**MEDIUM** (priority for third- line)
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	2019
Compound Patent Status in India:	Granted
Compound Patent Status in Other Countries:	Granted or pending in several LMICs, e.g. ARIPO, AM, AR, AZ, BR, CL, CN, EAPO, ID, KG, MY, MX, MD, OAPI, PH, RU, ZA, TR, UA, VN
Other Relevant Patents (expiry date):	Novel series (2026) New forms (2026)
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs
Current Voluntary Licences	No licence for manufacturing of generic product.
Number of suppliers with WHO Prequalified or FDA Approved products:	One manufacturer for adult formulations.
Market/IP priority:	**HIGH** (no generic suppliers; compound patent granted in India and in many other countries)

LAMIVUDINE (3TC)

GENERAL INFORMATION:	
First FDA approval: June 2006 Adult formulations*: • 3TC 150mg tablets • 3TC 300mg tablets	Therapeutic class: NRTI Paediatric formulations**: • 3TC 10mg/ml oral solution
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Recommended for first- and second-line (considered interchangeable with FTC)
	Paediatric: Recommended for first- and second-line (considered interchangeable with FTC)
Main missing formulations:	***Adult:*** TDF/3TC+NVP†; TDF/3TC/NVP; TDF/3TC+ATV/r†; 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‡
	Paediatric: ABC/3TC†; AZT/3TC (dispersible formulation)†; **TDF/3TC**; ABC/3TC/NVP; **ABC/3TC+EFV; AZT/3TC+LPV/r; ABC/3TC/LPV/r‡**; TDF/3TC+NVP; **TDF/3TC/EFV**
Clinical priority:	**HIGH** (priority for first- and second-line)
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	Expired in Feb. 2010
Compound Patent Status in India:	Not patented
Compound Patent Status in Other Countries:	Originally granted in several LMICs, but probably expired in most if not all jurisdictions
Other Relevant Patents (expiry date):	Crystal form (expired); Liquid composition (2018) Combination with ABC (2016)
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs but generally not perceived to be a barrier
Current Voluntary Licences	Yes, several licensees with a geographical scope of 69 countries. But given patent expiries, licenses on this ARV appear to no longer be required.
Number of suppliers with WHO Prequalified or FDA Approved products:	Over five manufacturers for adult formulations and four for paediatric formulations
Market/IP priority:	**LOW** (compound patent expired; many suppliers and competitive market; formulation patents generally not perceived to be a barrier; possible exception may be combination patent with ABC)

* Only main formulations of 3TC as stand-alone ARV have been listed as 3TC is part of most FDCs marketed today. These FDCs appear in other product cards.

** For paediatrics, only formulations as included in the list of formulations identified by the Interagency Task Team (IATT) Paediatric Working Group as optimal have been considered (last update presented at the Paediatric ARV Procurement Working Group (PAPWG) meeting, 11 December 2014, The Global Fund Secretariat).

LOPINAVIR (LPV)

GENERAL INFORMATION:	
First FDA approval: September 2000 Adult formulations: • LPV/r 200/50mg tablets	Therapeutic class: PI Paediatric formulations: • LPV/r 100/25mg tablets • LPV/r 80/20mg/ml oral solution
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Recommended for second-line (preferred)
	Paediatric: Recommended for first- line for children <three years of age, and otherwise for second-line
Main missing formulations:	***Adult:*** TDF/3TC+LPV/r; **AZT/3TC/LPV/r**; RAL+LPV/r‡
	Paediatric: **LPV/r (sprinkles)‡**; LPV/r†; **AZT/3TC+LPV/r; ABC/3TC/LPV/r‡**; 3TC/LPV/r‡
Clinical priority:	**HIGH** (priority for second-line in adults and first- and second-line in children)
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	2016
Compound Patent Status in India:	Not patented
Compound Patent Status in Other Countries:	Granted in AR, CN, CO, MX, PH, TH, UY and ZA.
Other Relevant Patents (expiry date):	LPV/r soft-gel caps (2017) LPV/r tablet formulation (2026) LPV/r tablet formulation (2024)
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs
Current Voluntary Licences	Paediatric formulations licensed to the MPP in December 2014 for countries accounting for 99% of children living with HIV
Number of suppliers with WHO Prequalified or FDA Approved products*:	Five manufacturers for adult formulations and three for paediatric formulations
Market/IP priority:	**HIGH** (compound patent in some countries; demand likely to increase; formulation and combination patents are pending or granted in several LMICs and being enforced; no voluntary licences).

* For paediatrics, only formulations as included in the list of formulations identified by the Interagency Task Team (IATT) Paediatric Working Group as optimal have been considered (last update presented at the Paediatric ARV Procurement Working Group (PAPWG) meeting, 11 December 2014, The Global Fund Secretariat).

NEVIRAPINE (NVP)

GENERAL INFORMATION:	
First FDA approval: June 1996 Adult formulations: • NVP 200mg tablet • AZT/3TC/NVP 300/150/200mg tablets	Therapeutic class: NNRTI Paediatric formulations: • NVP 50mg/5ml oral suspension • AZT/3TC/NVP 60/30/50mg tablets
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Alternative option in first- line.
	Paediatric: Recommended infant prophylaxis as part of PMTCT and alternative for first-line
Main missing formulations:	***Adult:*** TDF/3TC+NVP[†]; TDF/3TC/NVP
	Paediatric: ABC/3TC/NVP; TDF/3TC+NVP; NVP (50mg)[†]; **NVP (dispersible small strength)**
Clinical priority:	**MEDIUM** (no longer part of preferred first-line regimens but still needed for PMTCT)
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	Expired in Nov. 2010
Compound Patent Status in India:	Not patented
Compound Patent Status in Other Countries:	Originally granted in several LMICs but likely expired.
Other Relevant Patents (expiry date):	Patents on extended release formulation and paediatric formulation do not appear to be blocking
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs
Current Voluntary Licences	Patent holder has policy of non-assert declarations covering 78 countries
Number of suppliers with WHO Prequalified or FDA Approved products*:	Over five manufacturers for adult formulations and four for paediatric formulations
Market/IP priority:	**LOW** (compound patent expired and patents on extended release formulation would only impact on that formulation for which there is very limited uptake).

* For paediatrics, only formulations as included in the list of formulations identified by the Interagency Task Team (IATT) Paediatric Working Group as optimal have been considered (last update presented at the Paediatric ARV Procurement Working Group (PAPWG) meeting, 11 December 2014, The Global Fund Secretariat).

RALTEGRAVIR (RAL)

GENERAL INFORMATION:	
First FDA approval: June 2006 Adult formulations: • RAL 400mg tablets	Therapeutic class: INSTI Paediatric formulations: • RAL 100mg tablets • RAL 25mg tablets
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Recommended in third-line
	Paediatric: Recommended in third-line in older children
Main missing formulations:	***Adult:*** ETV+RAL; DRV/r+RAL; ATV/r+RAL[‡]; **DRV/r+ETV+RAL**; RAL+LPV/r[‡]
	Paediatric: **RAL**[‡]
Clinical priority:	**MEDIUM** (priority for third-line)
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	2022
Compound Patent Status in India:	Granted
Compound Patent Status in Other Countries:	Granted or pending in several LMICs. Granted in AL, CL, CN, CO, GE, ME, MX, PH, TR, UA (expires 2027), UZ, VN, ZA. Filed in BR.
Other Relevant Patents (expiry date):	Potassium salt (2025)
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs
Current Voluntary Licences	Paediatric licence with the MPP allows manufacturing and sale in 92 countries accounting for 98.1% of children living with HIV. Adult licences granted to two licensees covering SSA and LICs.
Number of suppliers with WHO Prequalified or FDA Approved products:	None
Market/IP priority:	**HIGH** (compound patent granted in India and other LMICs; patent on potassium salt also granted in many jurisdictions)

RITONAVIR (RTV or r)

GENERAL INFORMATION:	
First FDA approval: June 1999 Adult formulations: • RTV 100mg tablets • LPV/r 200/50mg tablets • ATV/r 300/100mg tablet	Therapeutic class: Pharmacokinetic booster Paediatric formulations: • RTV 80mg/ml oral solution • LPV/r 100/25mg tablets • LPV/r 80/20mg/ml oral solution
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Recommended for second- and third-line (as pharmacokinetic booster)
	Paediatric: Recommended for first-line (as pharmacokinetic booster) in children <three years of age and otherwise for second-line
Main missing formulations:	***Adult:*** RTV (heat-stable tablet)†; **ATV/r†; DRV/r‡;** TDF/3TC+ATV/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‡; **DRV/r+DTG**
	Paediatric: **RTV (heat-stable tablet); LPV/r (sprinkles)‡**; LPV/r; **ATV/r‡; ABC/3TC+ATV/r; AZT/3TC+LPV/r; ABC/3TC/LPV/r‡; DRV/r‡**
Clinical priority:	**HIGH** (priority for second- and third-line for adults and first- and second-line for paediatrics)
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	Dec. 2013/2014
Compound Patent Status in India:	Not Granted
Compound Patent Status in Other Countries:	Granted in few LMICs (e.g. MX, PH)
Other Relevant Patents (expiry date):	Crystalline polymorph (2019) RTV Tablet formulation (2024)
Geographical Coverage of Relevant Patents	Granted or pending in several LIC/ MICs
Current Voluntary Licences	Paediatric formulations licensed to the MPP in December 2014
Number of suppliers with WHO Prequalified or FDA Approved products*:	Five manufacturers for adult formulations (as stand-alone booster only two). Four manufacturers for paediatric formulations (as stand-alone booster only one)
Market/IP priority:	**HIGH** (few suppliers; no compound patent in India but in force in some LMICs; combination patents and patents on tablet formulation pending or granted in several countries may block competitive procurement of RTV in combination with LPV and possibly with other protease inhibitors)

* For paediatrics, only formulations as included in the list of formulations identified by the Interagency Task Team (IATT) Paediatric Working Group as optimal have been considered (last update presented at the Paediatric ARV Procurement Working Group (PAPWG) meeting, 11 December 2014, The Global Fund Secretariat).

TENOFOVIR DISOPROXIL FUMARATE (TDF)

GENERAL INFORMATION:	
First FDA approval: June 2006 Adult formulations: • TDF 300mg tablet • TDF/FTC 300/200mg tablet • TDF/3TC 300/300mg tablet • TDF/FTC/EFV 300/200/600mg tablet • TDF/3TC/EFV 300/300/600mg tablet	Therapeutic class: NtRTI Paediatric formulations: • TDF 150mg tablet • TDF 200mg tablet • TDF 250mg tablet • TDF 40mg/1g oral powder
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Recommended as part of the preferred regimen for first- and alternative for second-line.
	Paediatric: Recommended as part of the preferred first-line regimen for children <10 and as part of alternative options for other lines/age groups.
Main missing formulations:	***Adult:*** TDF/3TC+NVP†; TDF/3TC/NVP; **TDF/3TC+ATV/r†**; TDF/3TC/ATV/r; TDF/3TC+LPV/r; TDF/3TC+DRV/r; TDF/FTC/EVG/COBI†
	Paediatric: **TDF/3TC; TDF/3TC/EFV**; TDF/3TC+NVP
Clinical priority:	**Already licensed to the MPP**
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	2018
Compound Patent Status in India:	Rejected but process claims granted
Compound Patent Status in Other Countries:	Granted in CN, MX
Other Relevant Patents (expiry date):	Fumarate salt (2018) Ester prodrug (2017) Combination with FTC (2024) Combination with EFV + FTC (2026)
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs
Current Voluntary Licences	Yes, several licensees covering 112 countries. As a result of the unbundling provisions in the MPP/Gilead licence, generic manufacturers that have taken the MPP licence and made use of that flexibility have been able to supply additional developing countries in which TDF is not patented.
Number of suppliers with WHO Prequalified or FDA Approved products:	Over five manufacturers for adult formulations.
Market/IP priority:	**Already licensed to the MPP**

ZIDOVUDINE (AZT)

GENERAL INFORMATION:	
First FDA approval: March 1987 Main adult formulations: • AZT 300mg tablets • AZT/3TC 300/150mg tablets • AZT/3TC/NVP 300/150/200mg tablets	Therapeutic class: NRTI Main paediatric formulations: • AZT 60mg tablets • AZT 50mg/5ml oral solution • AZT/3TC 60/30mg tablets • AZT/3TC/NVP 60/30/50mg tablets
CLINICAL ANALYSIS:	
WHO guidelines:	***Adult:*** Part of the alternative first-line regimen and of the preferred second-line regimen.
	Paediatric: Part of the preferred first-line regimen in children <three years and of the preferred second-line regimen in children from three years of age. Part of alternative options for other lines/age groups.
Main missing formulations:	***Adult:*** **AZT/3TC/LPV/r; AZT/3TC+ATV/r**; AZT/3TC+EFV†
	Paediatric: AZT†; AZT/3TC (dispersible formulation)†; **AZT/3TC+LPV/r**
Clinical priority:	**HIGH** (part of first- and second-line regimens)
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	Expired in 2006
Compound Patent Status in India:	No
Compound Patent Status in Other Countries:	Expired
Other Relevant Patents (expiry date):	AZT/3TC tablet formulation (2017) but generally withdrawn or allowed to lapse in most LMICs
Geographical Coverage of Relevant Patents	Withdrawn in most countries, appears to be in force in a few. However, generally not perceived to be a barrier.
Current Voluntary Licences	Yes, several, covering 69 countries
Number of suppliers with WHO Prequalified or FDA Approved products*:	Over five manufacturers for adult and paediatric formulations.
Market/IP priority:	**LOW** (many suppliers; compound patent expired; patents on combinations in few jurisdictions, but barriers seem to be limited or non-existent)

* For paediatrics, only formulations as included in the list of formulations identified by the Interagency Task Team (IATT) Paediatric Working Group as optimal have been considered (last update presented at the Paediatric ARV Procurement Working Group (PAPWG) meeting, 11 December 2014, The Global Fund Secretariat).

COBICISTAT (COBI)

GENERAL INFORMATION:	
First FDA approval: August 27, 2012 (as part of TDF/FTC/EVG/COBI); Sept 24, 2014 (stand-alone) January 29, 2015 (DRV/COBI & ATV/COBI) EMA approval: May 28, 2013 (as part of TDF/FTC/EVG/COBI), September 25, 2013 (stand-alone) Adult formulations: • TDF/FTC/EVG/COBI 300 (or 245mg if tenofovir disoproxil)/200/150/150mg tablet (Stribild®) • COBI 150mg tablet (Tybost®) • DRV/COBI 800/150mg tablet (Prezcobix®) • ATV/COBI 300/150mg tablet (Evotaz®)	Therapeutic class: Pharmacokinetic booster Paediatric formulations: N/A
CLINICAL ANALYSIS:	
Safety/Efficacy:	Results from Phase III study (NCT01108510) showed non-inferiority of COBI compared to ritonavir as booster of ATV in combination with TDF/FTC at 48 weeks in treatment-naïve patients with similar safety profiles (44)
Tolerability:	In a Phase III study on patients with mild to moderate renal impairment (NCT01363011), patients treated with cobicistat-boosted PI showed some reduction of renal function similar to those treated with Stribild. However, no renal serious adverse events were found(45). Tolerability is comparable for both cobicistat and ritonavir(44).
Durability:	No antiretroviral activity unlike RTV, so it does not confer PI resistance when used as a pharmacoenhancer of a non-PI such as EVG. In studying NCT01108510, none of the 10 patients in the COBI group with available data developed any PI- or TDF-related mutations (44).
Specific populations:	PAEDIATRICS: In Phase II/III in treatment-naïve adolescents as part of the FDC TDF/FTC/EVG/COBI (NCT01721109; GS-US-236-0112) and of future FDC TAF/FTC/EVG/COBI (NCT01854775; GS-US-292-0106) (41). Paediatric formulations are in development (43). A Phase II/III study of cobicistat-boosted atazanavir (ATV) or cobicistat-boosted darunavir (DRV) in treatment-experienced children from three months to 17 years is currently recruiting (NCT02016924; GS-US-216-0128). TB: Dose adjustments may be necessary when co-administering cobicistat with rifampicin, rifapentine or rifabutin. Co-administration of COBI with bedaquiline has not been studied but may increase bedaquiline exposure and hence risk of adverse reactions (46). Preliminary data suggested that COBI 150mg twice daily might mitigate the inductive effect of rifabutin (reduction of effective COBI concentration) however no long-term safety data are available. PREGNANT WOMEN: Not yet approved for use in pregnant women and no ongoing studies.

Stability /Convenience /Cost:	Does not need refrigeration. One pill taken once daily. It was approved as part of single-tablet regimen Stribild® by US FDA and EMA, and subsequently as stand-alone formulation (Tybost®) (47). Stribild launched at high cost in the US (48). No information on cost in LMICs yet.
Combinations:	Cobicistat is part of Stribild®, Prezcobix® and Evotaz® (49). Week 48 results from completed Phase II study (NCT01565850) showed that while the study was underpowered to establish non-inferiority, STR of TAF/FTC/DRV/COBI achieved viral suppression comparable to that of TDF/FTC+DRV+COBI and with improved bone & renal safety. In Phase III: TAF/FTC/EVG/COBI (NCT01797445), TAF/FTC/EVG/COBI+DRV (NCT01968551) (41).
Clinical priority:	**Already licensed to the MPP**
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	2027
Compound Patent Status in India:	Pending
Compound Patent Status in Other Countries:	Pending in several LMICs, e.g. AL, ARIPO, AM, AR, BR, CN, EAPO, EG, ID, KG, MX, MA, OAPI, RU, ZA, TJ, VN. Granted in UA.
Other Relevant Patents (expiry date):	Two have been identified that expire in 2028
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs including India
Current Voluntary Licences	Yes, many licensees. Licence with the MPP covers 103 countries. Currently sub-licensed to eight manufacturers. Licence publicly available on the MPP website. Nine additional countries included in bilateral licences on a semi-exclusive basis.
Market/IP priority:	**Already licensed to the MPP**

DOLUTEGRAVIR (DTG)

GENERAL INFORMATION:	
First FDA approval: August 2013 EMA approval: January 21, 2014 Adult formulations: • DTG 50mg tablet (Tivicay®) • DTG/ABC/3TC 50/600/300mg tablet (Triumeq®)	Therapeutic class: INSTI Paediatric formulations: N/A
CLINICAL ANALYSIS:	
Safety/Efficacy:	Approved by US FDA on the basis of results of several Phase III clinical trials in treatment-naïve patients that showed superiority of DTG+ABC/3TC compared to EFV/TDF/FTC (SINGLE study, NCT01263015) at 48 weeks (15) and non-inferiority to twice daily RAL at 96 weeks in a background of 2 NRTIs (SPRING-2 study, NCT01227824) (50). In ARV-experienced but INSTI-naïve patients DTG showed superiority compared to RAL at 48-weeks in investigator-selected background regimen (SAILING study, NCT01231516) (17). DTG also showed potent antiviral activity and durable efficacy in highly treatment-experienced adults with resistance to RAL and/or EVG (VIKING-3 study, NCT01328041) (51) and similar conclusion was drawn for DTG from VIKING-4 study which included greater percentages of patients infected with Q148K mutants (NCT01568892) (52). Meta-analysis showed that with a backbone of 2NRTs, DTG achieved significantly higher odds of virologic suppression and CD4+ cell gains than ATV/r, DRV/r, LPV/r and EFV, with better or equivalent lipid profiles (53).
Tolerability:	DTG+ABC/3TC showed fewer drug-related adverse events than TDF/FTC/EFV in the SINGLE (15) study and DTG had no difference in tolerability compared to RAL in SPRING-2 (50). Compared with ATV/r, DRV/r, EFV, EVG/COBI and LPV/r, DTG is associated with lower odds of treatment discontinuation due to adverse events (53).
Durability:	In Phase III study (SPRING-2), no treatment-emergent resistance was observed in patients failing DTG-based regimen at 48 weeks unlike RAL (54), and that was maintained at 96 weeks (50). In Phase III study (VIKING-3) assessing DTG in patients with resistance to EVG and RAL, 69% achieved virological suppression at week 24 (18).

Specific populations:	PAEDIATRICS: DTG received FDA approval for adolescents 12 to 18 years old who are at least 40kg in weight and INSTI-naïve based on results of an ongoing Phase I/II trial IMPAACT P1093 that showed good tolerability and efficacy of DTG tablet at 24-weeks (55) as confirmed by week 48 (38). Similar week 24 results of efficacy and tolerability were shown in children aged 6 to <12 yrs within the same study (39). DTG granule formulation is being planned for study in children age six to <12 yrs with a target dose of ~0.64 mg/kg. Future cohorts of this study will include children age four weeks to six years (56). The oral granule formulation showed better oral bioavailability than tablet formulation in healthy adults (57). TB: A dose adjustment of DTG to 50 mg twice daily is recommended in treatment-naïve or treatment-experienced, INSTI-naïve patients when co-administered with rifampicin. In INSTI-experienced patients with possible INSTI resistance, co-administration should be avoided (55). Co-administration of DTG with rifapentine has not been studied but may decrease DTG concentration just like rifampicin hence requiring dose adjustment (58). A Phase IIIb study on DTG vs. EFV along with rifampicin-containing TB regimens will start soon for co-infected patients (NCT02178592). PREGNANT WOMEN: Pregnancy Category B. Women who become pregnant during ARIA study will continue receiving ABC/3TC/DTG FDC and be followed under a separate Phase III study (NCT02075593). A new Phase II/III study (NCT02245022) that is expected to commence in early 2015 will look into the use of TDF+3TC+DTG vs EFV600 in pregnant women in Uganda with the focus on DTG PK in these women and their new-born babies.
Stability /Convenience /Cost:	Does not need refrigeration. Can be used as one pill once daily, or twice daily if co-administered with potent CYP3A inducers such as EFV, fosamprenavir/r or tipranavir/r (55). Used in low dose, which facilitates co-formulations. Under study for dose-optimised regimens (59). Price in developing countries not known yet.
Combinations:	ABC/3TC/DTG once-daily 600/300/50mg was approved by FDA in Aug 2014 on the basis of the SINGLE trial and bioequivalence study. This single tablet regimen is currently in Phase III trial in comparison with TDF/FTC 300/200mg tablet + ATV 300mg capsule + ritonavir 100mg tablet in treatment-naïve women (ARIA, NCT01910402) (41). The combination is also being studied in a Phase II study in patients switching from ABC/3TC+NVP (SWAD, NCT02067767). DTG+RPV once-daily is being evaluated in a Phase II/III switch study in comparison with conventional HAART of 2 NRTIs + third agent (DORIS, NCT02069834), and DTG/RPV STR is under development. DTG+3TC 300mg dual therapy is being studied in treatment-naïve patients in Phase IV study PADDLE (NCT02211482). Other combinations not yet under development have been proposed, such as with TDF or TAF. New evidence supporting NRTI-sparing combinations of boosted PI with an INSTI to treat experienced patients has been published (60). A combination of DTG with DRV/r would be in line with this strategy, and has been identified by experts as a potentially needed combination (11). Other potential combinations include DTG+ATV/r or ATV/COBI.
Clinical priority:	**Already licensed to the MPP**

MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	2026
Compound Patent Status in India:	Pending
Compound Patent Status in Other Countries:	Granted or pending in several LMICs. Granted in AM, CN, CO, DZ, EAPO, EG, ID, MO, MD, MX, MY, PH, UA, VN, ZA
Other Relevant Patents (expiry date):	Synthesis processes (2029) Intermediates (2029)
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs, including India
Current Voluntary Licences	Paediatric formulations: licensed to the MPP with a geographical scope of 121 countries. Adult formulations: licensed to the MPP with a geographical scope of 73 countries. Also enables sale in approximately 50 additional countries in which DTG is not patented.
Market/IP priority:	**Already licensed to the MPP**

ELVITEGRAVIR (EVG)

GENERAL INFORMATION:	
First FDA approval: August 2012 Adult formulations: • TDF/FTC/EVG/COBI 300/200/150/150mg tablet (Stribild ®) • EVG 85mg tablet; 150mg tablet (Vitekta®) Adult formulations under development: • TAF/FTC/EVG/COBI 10/200/150/150mg tablet	Therapeutic class: INSTI Paediatric formulations under development: • TDF/FTC/EVG/COBI • TAF/FTC/EVG/COBI 10/200/150/150mg tablet
CLINICAL ANALYSIS:	
Safety/Efficacy:	Approved by US FDA in August 2012 on the basis of 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 (12,13). These results have been maintained at 96 weeks (63-65). Also approved as stand-alone ARV by EMA on November 2013 for naïve and experienced (INSTI-naïve) patients on the basis of an additional Phase III study (GS-US-183-0145) that showed non-inferiority to RAL in experienced patients. The US HHS recommends its use in first-line only for patients with pre-ART CrCl >70 mL/min (8).
Tolerability:	144-week combined analyses of two major Phase III studies showed similar rate of discontinuation due to adverse events when compared to EFV/TDF/FTC and ATV/r +TDF/FTC (66).
Durability:	Low rates of integrase gene resistance were found in patients who received TDF/FTC/EVG/COBI in two Phase III studies. However, these mutations conferred decreased susceptibility to EVG and RAL (12,13).
Specific populations:	PAEDIATRICS: 24-week results of a Phase II/III study in adolescents as part of the FDC TDF/FTC/EVG/COBI (study GS-US-236-0112) presented at AIDS2014 REF THPDB0104. The future FDC TAF/FTC/EVG/COBI (study GS-US-292-0106) and in combination with ritonavir are underway (study GS-US-183-0160) (41). TB: Co-administration with rifampicin is contraindicated as this may cause significant decrease in the plasma concentration of elvitegravir and cobicistat (49). Rifabutin induction effect can be mitigated administering twice-daily COBI (67). PREGNANT WOMEN: Not yet approved for use in pregnant women and no ongoing studies.
Stability /Convenience /Cost:	Does not need refrigeration. One pill once daily. Needs boosting. It has already been approved as part of a combination (Stribild®) and launched in the US. It has been registered as stand alone ARV in Europe and US (Vitekta®). No information on cost in LMICs yet.
Combinations:	EVG is part of Stribild® (TDF/FTC/EVG/COBI), which received regulatory approval on 27 August 2012. TAF/FTC/EVG/COBI recently entered Phase II (43).
Clinical priority:	**Already licensed to the MPP**
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	2023
Compound Patent Status in India:	Granted
Compound Patent Status in Other Countries:	Granted or pending in several LMICs, Granted in AL, CL, CN, CO, MX, PE, PH, RU, ZA
Other Relevant Patents (expiry date):	Crystal form (2025) Improved pharmacokinetics w/ RTV (2026)
Geographical Coverage of Relevant Patents	Granted or pending in several LMICs, including India
Current Voluntary Licences	Yes, several licensees. Licence with the MPP covers 103 countries. Currently sub-licensed by MPP to 8 manufacturers. Licence publicly available on the MPP website. Nine additional countries included in bilateral licences on a semi-exclusive basis.
Market/IP priority:	**Already licensed to the MPP**

RILPIVIRINE (RPV)

GENERAL INFORMATION:	
First FDA approval: May 2011 Adult formulations: • RPV 25mg tablet (Endurant®) • TDF/FTC/RPV 300/200/25mg tablet (Complera®)	Therapeutic class: NNRTI Paediatric formulations: N/A
CLINICAL ANALYSIS:	
Safety/Efficacy:	Pooled analysis at 96 weeks of two comparative studies of RPV vs. EFV showed non-inferiority in the proportion of patients that reached undetectable viral load in both groups. Higher incidence of virologic failure in the RPV group, although beyond week 48, the incidence of virologic failure was comparable between treatment groups (68). A Phase III study (SPIRIT) shows that switching from boosted PI regimen to FTC/TDF/RPV in virologically suppressed patients maintains virologic suppression at 48 weeks and improved lipidic profile (69).
Tolerability:	Pooled results of two Phase III clinical trials showed improved tolerability profile and fewer discontinuations due to adverse events compared with EFV (68,70). The same differences appeared in patients with low viral load at initiation (≤100,000 copies/mL) (14).
Durability:	Higher incidence of virologic failure was found in patients treated with RPV group compared to those treated with EFV at 96 weeks (68). This difference disappears when the analysis is done in the subgroup of patients with low viral load (≤100,000 copies/mL) (14).
Specific populations:	PAED: Results of a Phase II study (NCT00799864) in children 12 to 18 years presented at CROI 2014 showed that 25mg QD achieved comparable exposure in adolescents and adults (71). TB: Drug interactions with rifampicin and other anti-TB drugs such as rifabutin and rifapentine (58). PREGNANT WOMEN: Not yet approved for use in pregnant but currently under study (NCT00855335).
Stability /Convenience /Cost:	Does not need refrigeration. One pill once daily. Food restrictions. Potentially low price due to low dose used, but no information on price in LMICs available. A Phase II study for RPV long-acting formulation for use in PrEP will soon start recruiting (HTPN076). 48-week results of another Phase II study of RPV-LA in combination with GSK-744 as oral maintenance therapy (LATTE study) showed good tolerability and antiviral efficacy comparable to EFV+2NRTIs (72). Efficacy of an IM injection to be administered every 4 or 8 weeks after oral induction is underway (NCT02120352) (73).
Combinations:	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. A combination RPV/DTG 25/50mg tablet is under development. A Phase II/III study compares switching from conventional HAART to DTG+RPV with continuing on conventional HAART (DORISS Study – (41)).
Clinical priority:	**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. Long-acting formulation may be important in future).
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	2022
Compound Patent Status in India:	Granted
Compound Patent Status in Other Countries:	Granted or pending in several LMICs. Granted in AL, AR, ARIPO, AM, CL (expires 2026), CN, MX, OAPI, PA, RU, ZA, LK, TJ, TR, UA
Other Relevant Patents (expiry date):	Salt forms (2025) Comb. FTC/TDF (2024)
Geographical Coverage of Relevant Patents	Filed and granted in some LMICs
Current Voluntary Licences	Yes, four bilateral licensees covering 112 countries
Market/IP priority:	**HIGH** (compound patent granted in India and granted or pending in other countries; licensing terms and conditions are confidential and may be restrictive)

TENOFOVIR ALAFENAMIDE (TAF)

GENERAL INFORMATION:	
First FDA approval: Not yet approved (US and EU filings for TAF/FTC/EVG/COBI submitted in Nov & Dec 2014, respectively) Adult formulations under development: • TAF/FTC/EVG/COBI 10/200/150/150mg tablet (TAF as 11.2mg fumarate salt) • TAF/FTC/DRV/COBI 10/200/800/150mg tablet • TAF/FTC 10-25mg/200mg tablet	Therapeutic class: NRTI (Prodrug of tenofovir) Paediatric formulations under development: • TAF/FTC/EVG/COBI 10/200/150/150mg tablet
CLINICAL ANALYSIS:	
Safety/Efficacy:	Recently announced week 48 results from Phase III Studies 104 & 111 in treatment-naïve patients suggest that TAF/FTC/EVG/COBI was non-inferior to TDF/FTC/EVG/COBI, with more favourable bone and renal safety (19). Similar to the published Phase II results, patients in the TAF arm showed significantly higher increase in total cholesterol, HDL and LDL levels than the TDF arm. The total cholesterol / HDL ratio (indicative of heart disease risk) was suggested to be unchanged in both TAF and TDF arms according to Phase II data (74).
Tolerability:	Phase Ib showed that after administering 25mg of TAF, the circulating plasma level of tenofovir, which is associated with renal and bone toxicity, was 86% lower than that of 300 mg of TDF, whereas the intracellular concentrations of tenofovir diphosphate (the active drug responsible for the antiviral activity), was 5~7 times higher than that achieved by TDF 300mg (75). This was confirmed in Study 102 and explained in part why there is smaller decrease in bone mineral density and smaller increase in serum creatinine than TDF-based regimens (74).
Durability:	No resistances were observed in Study 102 (74). In vitro studies suggested TAF-resistant mutations would be similar to those associated with TDF, but TAF is expected to be clinically active against TDF-resistant HIV (76).
Specific populations:	PAEDIATRICS: A Phase II/III study of TAF/FTC/EVG/COBI (GS-US-292-0106; NCT01854775) in treatment-naïve adolescents is underway. No information on other age groups yet. No information available yet regarding TB or HCV patients but HCV protease inhibitors might decrease the effectiveness of TAF according to in vitro studies (77). There are no adequate and well-controlled studies in pregnant women but TAF is expected to fall under pregnancy category B (19). HBV: TAF is also active against HBV. A Phase IIIb study of TAF/FTC/EVG/COBI in HIV-HBV coinfected patients who are HBV-treatment-naïve is underway (NCT02071082). TAF 25mg vs TDF 300mg are also being studied in HBV mono-infected adults in two separate Phase III studies (41).
Stability /Convenience /Cost:	Potential for low cost due to the low dose in combination (10mg when combined with COBI which increases TAF level by 2.2-fold, 25mg otherwise). Once-daily administration. Does not need refrigeration.
Combinations:	TAF/FTC/EVG/COBI with or without ATV or DRV is being studied in various Phase III trials covering different patient populations (treatment-naïve or –experienced, with or without renal impairment, those switching from TDF-based regimens) (41). Week 48 results from completed Phase II study (NCT01565850) showed that while underpowered for non-inferiority, STR of TAF/FTC/DRV/COBI achieved viral suppression comparable to that of TDF/FTC+DRV+COBI and with improved bone & renal safety (78). Other relevant FDCs to be considered include combinations with low-dose EFV, such as TAF/3TC(or FTC)/EFV 400mg and TAF/3TC(or FTC)/DTG (11,27). TAF was found in vitro to have strong synergistic activity with EVG, RAL, DTG and FTC, and moderate synergy with EFV, ATV and DRV (ranked in order of decreasing synergism; synergy means the activity as a result of combination of two drugs is more than additive).
Clinical priority:	**Already licensed to the MPP**
MARKET/IP ANALYSIS:	
Expected Compound Patent Expiry Date:	2021
Compound Patent Status in India:	Granted
Compound Patent Status in Other Countries:	Granted or pending in ARIPO, BR, CN, ID, MX, OAPI, UA, TR, VN, ZA
Other Relevant Patents (expiry date):	None
Geographical Coverage of Relevant Patents	NA
Current Voluntary Licences	Yes, licensed to the MPP as well as bilaterally to three manufacturers with a geographical scope of 112 countries. Currently sub-licensed by MPP to eight manufacturers. Licence publicly available on the MPP website.
Market/IP priority:	**Already licensed to the MPP**

Annex IIc –Pipeline HIV medicines under active development

Products included in this table are in early stage of development (at least Phase II) and may not reach approval. The list is not exhaustive. Therapeutic HIV vaccines that are not being studied in combination with anti-latency drugs as "shock & kill" therapy are not included here. A full analysis, including indication of level of priority from a clinical and market/IP perspective, will be undertaken once results of Phase II studies are public and products enter Phase III.

COMPOUND	THERAPEUTIC CLASS	DEVELOPMENT STATUS	ORIGINATOR	CLINICAL HIGHLIGHTS
ALBUVIRTIDE (FB006M)	Entry inhibitor	Phase III (in China only)	Frontier Biotech-nologies	Long-acting (LA) injectable. Weekly dosing of albuvirtide + LPV/r was safe and effective and this combination is in Phase III (in China) as potential second-line therapy in comparison with TDF+3TC+LPV/r.
FOSTEMSAVIR (BMS-663068)	Entry inhibitor / attachment inhibitor	Phase II	BMS	Effective against both CCR5- and CXCR4-tropic HIV strains. BMS-663068 showed substantial suppression of HIV and good tolerability in a Phase II study. When combined with TDF+RAL in Phase IIb, BMS-663068 achieved response rates and safety profile comparable to ATV/r.
BMS-955176	Maturation inhibitor	Phase II	BMS	Unique and underdeveloped therapeutic class. No results have been made public. Phase II study of once-daily BMS-955176 alone and in combination with ATV or ATV/r in adults is underway.
CENICRIVIROC (CVC; TBR-652)	Entry inhibitor / dual CCR2 & CCR5 inhibitor	Phase II	Tobira & Takeda	Effective against CCR5-tropic HIV. When combined with TDF/FTC, CVC was as effective as 600mg EFV with better safety & tolerability profile in treatment-naïve patients. CVC/3TC FDC tablet has been optimized and will be compared with TDF/FTC in Phase III. How CVC compares with 400mg EFV remains to be examined.
CABOTEGRAVIR (GSK-744; S/ GSK-1265744)	Integrase inhibitor	Phase II	ViiV Healthcare	GSK744 is a DTG analogue that is under development for both prevention and treatment of HIV infection. Compared with EFV+2NRTIs, GSK744+RPV oral maintenance regimen was well tolerated with less risk of patient discontinuing treatment. Monthly or bimonthly injection of GSK744-LA (the long-acting injectable version)+RPV-LA is being studied in Phase IIb as maintenance therapy in treatment-naïve patients following induction with oral GSK744+ABC/3TC(+RPV). Animal studies showed that GSK744-LA was able to protect macaques against rectal challenges with SHIV. Quarterly injection of GSK744-LA following oral induction is now being explored in healthy adults in Phase IIa safety studies in preparation for PrEP efficacy studies.
DORAVIRINE (MK-1439)	NNRTI	Phase II	MSD	Week 24 results from phase II study PN007 on treatment-naïve patients (NCT01632345) showed that when combined with TDF/FTC, once daily doravirine achieved higher response rates than EFV 600mg with fewer adverse events. Doravirine also has a superior resistance profile compared to EFV. How doravirine compares with EFV 400mg remains to be explored. Doravirine 100mg has been chosen for phase III study.
IBALIZUMAB (TMB-355)	Entry inhibitor / Humanized antibody against CD4	Phase II + Expanded Access	TaiMed Biologics	LA injectable with PrEP potential. Effective against both CCR5- and CXCR4-tropic HIV strains. Biweekly or monthly infusion of ibalizumab was well tolerated and significantly reduced HIV viral load. Recently Wuxi PharmaTech obtained FDA approval for manufacturing ibalizumab for Expanded Access. Ibalizumab was also studied in at-risk healthy volunteers, with the aim of developing it as PrEP agent though no further PrEP study has taken place.

PRO-140 (PA14)	Entry inhibitor / Humanized antibody against CCR5	Phase II	CytoDyn	LA injectable. Effective against only CCR5-tropic HIV. A single infusion of PRO-140 was well tolerated in Phase IIa with prolonged anti-HIV activity, and similar findings were reported for weekly & biweekly injections. PRO-140 is also being studied as maintenance monotherapy or in combination with other ARVs in injection drug users who failed prior regimens. The potential of PRO-140 as PrEP is also being explored in animal models.
RILPIVIRINE, long-acting injectable (RPV-LA)	NNRTI LAI	Phase II	Janssen; PATH	LA injectable version of RPV. See above for co-development with GSK744-LA. RPV-LA remained in the plasma of healthy volunteers for 84d after a single injection of 600mg. Similarly, injection of RPV-LA achieved prolonged exposure in both male and female genital tracts. Bimonthly injection of RPV-LA is currently being explored for its PrEP potential in a Phase II safety study. However, recent mice studies suggested that the protective effect of monthly RPV-LA injection could diminish over time therefore its window of protection needs to be optimised.
VACC-4x	Immunotherapy / therapeutic vaccine	Phase II	Bionor Immuno	Immune "booster" that induces immune response to HIV p24. (1) As add-on to ART, with/ without other immune stimulator: Phase II results showed that Vacc-4x was safe and immunogenic, and could contribute to significant and long-lasting decrease of HIV viral load after ART interruption. (2) As part of "shock & kill" strategy: Phase I/II study REDUC will examine whether Vacc-4x combined with anti-latency agent romidepsin (FDA-approved anticancer agent by Celgene, not included separately in this table) could impact HIV reservoir.
VORINOSTAT (SAHA; VOR)	Anti-latency agent / HDAC inhibitor	Phase II	MSD	FDA-approved anticancer agent with potential new use as latency-reversing agent in "shock & kill" strategy. VOR can disrupt HIV latency in vitro and ex vivo. Concerns have been raised over the possibility of VOR to increase the susceptibility of uninfected CD4+ T cells to HIV thereby reseeding the viral reservoir instead of eliminating it. VOR is in Phase II latency reversing trials as (1) add-on to ART: VOR single agent in patients on suppressive ART, and (2) as part of "shock & kill" strategy: VOR in combination with HIV vaccines (ChAdV63. HIVconsv prime and MVA. HIVconsv boost by Oxford, not included separately in this table) in patients receiving raltegravir-based ART.

ACRONYMS

AIDS	acquired immune deficiency syndrome
API	active pharmaceutical ingredient
ARIPO	African Regional Intellectual Property Organization
ART	antiretroviral treatment
ARV(s)	antiretroviral(s)
CrCl	creatinine clearance rate
EAPO	Eurasian Patent Office
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FDC(s)	fixed-dose combination(s)
HIV	Human Immunodeficiency Virus
IATT	Interagency Task Team on the Prevention and Treatment of HIV in Pregnant Women, Mothers and Children
INSTI	integrase strand transfer inhibitors
IP	intellectual property
LA	long-acting
LDCs	least developed countries
LICs	low-income countries
LMICs	low- and middle-income countries
MPP	Medicines Patent Pool
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OAPI	Organisation Africaine de la Propriété Intellectuelle/African Organization of Industrial Property
PI	protease inhibitor
PLHIV	people living with HIV
PMTCT	prevention of mother to child transmission of HIV
PrEP	pre-exposure prophylaxis
SSA	Sub-Saharan Africa
STR	single-tablet regimen
TB	tuberculosis
WHO	World Health Organization

ARV medicines

3TC	lamivudine
ABC	abacavir
ATV	atazanavir
AZT	zidovudine
COBI	cobicistat
d4T	stavudine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETV	etravirine
EVG	elvitegravir
FTC	emtricitabine
LPV	lopinavir
LPV/r	lopinavir/ritonavir fixed-dose combination
NVP	nevirapine
r	ritonavir used as a booster
RAL	raltegravir
RPV	rilpivirine
RTV	ritonavir
TAF	tenofovir alafenamide
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
SA	South Africa
TJ	Tajikistan
TH	Thailand
TR	Turkey
UA	Ukraine
UY	Uruguay
UZ	Uzbekistan
VN	Vietnam

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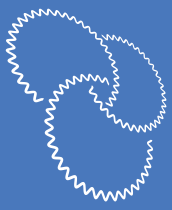

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