PRIORITY ANTIRETROVIRALS FOR THE MEDICINES PATENT POOL

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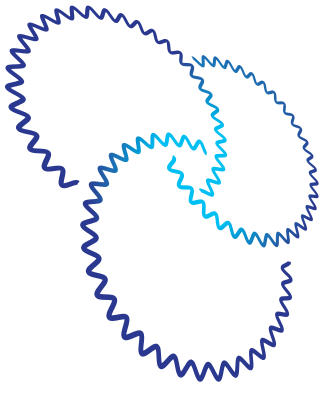

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INTRODUCTION

TO THE THIRD EDITION OF THE WORKING PAPER

Since the first antiretroviral (ARV) received regulatory approval by the US Food and Drug Administration in 1987, 27 single compounds have been approved for the treatment of HIV in various dosage forms, as well as several fixed-dose combinations (FDCs) that combine more than one ARV in a single pill. The constant flow of innovation in the field of HIV has led to treatment recommendations that evolve over time, and are likely to continue evolving as new drugs are approved and new formulations considered better suited to the needs of certain patients are developed. Prioritising ARVs is therefore a dynamic process: Treatment recommendations and needs change, market conditions shift, our understanding of HIV and of different ARVs evolves, and the regulatory and patent status of ARVs also changes.

The purpose of this working paper, now in its third annual edition, is to review the ARVs available today, as well as those in late stage clinical development, to prioritise among them and understand which of them should be the focus of the work of the Medicines Patent Pool (MPP). The central mandate of the MPP is to negotiate open, transparent and public health-oriented licences on patented HIV medicines in order to enhance access to more affordable and better-adapted formulations to treat HIV in developing countries. It is therefore important that it focuses on those medicines for which licences are likely to yield the greatest public health impact.

In order to develop a list of priority ARVs for the MPP, this paper analyses the current treatment guidelines, the latest data from clinical trials, and information on the patent status, regulatory status and market trends for different ARVs. Since the previous edition of this working paper in November 2012, the World Health Organization (WHO) issued new consolidated treatment guidelines (in July 2013), including a number of changes in the recommended ARV treatments for adults, adolescents and children. The patent status and regulatory status of various ARVs have also changed. This paper takes into consideration these changes and recommendations and considers whether new formulations of a given ARV are needed that have currently not been developed, and for which the MPP could potentially play a role. This may be the case, for example, for FDCs needed to treat children. Based on these analyses, a new list of priority ARVs for the MPP is presented in the conclusions of this document.

For the third edition of this working paper, the document structure has been revised in order to make it simpler and easier to read. Section 1 focuses on the treatment regimens recommended by the new WHO treatment guidelines, with sub-sections devoted to adults on the one hand and children and adolescents on the other. Section 2 includes an assessment of new ARVs that have recently obtained regulatory approval and ARVs that are in Phase III clinical trials. Detailed descriptions of the working paper's methodology, as well as product cards with an analysis of each ARV, are included in the annexes. The annexes also include preliminary information on products in early stages of development (clinical trial Phases I and II).

SECTION 1

ARV PRIORITISATION

IN LIGHT OF NEW WHO TREATMENT GUIDELINES

In July 2013, the WHO published a new edition of its treatment guidelines that combines in one document all the recommendations for the diagnosis, treatment, and care of people living with HIV, as well as the prevention of HIV infection (1). The 2013 guidelines include important changes in recommendations for treatment regimens.

The guidelines increased the numbers of people needing treatment significantly by recommending antiretroviral therapy begin earlier in disease progression, moving from a CD4 count of 350 to a CD4 count of 500. The WHO has recommended all children under five years of age be given treatment regardless of CD4 count (previous recommendations stated that children under three should be given treatment regardless of CD4). The WHO also streamlines its recommendations on particular treatment regimens.

This section provides an overview of the key treatment recommendations of the latest WHO guidelines and a brief analysis of the current market trends and patent status for the recommended regimens. Where possible, the focus is on treatment regimens rather than on individual ARVs, in order to be aligned with WHO recommendations. A detailed analysis of each individual ARV is included in the product cards in the annexes.

PRIORITY REGIMENS[1]

FOR ADULTS

Preferred First-Line Regimens

The once-daily FDC TDF/3TC (or FTC)/EFV, previously recommended as one of two preferred options for adults initiating ARV therapy, is now recommended as the preferred option for first-line treatment. This recommendation extends to adolescents, pregnant and breast-feeding women, women of childbearing age, and people co-infected with tuberculosis.

- **TDF/3TC (or FTC)/EFV[2]:** As the first-line treatment of choice, the market for this regimen will likely be significant and growing as treatment is initiated earlier[3] and countries phase out the use of d4T and gradually shift from other regimens. While manufacturing capacity and procurement options for this triple combination are still somewhat limited, the number of quality-assured suppliers has increased over the past year and more manufacturers are undergoing regulatory approval or are under assessment by WHO PQ. Patents on EFV, 3TC and FTC have generally expired and the voluntary licences on TDF negotiated by the MPP have helped to open the market for TDF-based combinations in most low and middle-income countries. However, there are patents pending or granted on the FTC-containing option, which will likely affect procurement choices for TDF/FTC/EFV (but may not apply to the regimen containing 3TC) in countries for which licences are not available.

Other important regimens in first-line

In light of new evidence, regimens based on NVP are now considered by the WHO to be alternative regimens in first-line,[4] which should lead to a decrease in demand for these regimens over time. Nevertheless, in the short term, certain NVP-containing regimens, such as **AZT/3TC/NVP** and **TDF/3TC+NVP** (currently under development as an FDC) are likely to continue to be widely used, especially in patients already on these regimens. Patents on these compounds have generally expired[5] and should therefore not impact on the competitive procurement of this combination.[6]

[1] 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 exists or is known to be possible. Otherwise, the sign "+" has been used.

[2] The WHO guidelines confirm that 3TC and FTC are pharmacologically comparable and interchangeable.

[3] WHO expanded ART eligibility by changing CD4 threshold for treatment initiation from 350 to 500 cells/mm3 in adults, adolescents and older children.

[4] This is the result of new evidence showing higher rate of treatment discontinuations due to adverse events for NVP, as compared to EFV (2). In addition, new data show use of EFV is safe during pregnancy(1).

[5] Note, however, that patents on once-daily NVP or on the paediatric formulation may be pending or granted in some countries.

[5] Other regimens using ABC and/or ddI as backbones with SQV/r, or triple NRTIs may be needed in special circumstances, like alternative for TB co-infected patients and in HIV-2.

Preferred Second-Line Regimens

The new treatment guidelines recommend AZT/3TC as the preferred NRTI backbone for second-line adult treatment, combined with one of two boosted protease inhibitors: LPV/r or ATV/r. In cases in which AZT or d4T was used in first-line, the guidelines recommend using TDF instead of AZT.

The market for second-line medicines is likely to expand significantly in the near future as more patients develop resistance to first-line medications and access to viral load and resistance testing in developing countries is enhanced. At present, the market is dominated by LPV/r-containing regimens but regimens containing ATV/r or DRV/r (if co-formulation becomes available) are likely to gain market share in the future given some of the advantages they have over LPV/r based regimens (see below).

AZT/3TC + LPV/r: There are today a significant number of quality assured suppliers for AZT and 3TC, as well as for the fixed dosed 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 fewer suppliers and the patent situation is more complex. Patents on LPV or on the heat-stable tablet formulation of LPV/r are pending or have been granted in many developing countries, thus limiting the countries that generic ARV manufacturers can supply. While there are no voluntary licences on LPV/r today[7], public health-oriented licensing could enable competitive procurement of LPV/r in many LIC/MICs and help reduce costs.

AZT/3TC + ATV/r: With the launch of the first quality-assured FDC of ATV/r in 2011, the potential market for ATV/r is likely to increase significantly over the coming years, given its comparable efficacy to LPV/r, once-daily dosing, improved side effect profile and lower production costs. More manufacturers are in the process of obtaining regulatory approval for this combination, which would likely result in more competitive procurement and lower prices. In December 2013, the MPP signed a licence agreement on ATV covering 110 countries which should contribute to opening up the market for this regimen and enhancing access to more affordable ATV in more countries. Existing patents on RTV (or r) will also have an impact on the competitive procurement of this formulation.[8] It should be noted, however, that the lack of registration of ATV in some developing countries could be an important barrier to its wider use.

Other important regimens in second-line

The choice of second-line regimen is determined to a large extent by the medicines taken in first-line. While WHO guidelines now recommend starting treatment on TDF-based regimens and moving on to AZT-based regimens in second-line, a large number of people who have relied on AZT or d4T-based regimens in first-line will require TDF in second-line. As a result, there is likely to be a significant demand for TDF-based second-line regimens in the short to medium term. Important priorities for such cases would be regimens containing **TDF/3TC (or FTC)+ATV/r** and **TDF/3TC + LPV/r**.

Preferred Third-Line Regimens

The WHO recommends the use of new ARV drugs or classes with minimal risk of cross-resistance with previously used regimens for third-line treatment, but does not provide a strong recommendation on which ARVs to use in which situation. Available evidence relates primarily to DRV/r, RAL and ETV, and the WHO lists these drugs as options for third-line treatment. The market for third-line medicines is presently very small, but may increase with wider access to viral load monitoring and as people are on treatment longer and develop drug resistance.

- **DRV/r:** DRV/r is recommended for third-line treatment and as an alternative for second-line regimens. Given its advantageous clinical profile, it may become a preferred option for second-line in the future if heat-stable combinations are developed and become available at an affordable price. There is currently no quality assured supplier for DRV/r as an FDC or co-pack and no quality-assured generic of stand-alone DRV.[9] The compound patent on DRV has generally expired, while secondary patents and patents on ritonavir, may still affect competition for DRV/r in certain countries outside of Sub-Saharan Africa.[10] Voluntary licensing could be important to ensure a competitive market in as many countries as possible to facilitate the development of a DRV/r FDC or co-pack, and potentially to facilitate co-formulation with other ARVs.

- **RAL:** RAL is recommended and used in first-line treatment in some countries such as the USA (3), but the new guidelines maintain RAL as a preferred option for third-line treatment. The product is patented (or the patent is pending) in many developing countries including in key countries of manufacture such as Brazil, China, India and South Africa. There is currently no quality-assured generic supplier although two manufacturers have been granted voluntary licences with a limited geographical scope.[11] Licensing of this ARV with a wider geographical scope could lead to improved availability and lower prices, thus stimulating demand.

- **ETV:** ETV has shown antiviral activity against NNRTI resistant HIV with a good safety profile (4) in combination with boosted PIs. It also showed efficacy in highly experienced patients in combination with other third-line agents such as RAL and DRV/r (5). 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 (only a distribution and packaging agreement with one supplier), and there are therefore no generic manufacturers today. Voluntary licensing of this medicine would likely lead to lower prices, which could help increase the presently low demand for this ARV.

[7] Some countries have issued compulsory licences, such as Ecuador and Thailand.

[8] Since ATV/r is only available from generic sources, un-licensed patents on ATV or r mean that the combination may not be available in certain countries

[9] One manufacturer's product has been reviewed by the Expert Review Panel (ERP) of the Global Fund. Products reviewed by the ERP are permitted for time-limited procurement by the Global Fund Quality Assurance Policy. Another manufacturer has launched DRV/r but has not yet obtained approval by an SRA or WHO Prequalification. Formulation studies for DRV with cobicistat are also under way.

[10] The main patent holder for DRV has announced its commitment not to enforce its patents in Sub-Saharan Africa

[11] One manufacturer's product has been reviewed by the ERP as per footnote 9.

[12] Except where compoulsory licences have been issued

Table 1:

SUMMARY TABLE FOR WHO PREFERRED ADULT REGIMENS

Regimen	Market trend in LIC/MICs	Patent status	Licensing status	No. of suppliers with WHO PQ or US FDA approved products
TDF/3TC/EFV	Current estimate: > 2 million patients. Demand expected to increase significantly over the next 5 years.	Patents on components of the FDC in at least four LICs/MICs	MPP licences on TDF covering 112 countries	3
TDF/FTC/EFV	Current estimate: 1 million patients. Demand likely to increase in 5 years.	Patents on the components in at least four countries and on the combination in at least 10 LIC/MICs	MPP licences on TDF and FTC covering 112 countries	4
AZT/3TC + LPV/r	Current estimate: 35% of adults in second-line. Volumes expected to increase in 5 years, although market share may remain stable.	Patents on LPV and/or r in over 30 LICs/MICs	No licensees for LPV/r[12]	AZT/3TC: 13 LPV/r: 5
AZT/3TC + ATV/r	Current estimate: 1.5% of adults in second-line. Expected to slightly increase in volume and market share over next 5 years. Volumes of ATV/r with other ARVs are expected to increase significantly.	Patents on ATV and/or r in over 20 LIC/MICs	Licence on ATV with the MPP covering 110 countries and a bilateral technology transfer agreement covering Brazil.	AZT/3TC: 13 ATV/r: 1
DRV/r-based regimens	Only used in third-line, which is still marginal. In 5 years time, the need for third-line will likely increase. However, DRV/r may also be demanded as part of second-line.	Secondary patents on DRV and/or r in over 20 LIC/MICs	One licensee for India and commitment not to enforce for SSA and LDCs	DRV: 1
RAL-based regimens	Only used in third-line, which is still marginal. In 5 years time, the need for third-line will likely increase.	Patents pending or granted in over 20 LICs/MICs (including India)	Two licensees for SSA and LICs	RAL: 1
ETV-based regimens	Only used in third-line, which is still marginal. In 5 years time, the need for third-line will likely increase.	Patents pending or granted in over 30 LICs/MICs (including India)	No voluntary licences (one packaging and distribution agreement)	ETV: 1

Sources: MPP market forecasts; MPP Patent Status Database; WHO Prequalification website for list of quality-assured suppliers (consulted 04/11/2013) and List of ARV Pharmaceutical Products classified according to the Global Fund Quality Assurance Policy (version 104, 01/09/2013 revised on 01/10/2013); websites of pharmaceutical companies.

PRIORITY REGIMENS[13]

FOR CHILDREN AND ADOLESCENTS

Treatment recommendations for children underwent significant changes in the 2013 WHO guidelines. The choice of regimens for children is constrained by a number of factors, including, for example, the fact that not all ARVs are approved for use in all age groups, and the fact that different formulations are required for treating children at different ages and weight bands. Persistent challenges make the use of recommended treatments difficult. These challenges include: lack of availability in suitable formulations for young children; lack of ARVs for children formulated as FDCs; and palatability problems and/or need for refrigeration, which can be problematic in resource-limited settings. These challenges as they relate to specific ARVs are discussed below and summarised in Table 3.

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 medium term. Nevertheless, with 3.3 million children living with HIV, and only one in three of those needing treatment currently having access to it, efforts to scale up paediatric treatment will likely result in a market expansion in the short term.

Preferred First and Second -Line Regimens

ABC or AZT/3TC+LPV/r: LPV/r based regimens are now the preferred option for first-line treatment in children below three years of age regardless of prior exposure to NNRTIs during pregnancy [14] or infant prophylaxis. These regimens are also recommended for second-line in children who failed after an NNRTI-based regimen. While the four ARVs are not available today in a single FDC, LPV/r is available in a low strength tablet and as syrup, but the former is not suitable for children under three and the latter has palatability problems, toxicity issues, and requires refrigeration.[15] Two four-in-one combinations of these regimens in granule formulations are under development,[16] and would be of great importance to enable scale-up of these regimens for children under three. While licences have been granted to the MPP on paediatric ABC/3TC covering at least 98.7% of children needing treatment, patents on LPV, RTV and on the combination could impact on the availability of these new formulations (as well as generic versions of existing ones) in several LIC/MICs.

[13] 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.

[14] In the 2010 edition of the guidelines, WHO recommended the use of LPV/r in first-line only for children below 24 months of age with previous exposure to NNRTIs (6)

[15] LPV/r minitabs are in clinical trials (CHAPAS-2). Ref: http://www.dndi.org/diseases-projects/portfolio/pi-sprinkles-chapas-2.html

[16] http://www.dndi.org/media-centre/press-releases/354-media-centre/press-releases/1605-dndi-cipla-advance-development-of-paediatric-4-in-1-arvs-to-fulfill-new-who-guidelines.html

- **ABC/3TC+EFV:** Another important change in the guidelines affects children from three to ten years of age, for whom the WHO now recommends the use of ABC/3TC + EFV. While this regimen could potentially be co-formulated as a very useful once-daily FDC, some challenges still persist in covering the recommended weight-bands for the three components, and warrant further discussion (7). From an IP perspective, patents on EFV are expiring in 2013 and licences have been granted to the MPP on ABC/3TC paediatric formulations.
- **TDF/3TC or FTC/EFV:** For children over ten years of age and over 35kg, WHO has harmonised treatment recommendations with those of adults. A paediatric formulation of this FDC would allow once-daily administration, but is yet to be developed although paediatric formulations of the separate components do exist. Children in this age group would have to take the three drugs separately, or otherwise use the adult triple FDC (8). The patent situation on this formulation is equivalent to that for the adult formulation described above.
- **NVP**: 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. While the compound patent on NVP has expired, there is a patent on the paediatric formulation that could affect competitive procurement in countries not covered by the patent holder's current access policy.

Other important regimens for children

A number of other regimens remain important for treating children, but are generally recommended as alternative regimens by WHO. This includes, for example, regimens containing nevirapine (NVP), which are widely used today and will likely remain important in the near future, in particular until improved formulations of some of the preferred regimens are developed. Regimens with NVP include **ABC/3TC+NVP** and **AZT/3TC/NVP**. Regimens containing d4T (e.g. **d4T/3TC/NVP**) will likely be progressively phased out and kept only for special situations.

Regimens containing ATV are less widely used and are only approved for children over 6 years of age. Second-line formulations including ATV/r would be: **ABC/3TC + ATV/r**, which could be administered once daily, and **AZT/3TC + ATV/r** (9). There are, however, no paediatric FDCs containing ATV boosted with RTV. Such FDCs may be difficult to achieve in the absence of a fixed ratio across weight bands.

DRV/r based combinations could be useful in second-line in 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 above 3 years of age in 2011. However, there is no FDC containing DRV boosted with RTV as yet, and its use in separate formulations is difficult with the currently approved dosing range for DRV (10).

Paediatric formulations of other third-line drugs, like **ETV** and **RAL**, have been approved in children above 6 and 2 years of age respectively, but their use has remained very limited. They are not available as FDCs, are widely patented and are not available from generic manufacturers.

Table 2:

SUMMARY TABLE FOR WHO PREFERRED PAEDIATRIC REGIMENS

Regimen	Market trend in LIC/MICs	Patent status	Licensing status	No. of suppliers with WHO PQ or US FDA approved products
ABC/3TC + LPV/r	Current estimate: 1.5% of patients in first-line and >30% in second-line. Volumes expected to increase and market share to increase in first-line and remain high in second-line over the next 5 years.	Patents on LPV and/or r in more than 30 LICs/MICs	Licences on ABC/3TC covering 98.7% of CLHIV No licences for LPV/r[17]	ABC/3TC: 3 LPV/r: 3*
AZT/3TC + LPV/r	Current estimate: 6% of patients in first-line and >20% in second-line. Volumes expected to slightly increase over the next 5 years although market share expected to diminish in first-line and increase in second-line.	Patents on LPV and/or r in more than 30 LICs/MICs	No licences for LPV/r[18]	AZT/3TC: 4 LPV/r: 3*
ABC/3TC + EFV	Current estimate: 3% of patients in first-line. Both market share and volumes expected to increase significantly in 5 years.	Patents on ABC and ABC/3TC in more than 30 countries; patents on EFV in at least one	Licences on ABC/3TC covering 98.7% of CLHIV	ABC/3TC: 3 EFV: 1*
TDF/3TC (or FTC)/EFV	Current estimate: 5% of children and adolescents in first-line. Both market share and volumes expected to increase significantly in 5 years.	Patents on components of the FDC in at least four countries	Several licensees on TDF covering 112 countries	None
NVP	Need for NVP will grow as PMTCT coverage increases to achieve elimination of the number of newly infected children by 2015 (11).	Patents on NVP paediatric in more than 10 countries	Non-assert declarations for all of Africa, LICs and LDCs	2*
DRV/r	Only used in third-line, which is still marginal. In 5 years time, the need for third-line will likely increase. Could be important for second-line if suitable formulations are developed.	Secondary patents on DRV and/or r in more than 20 countries	DRV: one licensee for India and commitment not to enforce for SSA and LDCs	1
ETV or RAL	Only used in third-line, which is still marginal. In 5 years time, the need for third-line will likely increase.	Patents pending or granted in over 30 LICs/MICs (including India)	ETV: No voluntary licences RAL: Two licensees for SSA and LICs	1

* For LPV/r, NVP and EFV paediatric tablets as included in the list of formulations identified by IATT Paediatric Working Group as optimal formulations (12).

Sources: MPP market forecasts; MPP Patent Status Database; WHO Prequalification website for list of quality-assured suppliers (consulted 04/11/2013) and List of ARV Pharmaceutical Products classified according to the Global Fund Quality Assurance Policy (version 104, 01/09/2013 revised on 01/10/2013); websites of pharmaceutical companies.

[17] Except where compoulsory licences have been issued.

[18] Except where compoulsory licences have been issued.

Table 3:

SUMMARY OF THE LIMITATIONS OF WHO PREFERRED REGIMENS FOR CHILDREN

Regimen	Main limitations of current formulations	Place in therapy
ABC/3TC + LPV/r	LPV/r palatability problems, high alcohol content and needs refrigeration. Not available as a 4-in-1 FDC.	First-line in children < 3 years and in second-line.
AZT/3TC + LPV/r	LPV/r palatability problems, high alcohol content and needs refrigeration. Not available as a 4-in-1 FDC.	First-line in children < 3 years and in second-line.
ABC/3TC + EFV	Not available as FDC.	First-line in children 3 to 10 years and second-line in children > 3 years.
TDF/3TC (or FTC)/EFV	Due to lack of age-specific formulation, caregivers may be obliged to use adult tablets or separate formulations.	First-line in children ≥10 years and ≥ 35 kg.
NVP	Only available as an oral suspension and 50mg tablet.	Infant prophylaxis as part of PMTCT and alternative for paediatric first-line.
DRV/r	Not available as FDC. Additional studies to establish appropriate dosing may be required.	Currently in second-line.
ETV or RAL	The use of these drugs may be possible only in older children (i.e. ETV is only approved in children above 6 years of age).	Third-line.

Efforts to overcome some of the above limitations and to develop the necessary formulations for paediatric treatment are necessary to addressing the huge treatment gap for children living with HIV.

Licensing that could enable development and production of the required adapted formulations and co-formulations will likely require broad-based partnerships that rely on the collaboration of pharmaceutical companies (originator and generics) as well as other important stakeholders.

SECTION 2

ARV PRIORITISATION

FOR NEW ARVS AND ARVS IN THE PIPELINE

There are four ARVs that have received regulatory approval since 2011 and one that has entered into Phase III clinical trials over the past year. These five ARVs (RPV, EVG, COBI, DTG and TAF) have not yet been included in WHO treatment guidelines but may become important components of treatment regimens in the future. In order to assess these ARVs from a clinical perspective, this document relies on published information on clinical trials and information included in the product labels for those that have regulatory approval. Each ARV was assessed against the following six criteria: safety/efficacy, tolerability, durability, specific populations, stability, convenience and cost.[19] While markets for these products in LIC/MICs are yet to develop, the patent status of these medicines is used to assess these products from a market/IP perspective.

The following brief summary will focus on the main FDCs/regimens[20] that are currently under development or have been proposed for future development[21] that contain these five ARVs, as future WHO recommendation of these ARVs will likely depend on whether they are integrated into regimens that offer advantages over existing recommended regimens.[22] Of the five ARVs reviewed in this section, RPV, EVG and COBI have already been approved in the form of FDCs, and DTG and TAF are being developed as part of FDCs. The following analysis provides a summary assessment of these regimens from a clinical and market/IP perspective with more detailed analysis for each individual ARV provided in the product cards in the annexes.

[19] These criteria were outlined in the WHO's target product profile, available in the report "Short-Term Treatment Optimization Priorities for ARV Drug Regimens", and have been the basis for clinical assessment of new ARVs in the past two editions of this working paper.

[20] 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 exists or is known to be possible. Otherwise, the sign "+" has been used.

[21] See in particular recommendations made by the Conference on ARV Drug Optimization (CADO), that took place in Cape Town in April 2013.

[22] The WHO has indicated a clear preference for the use of "simplified, less toxic and more convenient regimens as FDCs" whenever possible (1).

- **TDF/FTC/EVG/COBI:** This combination was approved for use in adult first-line in August 2012 by the US FDA and in May 2013 by the EMA. As the combination is the first once-daily pill to include an integrase inhibitor and has shown comparable efficacy to TDF/FTC/EFV in clinical trials (13,14), it may become an important option for the future if costs can be kept low. However, concerns over renal toxicity and drug interactions may be a limitation for this regimen (15). It should be noted that COBI is also being developed in combination with ATV and DRV. While there are patents or pending patent applications on EVG and COBI in a large number of developing countries, voluntary licences were granted to the MPP for this combination in 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 in patients that are intolerant or unable to adhere to EFV-based regimens. However, it is only recommended in treatment-naive adult patients with low viral load at initiation[23] (16), 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 load count. While RPV is patented in many developing countries, voluntary licences have been granted to some generic manufacturers with a geographical scope of 112 countries.

- **ABC/3TC/DTG:** This combination is being tested as an FDC in Phase III clinical trials as a once-daily first-line regimen. It is also being studied in children. DTG stand-alone was recently approved by the US FDA (August 2013) and clinical trials showed very promising results both in treatment naïve patients and treatment-experienced patients. Other positive characteristics of DTG are its favourable toxicity profile (17), the ease of administration (once daily and unboosted), its potential for low cost (only 50 mg are required) and its very high barrier to resistance. Due to these factors, DTG is a drug with the potential to become a key component of standard first or second-line treatment in the future, both in adults and children. DTG is patented in several developing countries and a patent is pending in India. Secondary patents on ABC and on the combination ABC/3TC may potentially also impact on the competitive supply of this combination.

- **TAF/FTC/EVG/COBI:** TAF is a pro-drug of tenofovir. According to preliminary results, it achieves similar virological suppression as TDF, but with a lower dose and with less risk of renal and bone toxicity (18). If results are confirmed in Phase III trials, TAF could eventually replace TDF in first-line treatment. Its approval is expected in late 2014 or early 2015 as part of this FDC. The combination also entered Phase III in adolescents (19), and the lower risk of bone metabolism toxicity makes this a particularly attractive potential for use in younger age groups. There are granted or pending patents on TAF, EVG and COBI in several developing countries, including granted patents in India on TAF and EVG. Voluntary licences were granted to the MPP for EVG and COBI covering 100 and 103 countries respectively.

- **TAF/FTC/DRV/COBI:** This is another potentially important combination that is currently under development (in Phase II studies) for use in first-line treatment.

[23] HIV-1 RNA less than or equal to 100,000 copies/mL.

Other Potential Future FDCs containing the New ARVs

While all the new ARVs are being developed and tested in the context of combinations with other ARVs, there are a number of promising combinations that are currently not being developed or tested that may still be important options for future treatment. These are:

TAF/3TC(or FTC)/EFV: If promising Phase II results for TAF are confirmed in Phase III, TAF could potentially replace TDF in first-line recommendations. This combination is not currently being tested and should be studied. Studies on dose reduction of EFV have also shown promising results that could further enhance the appeal of this combination in the future (20).

TAF/3TC (or FTC)/DTG: Clinical trials for DTG have indicated better tolerability over EFV in treatment naïve patients (17), and in light of its low dosage it may be possible to produce DTG at a lower cost. This would suggest that DTG could potentially replace 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 paediatric Conference on Drug Optimization (PADO) as a promising option that should be studied both in adults and children (21).

DTG+DRV/r:[24] This could represent a robust alternative for second-line treatment in adults, with or without accompanying backbone, in light of DTG's superiority compared to RAL in treatment experienced patients (21,22).

[24] NRTI-sparing regimens could eventually be cheaper, less toxic and potentially allow for less monitoring. However, despite several regimens showing promising results (i.e. LPV/r+3TC and LPV/r+RAL in the GARDEL and PROGRESS clinical trials), no NRTI-sparing combination has yet shown superiority in second-line.

CONCLUSIONS
AND THIRD EDITION LIST OF PRIORITY ARVS

The 2013 launch of new treatment guidelines by the WHO provides an opportunity to re-assess the priorities of the MPP in light of new clinical information, market trends, and changes in patent and regulatory status for the recommended ARVs.

The main objective of such an assessment is to concentrate MPP's work in obtaining voluntary licences on those medicines for which licensing is most needed and can have the greatest public health impact.

Prioritisation, however, cannot focus on currently recommended regimens alone. Given the time required by ARV manufacturers to develop new medicines, obtain regulatory approval for those medicines, and place them on the market, looking towards future needs is critical in order to ensure suppliers will be ready to meet treatment needs as they evolve. The availability of affordable versions of new treatments should help to ensure that the development of treatment recommendations are based on clinical criteria.

In light of the above analysis and the assessments of individual ARVs in the product cards included in the annexes, the following priority ARV medicines have been identified for the MPP **(Table on the following page).**

It should be noted that two ARVs that continue to be important from a clinical perspective have not been included in the list of priorities for the MPP, namely lamivudine (3TC) and zidovudine (AZT). Both ARVs are widely used, and 3TC is part of the preferred regimens for first and second-line. Nevertheless, the main patents on these ARVs have expired, there are several quality-assured manufacturers producing them, and market competition appears to be robust. Thus, there seems to be a limited need for voluntary licences on these ARVs.[25] Further, several ARVs have not been included in this assessment because they are not currently recommended in the WHO treatment guidelines, despite having obtained regulatory approval more than five years ago. They will be re-considered if they are included in the guidelines in the future, or if on-going clinical trials show promising results.

ARVs in Phase I and II clinical trials are included in Annex IIc. While not currently prioritised for inclusion in the MPP, their development will continue to be monitored and will be fully assessed once Phase II trials are completed and results are known.

The MPP's mission is to ensure that the best medicines are available for people living with HIV, and that treatment choices are not dictated by the lack of availability of needed regimens or by prices that render needed regimens out of reach. In order to ensure the maximum efficacy of its work, the MPP revises its Priority List annually, assessing the latest clinical data, the latest market trends, and the latest patent data on ARVs.[25] This analysis ensures that the focus of the MPP is directed at those medicines that are most essential to the health of adults and children living with HIV in developing countries, and that the MPP's mandate of negotiating voluntary licences is aimed at regimens for which sharing patents can achieve the greatest increase in access to medicines for the greatest number of people living with HIV.

MEDICINES PATENT POOL PRIORITY ANTIRETROVIRALS

ARV	Clinical Priority	Market/IP Priority
Atazanavir (ATV)*	High	High
Dolutegravir (DTG)**	High	High
Lopinavir (LPV)***	High	High
Ritonavir (RTV or r)***	High	High
Tenofovir Alafenamide Fumarate (TAF)**	High	High
Cobicistat (COBI)*	High	High
Elvitegravir (EVG)*	High	High
Abacavir (ABC) (paediatrics)[26]*	High	Medium
Emtricitabine (FTC)*	High	Medium
Efavirenz (EFV)	High	Medium
Tenofovir Disoproxil Fumarate (TDF)*	High	Medium
Darunavir (DRV)*°	Medium/High	Medium
Nevirapine (NVP)**	Medium/High	Medium
Etravirine (ETV)	Medium	High
Raltegravir (RAL)	Medium	High
Rilpivirine (RPV)	Medium	High

* ARVs already licensed to the Medicines Patent Pool.
** ARVs for which the Medicines Patent Pool is in negotiations.
*** ARVs for which the Medicines Patent Pool is in negotiations for paediatric formulations.
° The MPP has concluded a licence agreement for patents related to DRV with the US National Institutes of Health, but additional licences are needed to allow for generic manufacture.

[25] A possible exception is the patents on ABC/3TC. However, this combination is no longer recommended for adults and MPP licences on paediatrics already cover 98.7% of children living with HIV in LICs/MICs.

[26] Abacavir is identified as a priority for paediatrics in current treatment recommendations, but may become important for adult treatment in the future in the context of ongoing clinical trials on ABC/3TC/DTG.

ARVs were prioritised based on a set of clinical and market/ IP criteria as described in further detail below. Which clinical criteria were used differed between ARVs included in the WHO treatment guidelines (2013 edition) (1) and new ARVs that have received regulatory approval since 2011 or are in late stages of development.

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

1) Clinical Criteria

For ARVs included in WHO treatment guidelines, the MPP based its clinical prioritisation as follows: products recommended as preferred treatment options for first-line and second-line treatment in the guidelines were considered to be of high priority from a clinical perspective; products currently considered for third-line or as alternatives for first and second-line were considered to be of medium priority; and products that were only recommended in very specific circumstances 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. 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 (23), which are as follows:

- *Safety/Efficacy:* Products must be equivalent or superior to currently available products and require minimal laboratory monitoring.
- *Tolerability:* Products must have minimal side effects and toxicities to improve adherence and reduce treatment failure.
- *Durability:* Products should present a high barrier to resistance and have a long half-life to allow for flexibility in the dosing schedule and to minimise the likelihood of resistance developing as a result of missed doses.
- *Specific Populations:* Products should be effective in all populations and in conjunction with treatment for other conditions: men and women of all ages, pregnant women, infants and children, people who inject drugs and patients with other co-infections, including tuberculosis, malaria and viral hepatitis.
- *Stability:* Products should be heat-stable and simple to store over long periods of time with molecular stability.
- *Convenience:* Products should be suitable for once-daily dosing in 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:*[27] Products should be available at the lowest sustainable price.

The main source of information for data on clinical trials was the National Institutes of Health ClinicalTrials.gov website (19). 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 (24). Other important references include the TAG/i-Base 2013 Pipeline Report (25).

[27] Some of the factors influencing cost (e.g. availability of generics, degree of competition in the market and IP protection) were also considered when evaluating products from a market/IP perspective.

2) Market/IP Criteria:

Once ARVs had been evaluated according to their clinical significance, ARVs were separately evaluated according to a set of market/IP criteria. The goal of the market/IP assessment was to determine the size of the market and market trends, if there is a competitive market for the ARV, and whether there are patents that may impact on the procurement options for each ARV. The following criteria were used to evaluate ARVs from a market/IP perspective:

- *Expected Expiry Date of Compound Patent:* The expected expiry date of the compound patent relating to each ARV was estimated based on a 20-year term from the filing date of the related international patent application.[28] ARVs with a longer patent term left were considered to be of higher priority than ARVs for which the compound patent has expired or is close to expiry.
- *Compound Patent Status in India:* Given the leading role of Indian generic manufacturers in supplying ARVs to other developing countries,[29] the existence of a compound patent or patent application in India was considered to increase the level of priority for licensing of a given ARV from a market/IP perspective.
- *Compound Patent Status in Other Countries:* The extent to which compound patents were pending or granted in other LIC/MICs were reviewed. Illustrative examples of countries where compound patents were either granted or pending based on available information are included in the tables below.
- *Other Relevant Patents:* In addition to compound patents, patents often exist on specific chemical forms of the compound (e.g. the hydrate form of the drug salt), formulations, combinations, new indications and/or the manufacturing process for the drug. Such "secondary patents" may, in some cases, have a more limited impact on market competition, because manufacturers can often develop non-infringing ways to make the same drug, or because the validity of such patents may be challenged.[30] Secondary patents may also not be patentable in some jurisdictions. Nevertheless, in some cases, they may affect the development or procurement of a generic version of an ARV or of specific formulations. Therefore, information on secondary patents, their patent status in LICs/MICs and their date of expected expiry was considered in the prioritisation where such information was available.
- *Number of WHO Prequalified or FDA Approved (and tentatively approved) products:* The number of different manufacturers having a WHO prequalified or United States Food and Drug Administration (FDA) tentatively approved formulation containing the ARV under assessment has been noted as a proxy for the extent to which there is a potentially competitive market for a given ARV.
- *Market Trend:* Information on current and potential evolution of demand for each ARV indicates the relative importance of a given product. The estimation is based on the MPP's own forecasting. It is expressed in % of use (market share) of an ARV in the patient group for whom its use is recommended by WHO (adult or paediatric, first, second or third-line) at present. Several categories were identified:

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

[29] In 2006-2008, Indian generic manufacturers accounted for more than 80% of annual purchase volumes of donor-funded ARVs in developing countries (26).

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

- Very high demand: when it represents >50% of share in this line of treatment and population group
- High demand: when it represents >25% but <50% of share in this line of treatment and population group
- Medium/high demand: when it represents >15% but <25% of share in this line of treatment and population group
- Medium/low demand: when it represents >5% but <15% of share in this line of treatment and patient group
- Low demand: when it represents <5% of share in this line of treatment and population group

To show the expected market trend for an ARV, an estimation of the size of the demand in 5 years time is given. In this case, market share for a given ARV may not reflect an increase in absolute demand. For that reason, a mention of absolute demand is also given, expressed as: <1 time the present market (↓), >1 time but <2 times the present market (=), >2 times but <5 times the present market (↑), and >5 times the present market (↑↑). For those ARVs not used presently, market trend is expressed only as potential to decrease or increase.

When an ARV is demanded or expected to be demanded in patient groups for which it is not the preferred option, the estimates are also given.

Information on patent status was obtained from the MPP Patent Status Database for Selected HIV Medicines, a resource publicly available on the MPP's website. The database provides information on the patent status of selected ARVs in 83 LIC/MICs and is regularly updated and expanded to include more countries.

Information on the number of WHO prequalified or FDA approved generics was obtained from the website of the WHO Prequalification Programme (27).

The product cards below include details on the clinical and market/IP assessment for each ARV. For ARVs included in the WHO treatment guidelines, clinical information summarises their position in such guidelines. Only products recommended as part of preferred or alternative regimens have been considered, and not those that are mentioned in the guidelines exclusively as backup options (d4T, ddI, T-20, FPV, IDV, MVC, NFV and SQV). For ARVs recently approved or in late stages of development, the cards include updated information on the latest clinical trials and scientific evidence published or presented in major conferences, as detailed in Annex I methodology. The products considered in this category are COBI, DTG, EVG, RPV and TAF.

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 (23), and/or in the report on the Second Conference On ARV Drug Optimization (21)
- 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.

(†) Some of the combinations listed already exist, but not enough sources are available (↖ 3 sources for adult formulations, ↖ 1 source for paediatric formulations, as included in WHO PQ list consulted on 29/09/2013).
(‡) Some other drugs, regimens or combinations are not yet marketed but are under development (Phase II or Phase III).

ABACAVIR (ABC)

GENERAL INFORMATION	First FDA approval	December 1998
	Therapeutic class	NRTI
	Adult formulations	• ABC 300mg tablet • ABC/3TC 600/300mg tablet • ABC/3TC/AZT 300/150/300mg tablet
	Paediatric formulations	• ABC 20 mg/ml oral solution • ABC/3TC 30/60mg tablet
CLINICAL PRIORITISATION	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**
	Critical Priority	HIGH (priority for first and second-line in children)
MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	Expired in June/December 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 LIC/MICs. Paediatric solution granted in India and other LIC/MICs
	Current Voluntary Licences	Paediatric formulations: licence to the MPP covering at least 98.7% of children living with HIV in developing countries Adult formulations: several licensees, 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 trend:	• Medium/low demand in paediatric first-line, market expected to be 1 to 2 times present size in 5 years (=). • High demand in paediatric second-line, market expected to be 2 to 5 times present size in 5 years (↑). • High demand in adult second-line although no longer recommended. Expected to decrease (↓).
	Market trend:	MEDIUM FOR PAEDIATRICS (many suppliers; demand in paediatrics likely to increase while in adults likely to decrease; compound patent expired, but patents on paediatric formulation, hemisulfate salt and combination with 3TC could limit competitive supply in countries not covered by voluntary licences)

* For paediatrics, only formulations as included in the list of formulations identified by IATT Paediatric Working Group as optimal have been considered (12).

ATAZANAVIR (ATV)

GENERAL INFORMATION	First FDA approval	June 2003
	Therapeutic class	PI
	Adult formulations	• ATV 300mg capsule • ATV/r 300/100mg tablet
	Paediatric formulations	• ATV 100mg capsule • ATV 150mg capsule • ATV 200mg capsule
CLINICAL PRIORITISATION	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;**
	Critical Priority	HIGH (priority for second-line in adults)
MARKET/IP PRIORITISATION	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 LIC/MICs, e.g. granted in AR, BR, CL, CN, MX, MY, PH, RU, 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 LIC/MICs
	Current Voluntary Licences	Yes, four licensees, geographical scope covering SSA and India (49 countries)
	Number of suppliers with WHO Prequalified or FDA Approved products*:	Two manufacturers for adult formulations
	Market trend:	• Medium/low demand in adult second-line, market expected to be →5 times present size in 5 years (↑ ↑). • Not used in children yet, but demand expected to increase in 5 years (↑).
	Market/IP criteria:	HIGH (few suppliers; market likely to increase; compound patent pending in India and granted or pending in other developing countries).

DARUNAVIR (DRV)

GENERAL INFORMATION	First FDA approval	June 2006
	Therapeutic class	PI
	Adult formulations	• DRV 400mg tablet • DRV 600mg tablet • DRV 800mg tablet
	Paediatric formulations	• DRV 75mg tablet • DRV 150mg tablet • DRV 100mg/ml oral suspension
CLINICAL PRIORITISATION	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‡ • Paediatric: **DRV/r‡;**
	Critical 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 come down; also being tested in new combination)
MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	August 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 LIC/MICs.
	Current Voluntary Licences	Yes, one 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 trend:	• Very high demand in adult third-line, market expected to be 2 to 5 times present size in 5 years (↑). • Not used in adult second-line yet, but demand expected to increase in 5 years (↑).
	Market/IP criteria:	MEDIUM (compound patent expired or not filed in LIC/MICs for which information is available, but patents on combinations and a number of other secondary patents are pending/ granted in many countries; no quality-assured generics currently on the market; market likely to increase).

EFAVIRENZ (EFV)

GENERAL INFORMATION	First FDA approval	June 2006
	Therapeutic class	NNRTI
	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
	Paediatric formulations	• EFV 50mg capsule or tablet • EFV 100mg capsule • EFV 30mg/ml oral suspension
CLINICAL PRIORITISATION	WHO guidelines	• Adult: Recommended as part of the preferred first-line • Paediatric:Recommended as part of the preferred first-line in 3 to 10years and adolescents and in second-line for →3years that were on LPV/r in first-line.
	Main missing formulations	• Adult: **TDF/3TC/EFV†;** AZT/3TC+EFV†; **TDF/3TC/EFV (400mg tablet)‡** • Paediatric: **ABC/3TC+EFV; TDF/FTC/EFV; TDF/3TC/EFV; EFV (200mg)†**
	Critical Priority	HIGH (priority for first-line in children, adolescents and adults)
MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	August 2013
	Compound Patent Status in India:	Not patented
	Compound Patent Status in Other Countries:	Granted or pending in some LIC/MICs, 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 LIC/MICs
	Current Voluntary Licences	Yes, several licensees, geographical scope covering South Africa and 10 countries in SSA.
	Number of suppliers with WHO Prequalified or FDA Approved products*:	Over five manufacturers for adult formulations and one for paediatrics
	Market trend:	• High demand in adult first-line, market expected to be 2 to 5 times present size in 5 years (↑). • Medium/low demand in paediatric first-line, market expected to be →5 times present size in 5 years (↑ ↑). • Medium/low demand in paediatric second-line, market expected to be 2 to 5 times present size in 5 years (↑).
	Market/IP criteria:	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 LIC/MICs)

* For paediatrics, only formulations as included in the list of formulations identified by IATT Paediatric Working Group as optimal have been considered (12).

EMTRICITABINE (FTC)

GENERAL INFORMATION	First FDA approval	June 2006
	Therapeutic class	NRTI
	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
	Paediatric formulations	• FTC 10mg/ml oral solution
CLINICAL PRIORITISATION	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
	Critical Priority	HIGH (priority for first and second-line both in children and adults; considered interchangeable with 3TC).
MARKET/IP PRIORITISATION	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 LIC/MICs, (e.g. CN, MY, OAPI, PH, RU and ZA) but probably expired in most if not all LIC/MICs.
	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 LIC/MICs
	Current Voluntary Licences	Yes, immunity from suit issued in context of TDF licence (112 countries)
	Number of suppliers with WHO Prequalified or FDA Approved products*:	Three manufacturers for adult formulation
	Market trend:	• Medium/low demand in adult first-line, market expected to be 2 to 5 times present size in 5 years (↑). • Medium/low demand in adult second-line, market expected to be →5 times present size in 5 years (↑ ↑). • Medium/low demand in paediatric first-line, market expected to be 2 to 5 times present size in 5 years (↑). • Medium/low demand in paediatric second-line, market expected to be →5 times present size in 5 years (↑ ↑).
	Market/IP criteria:	MEDIUM (compound patent expired, three suppliers for adult formulations, but patents on combinations pending or granted in several LICs/MICs)

ETRAVIRINE (ETV)

GENERAL INFORMATION	First FDA approval	January 2008
	Therapeutic class	NNRTI
	Adult formulations	• ETV 100mg tablets • ETV 200mg tablets
	Paediatric formulations	• ETV 25mg tablets
CLINICAL PRIORITISATION	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†**
	Critical Priority	MEDIUM (priority for third-line)
MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	2019
	Compound Patent Status in India:	Granted
	Compound Patent Status in Other Countries:	Granted or pending in several LIC/MICs, 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 LIC/MICs
	Current Voluntary Licences	One for packaging and distribution covering SSA and LDCs
	Number of suppliers with WHO Prequalified or FDA Approved products*:	One manufacturer for adult formulations.
	Market trend:	• Currently medium/low demand in adult third-line, market expected to be →5 times present size in 5 years (↑ ↑). • Currently not used in paediatric third-line, but demand expected increase (↑).
	Market/IP criteria:	HIGH (no generic suppliers; compound patent granted in India and in many other countries)

LAMIVUDINE (3TC)

GENERAL INFORMATION	First FDA approval	June 2006
	Therapeutic class	NRTI
	Adult formulations	• 3TC 150mg tablets • 3TC 300mg tablets
	Paediatric formulations	• 3TC 10mg/ml oral solution
CLINICAL PRIORITISATION	WHO guidelines	• Adult: Recommended for first and second-line (considered interchangeable with FTC) • Paediatric: Recommended for 1st and 2nd line (considered interchangeable with FTC)
	Main missing formulations	• Adult: **TDF/3TC/EFV†;** 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**
	Critical Priority	HIGH (priority for first and second-line)
MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	Expired in February 2010
	Compound Patent Status in India:	Not patented
	Compound Patent Status in Other Countries:	Originally granted in several LIC/MICs, but probably expired or due to expire shortly.
	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 LIC/MICs but generally not perceived to be a barrier
	Current Voluntary Licences	Yes, several licensees, but possible restrictions and limited geographical scope (69 countries)
	Number of suppliers with WHO Prequalified or FDA Approved products*:	Over five manufacturers for adult formulations and four for paediatric formulations
	Market trend:	• Very high demand in adult first-line, market expected to be 2 to 5 in 5 times present size years (↑). • Very high demand in adult second-line, market expected to be 2 to 5 in 5 times present size years (↑). • Very high demand in paediatric first-line, market expected to be 2 to 5 times present size in 5 years (↑). • Very high demand in paediatric second-line, market expected to be 2 to 5 times present size in 5 years (↑).
	Market/IP criteria:	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 FDC marketed today. These FDCs appear in other product cards.
** For paediatrics, only formulations as included in the list of formulations identified by IATT Paediatric Working Group as optimal have been considered (12).

LOPINAVIR (LPV)

GENERAL INFORMATION	First FDA approval	September 2000
	Therapeutic class	PI
	Adult formulations	• LPV/r 200/50mg tablets
	Paediatric formulations	• LPV/r 100/25mg tablets • LPV/r 80/20mg/ml oral solution
CLINICAL PRIORITISATION	WHO guidelines	• Adult: Recommended for second-line (preferred) • Paediatric: Recommended for first-line for children←3 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‡**
	Critical Priority	HIGH (priority for second-line in adults and first and second-line in children)
MARKET/IP PRIORITISATION	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 LIC/MICs
	Current Voluntary Licences	None
	Number of suppliers with WHO Prequalified or FDA Approved products*:	Five manufacturers for adult formulations and three for paediatric formulations
	Market trend:	• Very high demand in adult second-line, market expected to be →5 times present size in 5 years (↑ ↑). • Medium/low demand in paediatric first-line, market expected to be →5 times present size in 5 years (↑ ↑). • Very high demand in paediatric second-line, market expected to be 1 to 2 times present size in 5 years (=).
	Market/IP criteria:	HIGH (compound patent in some countries; demand likely to increase; formulation and combination patents are pending or granted in several LIC/MICs and being enforced; no voluntary licences).

* For paediatrics, only formulations as included in the list of formulations identified by IATT Paediatric Working Group as optimal have been considered (12).

NEVIRAPINE (NVP)

GENERAL INFORMATION	First FDA approval	June 1996
	Therapeutic class	NNRTI
	Adult formulations	• NVP 200mg tablet • AZT/3TC/NVP 300/150/200mg tablets
	Paediatric formulations	• NVP 50mg/5ml oral suspension • AZT/3TC/NVP 60/30/50mg tablets
CLINICAL PRIORITISATION	WHO guidelines	• Adult: TDF/3TC+NVP†; TDF/3TC/NVP • Paediatric: ABC/3TC/NVP; TDF/3TC+NVP; NVP (50mg)†; **NVP (dispersible small strength)**
	Main missing formulations	• Adult: TDF/3TC/EFV†; 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
	Critical Priority	MEDIUM/HIGH (no longer part of preferred 1st line regimens but still needed for PMTCT)
MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	Expired in November 2010
	Compound Patent Status in India:	Not patented
	Compound Patent Status in Other Countries:	Originally granted in several LIC/MICs but likely expired.
	Other Relevant Patents (expiry date):	Hemihydrate formulation (2018); Extended release formulation (2028)
	Geographical Coverage of Relevant Patents	Granted or pending in several LIC/MICs
	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 trend:	• Very high demand in adult first-line, market expected to be 1 to 2 times present size in 5 years (=). • Very high demand in paediatric first-line, market expected to be ←1 times present size in 5 years (↓). • The number of new HIV infections among children was estimated to be 260,000 in 2012, and decrease to 40,000 by 2015 according to latest UNAIDS data (↓).
	Market/IP criteria:	MEDIUM (compound patent expired but formulation patents may impact on competitive procurement of those formulations in countries not covered by the patent holder's access policy)

* For paediatrics, only formulations as included in the list of formulations identified by IATT Paediatric Working Group as optimal have been considered (12).

RALTEGRAVIR (RAL)

GENERAL INFORMATION	First FDA approval	June 2006
	Therapeutic class	INSTI
	Adult formulations	• RAL 400mg tablets
	Paediatric formulations	• RAL 100mg tablets • RAL 25mg tablets
CLINICAL PRIORITISATION	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‡**
	Critical Priority	MEDIUM (priority for third-line)
MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	2022
	Compound Patent Status in India:	Granted
	Compound Patent Status in Other Countries:	Granted or pending in several LIC/MICs. Granted in AL, CL, CN, CO, GE, ME, MX, PH, TR, UA (expires 2027), UZ, VN, ZA. Filed in BR, CL.
	Other Relevant Patents (expiry date):	Potassium salt (2025)
	Geographical Coverage of Relevant Patents	Granted or pending in several LIC/MICs
	Current Voluntary Licences	Yes, two licensees covering SSA and LICs.
	Number of suppliers with WHO Prequalified or FDA Approved products*:	None
	Market trend:	• Very high demand in adult third-line, market expected to be 2 to 5 times present size in 5 years (↑). • Currently not used in paediatric third-line, but demand expected to increase in 5 years(↑).
	Market/IP criteria:	HIGH (compound patent granted in India and other LIC/MICs; patent on potassium salt also granted in many jurisdictions)

RITONAVIR (RTV or r)

GENERAL INFORMATION	First FDA approval	June 1999
	Therapeutic class	PHARMACOKINETIC BOOSTER
	Adult formulations	• RTV 100mg tablets • LPV/r 200/50mg tablets • ATV/r 300/100mg tablet
	Paediatric formulations	• RTV 80mg/ml oral solution • LPV/r 100/25mg tablets • LPV/r 80/20mg/ml oral solution
CLINICAL PRIORITISATION	WHO guidelines	• Adult: Recommended for second and third-line (as pharmacokinetic booster) • Paediatric: Recommended for first-line (as pharmacokinetic booster) in children ←3 years of age and otherwise for 2nd 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‡**
	Critical Priority	HIGH (priority for second, and third line for adults and first and second-line for paediatrics)
MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	December 2013/2014
	Compound Patent Status in India:	Not granted
	Compound Patent Status in Other Countries:	Granted in few LIC/MICs (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	None
	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 trend:	• Very high demand in adult second-line, market expected to be 2 to 5 times present size in 5 years (↑). • Very high demand in adult third-line, market expected to be 2 to 5 times present size in 5 years (↑). • Medium/low demand in paediatric first-line, market expected to be →5 times present size in 5 years (↑ ↑). • Very high demand in paediatric second-line, market expected to be 2 to 5 times present size in 5 years (↑). • Currently not used in paediatric third-line, but demand expected to increase in 5 years (↑).
	Market/IP criteria:	HIGH (few suppliers; no compound patent in India but in force in some LIC/MICs; combination patents and patents on tablet formulation pending or granted in several countries block generic sale 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 IATT Paediatric Working Group as optimal have been considered (12).

TENOFOVIR DISOPROXIL FUMARATE (TDF)

GENERAL INFORMATION	First FDA approval	June 2006
	Therapeutic class	NtRTI
	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
	Paediatric formulations	• TDF 150mg tablet • TDF 200mg tablet • TDF250mg tablet • TDF 40mg/1g oral powder
CLINICAL PRIORITISATION	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 over 10 and as part of alternative options for other lines/age groups.
	Main missing formulations	• Adult: TDF/3TC+NVP†; TDF/3TC/NVP; TDF/3TC/EFV†; **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;
	Critical Priority	HIGH (priority for first-line in adults and children)
MARKET/IP PRIORITISATION	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 LIC/MICs
	Current Voluntary Licences	Yes, several licensees covering 112 countries[31]
	Number of suppliers with WHO Prequalified or FDA Approved products*:	One manufacturer for adult formulations. Over five manufacturers for adult formulations.
	Market trend:	• High demand in adult first-line, market expected to be 2 to 5 times present size in 5 years (↑). • Medium/high demand in adult second-line, market expected to be 2 to 5 times present size in 5 years (↑). • Medium/high demand in paediatric first-line, market expected to be 2 to 5 times present size in 5 years (↑). • Medium/high demand in paediatric second-line, market expected to be 2 to 5 times present size in 5 years (↑).
	Market/IP criteria:	MEDIUM (many suppliers; patents on the fumarate salt in a few LIC/MICs, process patents in India and combination patents in many LIC/MICs; licensees now able to sell in more countries as a result of MPP licence)

[31] On July 12, 2011, Gilead Sciences granted a licence covering TDF to the MPP with a geographical scope of 112 countries. The MPP licence includes a number of key flexibilities that are contributing to opening up the market for TDF. Details and the text of the licence are available at www.medicinespatentpool.org.

ZIDOVUDINE (AZT)

GENERAL INFORMATION	First FDA approval	March 1987
	Therapeutic class	NRTI
	Adult formulations	• AZT 300mg tablets • AZT/3TC 300/150mg tablets • AZT/3TC/NVP 300/150/200mg tablets
	Paediatric formulations	• AZT 60mg tablets • AZT 50mg/5ml oral solution • AZT/3TC 60/30mg tablets • AZT/3TC/NVP 60/30/50mg tablets
CLINICAL PRIORITISATION	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 ←3 years and of the preferred second-line regimen in children from 3 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**;
	Critical Priority	HIGH (part of first and second-line regimens)
MARKET/IP PRIORITISATION	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 LIC/MICs
	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 trend:	• High demand in adult first-line, market expected to be 1 to 2 times present size in 5 years (=). • High demand in adult second-line, market expected to be 2 to 5 times present size in 5 years (↑). • Very high demand in paediatric first-line, market expected to be ←1 times present size in 5 years. (↓). • High demand in paediatric second-line, expected to be 1 to 2 times present size in 5 years (=).
	Market/IP criteria:	LOW (many suppliers; compound patent expired; patents on combinations in few jurisdictions, but barriers seem to be limited)

* For paediatrics, only formulations as included in the list of formulations identified by IATT Paediatric Working Group as optimal have been considered (12).

COBICISTAT (COBI)

GENERAL INFORMATION	First FDA approval	August 2012 (in combination)
	Therapeutic class	PHARMACOKINETIC BOOSTER
	Approved by EMA:	September 2013 (stand-alone)
	Adult formulations	• TDF/FTC/EVG/COBI 300/200/15/150mg tablet
	Paediatric formulations	N/A
CLINICAL PRIORITISATION		
Safety/Efficacy:	In Phase III study that showed non-inferiority compared to ritonavir as boosters of ATV at 48-weeks and similar safety profiles (28).	
Tolerability:	In a Phase III study, patients treated with cobicistat showed some reduction of renal function. However, no renal serious adverse events were found (29). That aside, tolerability is comparable for both products (cobicistat and ritonavir) (28).	
Durability:	No antiviral activity, so it does not induce resistance. Studies confirmed no development of protease inhibitor-related mutations (28).	
Specific populations:	• PAEDIATRICS: In Phase II/III in adolescents as part of the FDC TDF/FTC/EVG/COBI (study GS-US-236-0112) and of future FDC TAF/FTC/EVG/COBI (study GS-US-292-0106) (19). Paediatric formulations are in development (25) and a study of cobicistat-boosted atazanavir (ATV) or cobicistat-boosted darunavir (DRV) in children from 3 to less than 18 years is planned. • TB: Cobicistat may need dose adjustments with rifampicin or use with rifabutin (30). • PREGNANT WOMEN: Not yet approved for use in pregnant women and no on-going studies	
Stability /Convenience /Cost:	Does not need refrigeration. One pill once daily. Has been submitted for regulatory approval as a stand-alone drug in June 2012 but in 2013 US FDA rejected the application in its current form due to "deficiencies in documentation and validation" of analytical methods (31). It has already been approved as part of a combination (Stribild®) and as stand-alone formulation (Tybost®) by EMA (32). Stribild launched at high cost in the US (33). It recently received approval by EMA. No information on cost in LIC/MICs yet.	
Combinations:	Cobicistat is part of Stribild® (EVG/COBI/FTC/TDF), which received regulatory approval on 27 August 2012 (34). DRV/COBI and ATV/COBI are in phase III, TAF/FTC/EVG/COBI recently entered phase III and TAF/FTC/DRV/COBI recently entered phase II (19).	
Clinical priority:	HIGH (part of potentially important single tablet regimen, under study in combination with protease inhibitors (PIs) and only booster in addition to ritonavir. Has also been submitted for registration as a stand-alone drug)	

MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	2027
	Compound Patent Status in India:	Pending
	Compound Patent Status in Other Countries:	Pending in several LIC/MICs, 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, which expire in 2028
	Geographical Coverage of Relevant Patents	Granted or pending in several LIC/MICs including India
	Current Voluntary Licences	Yes,[32] nine licensees. Licence with the MPP is public.
	Market trend	Expected to share market with ritonavir as pharmacokinetic enhancer but no overtake in the next years.
	Market/IP criteria:	HIGH (compound patent pending in India and granted or pending in several other countries)
	Market/IP criteria:	HIGH (few suppliers; no compound patent in India but in force in some LIC/MICs; combination patents and patents on tablet formulation pending or granted in several countries block generic sale of RTV in combination with LPV and possibly with other protease inhibitors)

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

DOLUTEGRAVIR (DTG)

GENERAL INFORMATION	First FDA approval	August 2013
	Therapeutic class	INTI
	Adult formulations	• DTG 50mg tablet
	Paediatric formulations	N/A
CLINICAL PRIORITISATION		
Safety/Efficacy:	Approved by US FDA on the basis of the results of several Phase III clinical trials in naïve-patients that showed superiority compared to EFV (SINGLE study) at 48-weeks (35) and non-inferiority to RAL at 96 weeks (SPRING-2 study) (36), and in experienced patients showing superiority compared to RAL at 48-weeks (SAILING study) (37). DTG also showed antiviral in HIV-1 infected adults with resistance RAL and EVG (VIKING 3 study) (38)	
Tolerability:	DTG showed fewer drug-related adverse events compared to EFV in SINGLE (39) study and no difference in tolerability compared to RAL in SPRING-2.	
Durability:	• In Phase III study (SPRING-2), no treatment emerging resistance was observed in the DTG at 48-weeks (17), and that was maintained at 96 weeks (36). • In a Phase III study (VIKING-3) assessing DTG in patients with resistance to EVG and RAL, 69% achieved virological suppression at week 24 (14).	
Specific populations:	• PAEDIATRICS: DTG received FDA approval for children 12 to 18 years old based on results of a Phase I/II trial IMPAACT P1093 that showed good tolerability and efficacy at 24-weeks (35). • Recruitment children from 6 to 12 years has started using tablets and a granule formulation (25) that already showed good oral bioavailability compared to adult tablets (40). • TB: A dose adjustment of TIVICAY 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, co-administration should be avoided (35). • PREGNANT WOMEN: Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women (35).	
Stability /Convenience /Cost:	Does not need refrigeration. Can be used as one pill once daily. Used in low dose, which facilitates co-formulations. Under study for dose-optimised regimens (41). Price in developing countries not known yet.	
Combinations:	ABC/3TC/DTG 600/300/50mg tablets entered Phase III trial comparing it with TDF/FTC 300/200mg tablet + ATV 300mg capsule + ritonavir 100mg tablet (study NCT01910402)(19). Other combinations not under development could consider better-tolerated drugs instead of ABC, as TDF or TAF. New evidence supporting combinations of boosted PI with an INSTI to treat experienced patients has been recently published (42). A combination with DRV/r would be in line this strategy, and has been identified by experts as potential needed combination (21).	
Clinical priority:	HIGH (promising compound that has so far shown to be safe and effective in all lines of treatment, may be easy to combine, is being developed in FDCs both for adults and children and has potential for low cost)	

MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	2026
	Compound Patent Status in India:	Pending
	Compound Patent Status in Other Countries:	Granted or pending in several LIC/MICs. Granted in AM, AZ, CN, CO, DZ, EAPO, ID, IN, KG, MO, MD, PH, RU, TJ, UA, VN, ZA
	Other Relevant Patents (expiry date):	Synthesis processes (2029) Intermediates (2029)
	Geographical Coverage of Relevant Patents	Granted or pending in several LIC/MICs, including India
	Current Voluntary Licences	No
	Market trend:	Expected to become part of first-line regimen in adults and children.
	Market/IP criteria:	HIGH (compound patent pending in India and granted or pending in several other countries)

ELVITEGRAVIR (EVG)

GENERAL INFORMATION	First FDA approval	August 2012
	Therapeutic class	INTI
	Adult formulations:	• TDF/FTC/EVG/COBI 300/200/150/150mg tablet
	Adult formulations **under development:**	• TAF/FTC/EVG/COBI 300/200/15/150mg tablet • EVG 200mg tablet
	Paediatric formulations **under development:**	• TDF/FTC/EVG/COBI 300/200/150/150mg tablet • TAF/FTC/EVG/COBI 10/200/150/150mg tablet
CLINICAL PRIORITISATION		
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 (13,14). These results have been maintained at 96 weeks (43-45) The US HHS guideline panel issued a statement recommending its use as an alternative in naïve patients, on the basis of renal toxicity and potential for drug-to-drug interactions mainly (15). Recent results of another Phase III study in treatment experienced patients showed non-inferiority of EVG compared to RAL at 96 weeks (46). US FDA approval of EVG in experienced patients is pending (31)	
Tolerability:	96-weeks 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 (45).	
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 (13,14).	
Specific populations:	• PAEDIATRICS: In Phase II/III in adolescents as part of the FDC TDF/FTC/EVG/COBI (study GS-US-236-0112), the future FDC TAF/FTC/EVG/COBI (study GS-US-292-0106) and in combination with ritonavir (study GS-US-183-0160) (19). • TB: Co-administration with rifampicin is contraindicated as this may cause significant decrease in the plasma concentration of elvitegravir and cobicistat (34). • PREGNANT WOMEN: Not yet approved for use in pregnant women and no on-going studies.	
Stability /Convenience /Cost:	Does not need refrigeration. One pill once daily. It has already been approved as part of a combination (Stribild®) and launched at high cost in the US (33). No information on cost in LIC/MICs yet.	
Combinations:	• EVG is part of Stribild® (TDF/FTC/EVG/COBI), which received regulatory approval on 27 August 2012 (34). • EVG as stand alone formulation has been the application in its current form due to" deficiencies in documentation and validation" of analytical methods (31). • TAF/FTC/EVG/COBI recently entered Phase II (19).	
Clinical priority:	HIGH (first integrase inhibitor combined in a once-daily regimen that could be used in first-line; also being tested in new combination with TAF)	

MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	2023
	Compound Patent Status in India:	Granted
	Compound Patent Status in Other Countries:	Granted or pending in several LIC/MICs, 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 LIC/MICs, including India
	Current Voluntary Licences	Yes,[33] nine licensees. Licence with the MPP is public.
	Market trend:	Expected to be used marginally in first-line and mainly in experienced patients.
	Market/IP criteria:	HIGH (compound patent granted in India and granted or pending in several other countries)

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

RILPIVIRINE (RPV)

GENERAL INFORMATION	First FDA approval	May 2011
	Therapeutic class	INTI
	Adult formulation:	• RPV 25mg tablet • TDF/FTC/RPV 300/200/25mg tablet
	Paediatric formulations:	N/A
CLINICAL PRIORITISATION		
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 (47). 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 (48).	
Tolerability:	Pooled results of two Phase III clinical trials showed improved tolerability profile and fewer discontinuations due to adverse events compared with EFV (47,49). The same differences appeared in patients with low viral load at initiation (↖100,000 copies/mL) (16).	
Durability:	Higher incidence of virologic failure was found in patients treated with RPV group compared to those treated with EFV at 96 weeks (47). This difference disappears when the analysis is done in the subgroup of patients with low viral load (↖100,000 copies/mL) (16).	
Specific populations:	• PAED: Phase II study (NCT00799864) in children 12 to 18 years (19). • TB: Drug interactions with rifampicin and other anti-TB drugs such as rifabutin and rifapentin (50). • 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. Food restrictions. Potentially low price due to low dose used, but no information on price in LIC/MICs available. RPV long-acting Phase I study is already recruiting (study NCT01656018). Another Phase I study in combination with GSK-744 (study NCT01593046) is also ongoing. In both studies, the frequency of administration tested is every 2 and 4 months (19).	
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. • The combination of a dual therapy DRV/r+RPV is being studied (Phase III) NCT01792570 (19).	
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. Not yet assessed by WHO ART guidelines)	

MARKET/IP PRIORITISATION	Expected Compound Patent Expiry Date:	2022
	Compound Patent Status in India:	Granted
	Compound Patent Status in Other Countries:	Granted or pending in several LIC/MICs. 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 LIC/MICS
	Current Voluntary Licences	Yes, four licensees covering 112 countries
	Market trend:	Expected to share market with EFV and INSTIs in first-line but to a lesser extent.
	Market/IP criteria:	HIGH (compound patent granted in India and granted or pending in other countries; licences may be restrictive and geographical scope could be further expanded)

TENOFOVIR ALAFENAMIDE FUMARATE (TAF)

GENERAL INFORMATION	First FDA approval	Not yet approved
	Therapeutic class	INTI
	Adult formulations under development	• TAF/FTC/EVG/COBI 10/200/150/150mg tablet • TAF/FTC/DRV/COBI 10/200/800/150mg tablet
	Paediatric formulations under development	• TAF/FTC/EVG/COBI 10/200/150/150mg tablet
CLINICAL PRIORITISATION		
Safety/Efficacy:	Phase II results in naïve patients showed high levels of virologic suppression at week 24, and better bone and renal toxicity profiles when compared to TDF/FTC/EVG/COBI.	
Tolerability:	Phase Ib showed that after administering 25mg of TAF, the plasma level of tenofovir, which is linked with renal and bone toxicity, was among 80% lower, whereas concentrations of tenofovir di-phosphate in lymphoid cells (responsible for the activity), was seven times the concentration reached after oral administration of TDF 300mg OD (51). This was confirm in Phase II trial and explains that there is no change in bone mineral density and only small increase in serum creatinine compared to TDF/FTC/EVG/COBI (18).	
Durability:	No resistances occurred in Phase II studies (18).	
Specific populations:	PAED: A Phase II/III study (GS-US-292-0106) in adolescents already recruiting. No information on other age groups yet. No information available yet in TB patients and pregnant women.	
Stability /Convenience /Cost:	Potential for low cost due to the low dose in combination (10mg when combined with COBI, 25mg otherwise). Once daily administration. Does not need refrigeration.	
Combinations:	Already in development in two FDCs (i.e. TAF/FTC/EVG/COBI and TAF/FTC/DRV/r). Other relevant FDC that need to be developed include combinations with low-dose EFV; TAF/3TC or FTC/EFV 400mg and TAF/3TC or FTC/DTG (20,21).	
Clinical priority:	HIGH (promising results in phase II, lower dose and better safety than the most recommended backbone drug TDF, and part of once daily FDCs under development)	
MARKET/IP PRIORITISATION	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, RU, UA, VN, ZA
	Other Relevant Patents (expiry date):	None
	Geographical Coverage of Relevant Patents	NA
	Current Voluntary Licences	
	Market trend:	Expected to replace TDF in the coming years.
	Market/IP criteria:	HIGH (patented in several LIC/MICs including key manufacturing countries)

* Products included in this table are in early stage of development and may not reach approval. The list is not exhaustive. A full analysis, including indication of level of priority from a clinical and market/IP perspective, will be undertaken once products enter Phase III.
** Based on information available through on-line databases of a few patent offices (information is incomplete and preliminary in nature).

Compound	Therapeutic Class	Development Phase	Company	Preliminary Clinical Information	Preliminary Information on Patent Status**
APRICITABINE (ATC)	NRTI	Phase II	Avexa	Development resumed recently. In Phase II (NCT00367952) showed no cross resistance with other NRTIs, and activity against the M184V and L74V mutations and TAMs, at 144-weeks (52). A Phase III was planned by Q1 2013, but has not yet started (19).	No information currently available
BMS-663068 (pro-drug of BMS-625529)	Attachment inhibitor	Phase II	Bristol-Myers Squibb	New therapeutic class. Phase II trial showed substantial declines in plasma HIV-1 RNA levels and good tolerability after 8 days therapy (53). Another Phase IIb study of BMS-663068 at 48 and 96-weeks primary and final analysis in combination is ongoing (19).	International Patent Application: WO2005090367 Filed: BR, GE, IN, PE, RU, VN, ZA Granted: AR, CN, MY, PH
tBMS-986001	NRTI	Phase II	Bristol-Myers Squibb	Results at 24-weeks on phase II study comparing BMS-986001 with TDF, in combination with EFV and 3TC, not yet published (19). In vitro safety and resistance studies showed no mitochondrial toxicity compared to other NRTIs, no evidence of renal or bone toxicity (54).	International Patent Application: WO2005011709 Filed: MX, VN, ZA Granted: CN
CENICRIVIROC (CVC)	CCR5 inhibitor	Phase II	Tobira Therapeutics	24-weeks data comparing cenicriviroc + TDF/FTC vs. TDF/FTC/EFV showed similar virologic suppression with lower rates of adverse events, and a reduction of inflammatory biomarkers associated will all-cause mortality (55). Phase III of CVC-containing regimens are already planned (56).	No information currently available
DAPIVIRINE	Vaginal microbicide	Phase II	Janssen	Long-acting properties. Two Phase II studies (ASPIRE and IPM027) already started and results expected in 2014 and 2015 respectively (57).	No information currently available
DORAVIRIVE (MK-1439)	NNRTI	Phase II	Merck	Results presented at CROI 2013 showed potent antiviral activity and no major safety issues at 7 days (58,59). A Phase II study comparing TDF/FTC/EFV vs TDF/FTC+DORAVIRINE is enrolling patients (19).	No information currently available

Compound	Therapeutic Class	Development Phase	Company	Preliminary Clinical Information	Preliminary Information on Patent Status**
IBALUZIMAB	CD4 monoclonal antibody	Phase II	TaiMed Biologics/ Ambrillia Biopharma	New therapeutic class. Interesting as long-acting product with potential for weekly administration. Results of a Phase IIb study were published in 2011 (62). No news since then.	No information currently available
RPV-LA	NRTI	Phase II	Janssen	Co-developed with GSK-744 (see above). No news on development of RPV-LA depot as PREP since CROI 2012 (63).	As for rilpivirine (see above)
PHASE I, NO RECENT NEWS ON DEVELOPMENT OR DEVELOPMENT HALTED RECENTLY					
ALBUVIRTIDE (FB006M)	Fusion inhibitor	Phase I	Chongquing Frontier Biotechnologies	Results of Phase I clinical trials showed that weekly administration could be possible (64).	No information currently available
AMDOXOVIR (DAPD)	NRTI	Phase II	RFS Pharma		No information currently available
CMX-157	NRTI	Phase I	Merck	A lipid conjugate of tenofovir that achieves high intracellular levels of tenofovir diphosphate (65), the active metabolite. Currently in Phase II, but no results published. Chimerix licensed CMX-157 to Merck in July 2012 (66).	International Patent Application: WO200139724 Filed: CN, MX, RU, ZA
CTP-518	PI	Phase I/II	Concert Pharmaceuticals/ GSK	No news, apparently development on hold.	No information currently available
AMD11070	CXCR4	Phase II	Genzyme	No news since 2012 17th International Symposium on HIV and Emerging Infectious Diseases (ISHEID) (67,68)	No information currently available
ELVUCITABINE	NRTI	Phase II completed	Achillion	Potential to be once-daily, weekly or monthly. No recent information published, but no news regarding the development has been halted.	No information currently available
EFdA	NRTI	Phase I	Merck	Merck signed a deal to develop EFdA, a novel NRTI currently in phase I (69).	
FOZIVUDINE	NRTI	Phase II	Boehringer-Ingelheim	No news since 2005.	No information currently available
KP-1461	Viral decay accelerator.	Phase II	Koronis Pharmaceuticals	New therapeutic class that provokes mutations in HIV and is well tolerated. No recent news (70).	No information currently available

Compound	Therapeutic Class	Development Phase	Company	Preliminary Clinical Information	Preliminary Information on Patent Status**
LERSIVIRINE	NNRTI	Phase II	ViiV	ViiV announced that development of Lersivirine was halted in February 2013 (25) despite recently published results showed similar efficacy than EFV with better safety profile (71).	Not relevant anymore
PRO-140	Monoclonal CCR5 antibody	Phase II	CytoDyn	Phase II trials still active after acquisition of PRO 140 by CytoDyn from Progenics Pharmaceutical on October 2012 (72).	No information currently available
PRO-542	Monoclonal CCR5 antibody	Completed a Phase II in 2005	Progenics Pharmaceu-ticals	Not moving to Phase III, but no news about stopping development	No information currently available
RACIVIR	NRTI	Phase II (RCV-04-201) completed in 2006	Pharmas-set/Gilead	Unclear if discontinued or not.	No information currently available
RDEA-806	NNRTI	Phase IIa	Ardea Biosciences	Safe and effective according to Phase IIa clinical trials (73). No news since then and no longer in Ardea Bioscineces pipeline according to corporate website (74).	No information currently available
SB-728	Gene therapy	Phase I/IIa	Sangamo	No updated information on this new therapeutic class. Phase I/II study already recruiting patients (19).	No information currently available
VS411	AV-HALTs	Phase II	ViroStatics	New therapeutic class that aims to activate the immune system, increasing proliferation of CD4 cells. Promising results presented in 2011 (75), but no updated information since then.	No information currently available

Annex III

Acronyms & Definitions

Acronym	
AIDS	Acquired Immune Deficiency Syndrome
ARIPO	African Regional Intellectual Property Organization
ART	ARV treatment
ARV	Antiretroviral
AV-HALTS	AntiViral- HyperActivation Limiting Therapeutics
EAPO	Eurasian Patent Organization
EMA	European Medicines Agency
CLHIV	Children living with HIV
FDA	United States Food and Drug Administration
FDC	Fixed-Dose Combination
HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Transfer Inhibitors
IP	Intellectual Property
LDC	Least Developed Countries
LIC	Low Income Countries
MIC	Middle Income Countries
NIH	United States National Institutes of Health
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
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
WHO	World Health Organization
WIPO	World Intellectual Property Organization

ARV Medicines

3TC	Lamivudine
ABC	Abacavir
ATV	Atazanavir
AZT	Zidovudine
COBI	Cobicistat
d4T	Stavudine
ddI	Didanosine
DTG	Dolutegravir
DRV	Darunavir
EFV	Efavirenz
ETR	Etravirine
EVG	Elvitegravir
FPV	Fosamprenavir
FTC	Emtricitabine
IDV	Indinavir
LPV	Lopinavir
MVC	Maraviroc
NVP	Nevirapine
RAL	Raltegravir
RPV	Rilpivirine
RTV	Ritonavir
r	Ritonavir used as booster
SQV	Saquinavir
TAF	Tenofovir Alafenamide Fumarate
TDF	Tenofovir Disoproxil Fumarate

Country Codes

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

Other definitions

FIRST-LINE	Regimen used to treat HIV in people that have not received ARVs before or that have been switched due to toxicity. People taking first-line regimens are also referred to as treatment naïve patients.
SECOND-LINE	Regimen used in people after first-line failure (i.e. the HIV virus becomes resistant to first-line drugs), containing other therapeutic classes to which the virus is still susceptible. People on second-line regimens are also referred to as experienced or treatment experienced patients.
THIRD-LINE	Regimen used in patients after second-line failure (i.e. the HIV becomes resistant to second-line drugs), containing other therapeutic classes to which the virus is still susceptible. People on third-line regimens are also referred to as highly experienced patients.
QUALITY ASSURED	Medicines are subject to review by the health authorities (or regulatory bodies) of the country where they will be used to ensure they have been manufactured according to agreed quality standards. It is up to these authorities to establish which standards should apply, though they should include the requirements that the medicine be both safe and effective at its labelled use. The WHO also assesses certain groups of medicines under its Prequalification Programme, including ARVs. If ARVs meet WHO quality standards, they are suitable to be procured by UN bodies for HIV-related programs. For the purpose of this paper, a quality assured ARV is one that has been approved by a stringent regulatory authority, such as the US FDA or the WHO Prequalification Programme, and is eligible for procurement by the UN, the Global Fund, PEPFAR or UNITAID.
REGULATORY APPROVAL	Refers to the process conducted by the health authority (or regulatory body) of a country in order to ensure a medicine complies with quality standards and is safe and effective for its intended use in that country, thus giving a manufacturer the right to market such a product.
THERAPEUTIC CLASS (referred to ARVs)	There are currently five classes of ARVs approved (i.e. NRTIs, NNRTIs, PIs, INSTIs and entry inhibitors). Each class has a different mechanism of action against the HIV virus. Mutations conferring resistance to one therapeutic class do not necessarily confer resistance to other classes, thus allowing treatment sequencing.

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