UNITAID

2014

HIV Medicines Technology and Market Landscape

1st Edition

MARCH 2014

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CONTENTS

Abbreviations

AIDS	acquired immunodeficiency syndrome
API	active pharmaceutical ingredient
APIMF	API Master File
ART	antiretroviral therapy
ARV	antiretroviral
BMS	Bristol-Meyers Squibb
bPI	boosted protease inhibitor
CCR5	C-C chemokine receptor type 5
CHAI	Clinton Health Access Initiative
DMF	Drug Master File
DNDi	Drugs for Neglected Diseases *initiative*
EMA	European Medicines Agency
FDA	Food and Drug Administration (United States)
FDC	fixed dose combination
FPP	finished pharmaceutical product
g	gram
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	good manufacturing practices
HII	Herfindahl-Hirschman Index
HIV	human immunodeficiency virus
IATT	Inter-Agency Task Team
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INI	integrase inhibitor
k	thousand
kg	kilogram
M	million
mg	milligram
mL	millilitre
mm	millimetre
MPP	Medicines Patent Pool
MSF	Médecins sans Frontières
NIH	National Institutes of Health
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
PDP	product development partnership
PEPFAR	President's Emergency Plan for AIDS Relief
PI	protease inhibitor
PFSCM	Partnership for Supply Chain Management
PK	pharmacokinetics
PLWH	people living with HIV
Q	quarter
R&D	research and development
SCMS	Supply Chain Management System
SRA	stringent regulatory authority
TB	tuberculosis
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
US	United States
USAID	United States Agency for International Development
VPP	Voluntary Pooled Procurement
WHO	World Health Organization

Medicines

3TC	lamivudine
ABC	abacavir
ATV	atazanavir
AZT	zidovudine
COBI	cobicistat
d4T	stavudine
ddI	didanosine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FTC	emtricitabine
LPV	lopinavir
MVC	maraviroc
NVP	nevirapine
r	ritonavir
RAL	raltegravir
RPV	rilpivirine
RTV	ritonavir
T-20	enfuvirtide
TAF	tenofovir alafenamide fumarate
TDF	tenofovir disoproxil fumarate

Executive summary

The public health problem of HIV and access issues related to ARVs

Despite the fact that new HIV infections and AIDS-related deaths have decreased by almost one third since the early 2000s, HIV/AIDS remains a substantial global health problem. In 2012, there were 35.3 million people living with HIV (PLWH). Low- and middle-income countries had 98% of the AIDS-related deaths, with sub-Saharan Africa bearing a disproportionate burden, accounting for 70.8% of all PLWH.

Access to appropriate antiretroviral therapy (ART) is vital to prevent HIV morbidity and mortality, and high ART coverage also promotes HIV prevention by lowering the amount of virus circulating in people within a particular setting or population. The World Health Organization (WHO) released new treatment recommendations in June 2013 that raise the CD4 cell count threshold for ART initiation for most people (from 350 to 500 cells/mL) and expand the number of populations that should receive treatment irrespective of their immune status. These changes have substantially increased the number of people eligible for ART. At the end of 2012, almost 10 million people were receiving ART in low- and middle-income countries, or about 34% of the total eligible population under the 2013 WHO treatment guidelines (28.6 million). The access level in children was falling behind at an estimated 20% of the total paediatric population in need of ART; while 647 000 children were receiving ART as of December 2012, an additional 2.6 million children were eligible for ART under current WHO treatment guidelines, but not receiving it.

In addition, access to second-line treatment remains limited, estimated by WHO at 4% where data from countries having access to viral load suggest much greater needs, with 14% of patients failing first-line treatment in South Africa within five years.

Antiretroviral (*ARV) technology landscape*

Emerging ARVs could play a key role for treatment in resource-limited settings. Integrase inhibitors (INIs) are a new class of ARVs with the potential to simplify treatment regimens, although their optimal role in the management of HIV is still being determined. The INI dolutegravir (DTG), approved by the United States Food and Drug Administration (FDA) in August 2013, is a well-tolerated compound with a very high barrier to resistance and high potential for all age groups with production costs that may be lower than other treatment options due to relatively low dose (50 mg, once-daily dosing). A combination is in the pipeline with DTG and abacavir + lamivudine (ABC + 3TC); other potentially beneficial combinations need to be considered as well, including a combination with tenofovir: tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate (TAF). Studies of DTG with ritonavir (RTV)-boosted darunavir (DRV/r) are under discussion that could prove their role in second-line therapy and potentially co-formulated as a single full-regimen tablet. A number of paediatric trials are under way or planned and a granule formulation is in development.

TAF is currently in Phase III trials and would eventually replace TDF in all combinations. This is a watershed development as TAF has the potential to be dosed at levels up to 30 times lower than TDF, which

could dramatically improve its safety profile. Initial estimates suggest that the cost to manufacture TAF could be significantly lower than for TDF. It is critical that the potential for this compound is recognized in combination with different ARVs, and not only for the fixed-dose combinations (FDCs) currently in development by Gilead. As new trial data emerge and as products move closer to market, the place of these investigational ARVs in future treatment guidance should become clearer.

The ARV pipeline includes several other promising candidates that may emerge as treatment options over the longer term. Long-acting injectable ARVs, for example, might help increase adherence to treatment or be used as a preventive measure.

In order to improve their safety profile and reduce cost, a number of trials are evaluating the possibility of administering lower doses and optimizing the existing formulations of some key ARVs. For example, a recent study (ENCORE 1) found a 400 mg dose of efavirenz (EFV) to be non-inferior to the current 600 mg dose; if widely implemented, this lower dose has the potential to substantially reduce the drug's cost. However, this strategy still needs to be evaluated in special populations such as tuberculosis (TB) co-infected and pregnant individuals. Optimization activities also are planned or undergoing for protease inhibitors (PIs) such as atazanavir (ATV), DRV and RTV.

A number of new combinations, including DRV/r, are under development and could bring numerous advantages compared to existing products. A few formulations are under development for infants and young children, tailored to the needs of resource-limited settings, but more adapted formulations are needed to enable countries to adhere to the new WHO treatment recommendations.

ARV market landscape

The market for ARVs in low- and middle-income countries continues to grow, and it was worth an estimated US$ 1.53 billion in 2012. With roughly two thirds of people eligible for ART in low- and middle-income countries not currently receiving treatment, the potential for increased demand for ARVs is apparent; in 2012 alone, the ARV market in low- and middle-income countries grew by 33% (or 26% if some middle-income countries purchasing non-generic products are included as well in the estimations).

Nonetheless, despite people in low- and middle-income countries accounting for more than 90% of people receiving ART worldwide, the ARV market in those countries represents less than 10% of the monetary value of the global ARV market.

International donors, especially the United States and the Global Fund to Fight Aids, Tuberculosis and Malaria (Global Fund), continue to play important roles in financing the supply of ARVs, accounting for over 6.2 million person-years of treatment in 2012; however, domestic funding in low- and middle-income countries now accounts for a majority of total support for HIV-treatment and care expenditure (53%) according to the Joint United Nations Programme on HIV/AIDS (UNAIDS) Global Report 2013.

The ARV market is seeing consolidation on both the supply and demand sides, especially for donor-led procurement. Increasing volumes have continued to be channelled through the Global Fund Voluntary Pooled Procurement (VPP) mechanism, with nearly one third of all Global Fund-financed ARV procurement in 2012. The VPP mechanism uses the Partnership for Supply Chain Management (PFSCM), the same procurement agent as the United States President's Emergency Plan for AIDS Relief (PEPFAR) for the procurement of ARVs. As a result, by 2012, the procurement agency used until now by both the Global Fund and PEPFAR accounted for 35% of all ARV purchases in low- and middle-income countries. The recent evolution of procurement strategies at the Global Fund, with its increased direct role in the selection and contracting of manufacturers, will modify this situation.

Across the ARV market, a relatively small number of manufacturers are engaged in product development or sales for the market in low- and middle-income countries, effectively limiting competition. According to a recognized international index, Herfindahl-Hirschman Index (HHI), the market in low- and middle-income countries is highly concentrated. Generic manufacturers play a critical role, with generics accounting for 96% of all donor-purchased ARVs in 2012. The majority of ARVs used in low- and middle-income

countries are produced by generic manufacturers in India and four generic firms—Mylan Laboratories Ltd (hereafter Mylan), Hetero, Aurobindo, and Cipla Ltd—captured 85% of all donor-funded sales by 2012.

Since 2006, WHO has taken steps to radically simplify first-line regimens, with the 2013 guidelines recommending a once-daily one-pill FDC of TDF/3TC (or FTC)/EFV for all adolescents and adults, including pregnant women. By 2012, stavudine (d4T)-based regimens represented less than 20% of first-line regimens in use in countries, an 8% of donor-funded procurement volumes, while tenofovir-based regimens accounted for 35% of regimens in use in countries and 48% of reported volumes procured with donor funding.

Prices for the currently WHO-preferred formulations, the single-pill regimen including (TDF/3TC [or FTC]/EFV, with a lesser number of sources and demand, remain considerably higher than older combinations including AZT/3TC/NVP (US$ 128–140 versus US$ 99 per person per year). However, prices for TDF-triple ARV FDCs have seen a significant decrease on 2013 and are projected to continue to go down.

The share of the low- and middle-income countries' market devoted to second-line regimens remains marginal (4% in volume and 11% in value) compared with that of first-line regimens. While the price gap between first- and second-line regimens has declined, second-line regimens remain far costlier (at a minimum, doubling the first-line price), and the market is less competitive than the first-line ARV market. In addition, no single-tablet regimen is yet available for second-line therapy. Drug-drug interactions complicate treatment for HIV/TB co-infection, specifically in the case of second-line ART with PIs.

The current third-line market remains negligible, with procurement of treatments for less than one thousand people being reported with donor funds. Prices remain extremely high compared with first- and second-line regimens. The DRV price ranged from US$ 810 per person per year in 2012 in low-income countries in Africa, to more than US$ 13 000 per person per year in Georgia. The price reported for the full recommended regimen—DRV, RTV, raltegravir (RAL), etravirine (ETR)—ranged from US$ 2244 in Uganda to US$ 34 120 per person per year in Georgia, representing, at the lowest end, a 7–17 fold increase from second- and first-line, respectively.

The market for paediatric ARVs represents a mere 7% of the global ARV market. Demand for paediatric ARV formulations is likely to increase in coming years, as programmes work to address the unmet need for HIV treatment among children, including reinforcing diagnostic capacities for infants. In the longer-term, however, the market is likely to decline, as enhanced prevention efforts reduce the number of children who acquire HIV. Due to the limited size and heavy concentration of the paediatric market, prices for paediatric ARVs have not fallen to the same degree that drug prices for adults have declined.

Active pharmaceutical ingredients (API) market overview

APIs typically represent the most important element in the pricing of finished ARVs in the low- and middle-income countries' market. The cost of APIs includes expenses associated with raw materials, production costs, overhead and labour, and equipment and facilities.

Several strategies have been successfully applied to reduce the cost of APIs, by efficiencies on the production processes and procurement of starting materials, completing the economies sought with dose-reduction and reformulation strategies. Indeed, in recent years, important price decreases for key APIs, such as TDF and EFV, have been achieved. Additional reductions for high-volume products are not likely to emanate from economies of scale; the greatest opportunity for future price reductions will come from improvements to synthetic methods, dose reduction and, in some cases, reductions in the cost of starting materials.

The ARV API market is highly concentrated in China and India, and while there are regulatory mechanisms in place for quality control, the existence of different API markets depending on the degree of stringency of reviews, increases the risk of substandard API products moving into the international market. It is expected that in the near future the WHO Prequalification Programme for APIs, running since 2010, will establish a substantial base of WHO prequalified API vendors across the range of key ARVs; increasing the

number of APIs in the list will simplify and expedite prequalification of finished pharmaceutical products (FPPs), by reviewing the two main elements—good manufacturing practices (GMP) and specifications—of quality assurance for API sources.

Overall, the demand for first-line ART is not expected to outstrip global supply capacity of any single API. With the 2013 WHO guidelines, use of nevirapine (NVP) and zidovudine (AZT) is projected to decline, in favour of TDF and EFV. Demand for emtricitabine (FTC) is growing, in part due to large purchases of the drug by South Africa. The rapid rates of change in demand for EFV, TDF and FTC may create only short-term bottlenecks in supply for any of these ARVs, provided that manufacturers continue to increase production capacity for key ARVs, such as EFV.

Lopinavir (LPV) and RTV are becoming important products in the API market due to new paediatric WHO guidance recommending it for all children under 3 years old, and an expected increased market if in second-line use. With the current WHO recommendations for paediatric care, an increase in demand for ABC API is expected, but supply appears to be adequate to meet anticipated needs.

Several companies have filed Drug Master Files (DMFs) with the FDA for DRV and for ATV. Due to the current low volume demand (less than 10 metric tonnes), substantial unused production capacity exists for these products. The ATV API cost is potentially lower than LPV, and the price should come down with increased demand. DRV demand is currently quite low, due to its current high cost and the unavailability of a DRV combination formulation with RTV as boosting agent.

Licenses have been granted and DMFs submitted for a number of newer ARV APIs, including rilpivirine (RPV), elvitegravir (EVG) and RAL, and for the booster cobicistat (COBI), although it is presently not possible to anticipate when or even if these products will become part of established ART in low- and middle-income countries.

Intellectual property issues for key ARVs

Patents are increasingly becoming a barrier to access to ARVs. The patent situation regarding several of currently used ARVs is complex in a number of low- and middle-income countries, especially with regard to PI FDCs, such as LPV/r or ATV/r. However, promising new and emerging products appear to be more widely patented, including in countries with significant production capacity, such as China and India as well as in a greater number of low-income countries. Patents on most new and emerging medicines will still remain in force for the next decade, and in some cases even longer.

It is noteworthy that a patent on just one drug in a two- or three-drug FDC, or a secondary patent on the combined formulation, can pose barriers for accessing a new generic FDC and, therefore, increase the pill-burden and complexity and cost to logistics of the territories where the generic cannot be purchased. Patents related to the FDC formulation can expire a long time after the individual patents on the drugs, such as in the case of combination of PIs with RTV.

Voluntary licenses can be an important means of overcoming patent barriers, but usually do not include all low- and middle-income countries and clear information about bilateral licenses is not readily available. An increasing number of pharmaceutical companies are entering into licensing agreements with the Medicines Patent Pool (MPP), and efforts to extend the benefits of such pro-public health licenses must continue. To date, no voluntary licenses have been granted for some important products, notably LPV, RTV and their combinations. The same is true for key new emerging products such as TAF and DTG, for which the MPP have already entered into negotiations of licenses that could benefit many low- and middle-income countries.

At the same time, new barriers that hamper generic competition, such as data exclusivity, are emerging. By providing originator companies exclusive rights over registration data, data exclusivity delays the registration, and thus the use, of generic medicines.

ARV market shortcomings

While interventions in the ARV market over the last decade have resulted in profound market and public health impact, numerous market shortcomings persist that limit access to this life-saving treatment. Current shortcomings in the ARV market are summarized below. A detailed discussion of the factors contributing to these shortcomings is provided in Section 6 of this report: Market shortcomings and their reasons. Common shortcomings are listed first; shortcomings related to specific regimens (i.e. first-line, second-line, third-line and paediatric) are noted in bold.

Availability	■ No ideal ART regimen exists for use in low- and middle-income countries. ■ **Paediatric therapy:** A long lag time exists between approval of adult and paediatric formulations, as paediatric clinical trials are typically launched long after adult trials. Few ARVs are approved for use in children, especially under two years old (only 10 out of 29 ARVs approved for adult use).
Adaptability	■ Few adequate formulations are available for resource-limited settings. When new products emerge, they do so long after approval of newer ARVs in high-income countries (e.g. FDA approved DRV in February 2008, but it is not yet marketed in co-formulation with the booster RTV to support its greater use). ■ When improved dosage forms or combinations are only available as generics, patent status in some countries and complexity in companies' licensing strategies can impede use of the best-adapted formulations (e.g. ATV/r, TDF/3TC/EFV, infant-friendly combination of LPV/r). ■ **Second- and third-line therapy:** no single-tablet regimen exists; PI options are limited by the absence of DRV/r heat-stable FDC. ■ **Second-line therapy in TB co-infected patients:** Limited options exist for second-line treatment while on TB first-line treatment; existing options carry increased cost and pill burden. ■ **Paediatric therapy:** Few child-friendly formulations exist, making implementation of WHO treatment recommendations a challenge and perpetuating the use of less efficient (e.g. NVP-based regimens) or more toxic (e.g. d4T-based regimens) treatments.
Affordability	■ Although sharp reductions in ARV prices have enabled a dramatic expansion of ART over the past decade, affordability remains a challenge, especially for newer drugs. ■ For emerging products, a high level of prices (e.g. DTG price for the United States market is over US$ 14 000 per person per year). ■ **First-line therapy:** Current preferred options are more expensive than their predecessors. Despite recent reductions in prices of TDF-triple FDCs (20% decrease in the first six months of 2013), the difference with AZT-triple FDCs remains substantial (23% cheaper than the lowest price reported for TDF-triple FDCs). An even greater difference (55%) exists compared with d4T-triple FDC regimens that were previously used widely in low- and middle-income countries. In addition, up to mid-2013, the combination treatment with TDF, 3TC and EFV was up to US$ 40 more expensive as a single-tablet than two separate tablets. ■ **Second-line therapy:** Lowest price available is at least double that of first-line treatments. A higher price premium exists where generics cannot be purchased (e.g. LPV/r is priced at US$ 740 per year per person by AbbVie for some low- and middle-income countries; generic products elsewhere are priced at US$ 215 per person per year). ■ **Third-line therapy:** According to reports from the small number of low- and middle-income countries that have used Global Fund resources to purchase third-line regimens, prices range between almost US$ 2500 per person per year in low-income countries to over US$ 30 000 in middle-income countries. ■ **Paediatric therapy:** Recommended first-line therapy for infants is twice the annual cost of the first-line regimen for adults (TDF-based regimen is US$ 250–350 per person per year for infants compared to US$ 128–140 per person per year for adults).
Quality	■ Risk of substandard quality products gaining greater market share as treatment is scaled up. ■ **Paediatric therapy:** Regulatory approval pathways are complex for paediatric products and combinations.
Delivery	■ Temporary risk of supply shortages after changes in treatment recommendations, especially in small-volume countries (e.g. lead time for TDF-triple FDCs increased in 2013 as a consequence of changes in WHO treatment guidelines). ■ **Paediatric therapy:** Limited uptake and coverage (only a fraction of children in need receive ART). Few children are initiated on HIV treatment prior to 18 months old as recommended.

UNITAID interventions in ARV market to date

From its inception, UNITAID has supported ARV-related market interventions and has worked with stakeholders at the international and national levels to address ARV market shortcomings.

UNITAID interventions in ARV market to date

(implementing partner noted in parentheses)

Previous UNITAID interventions:

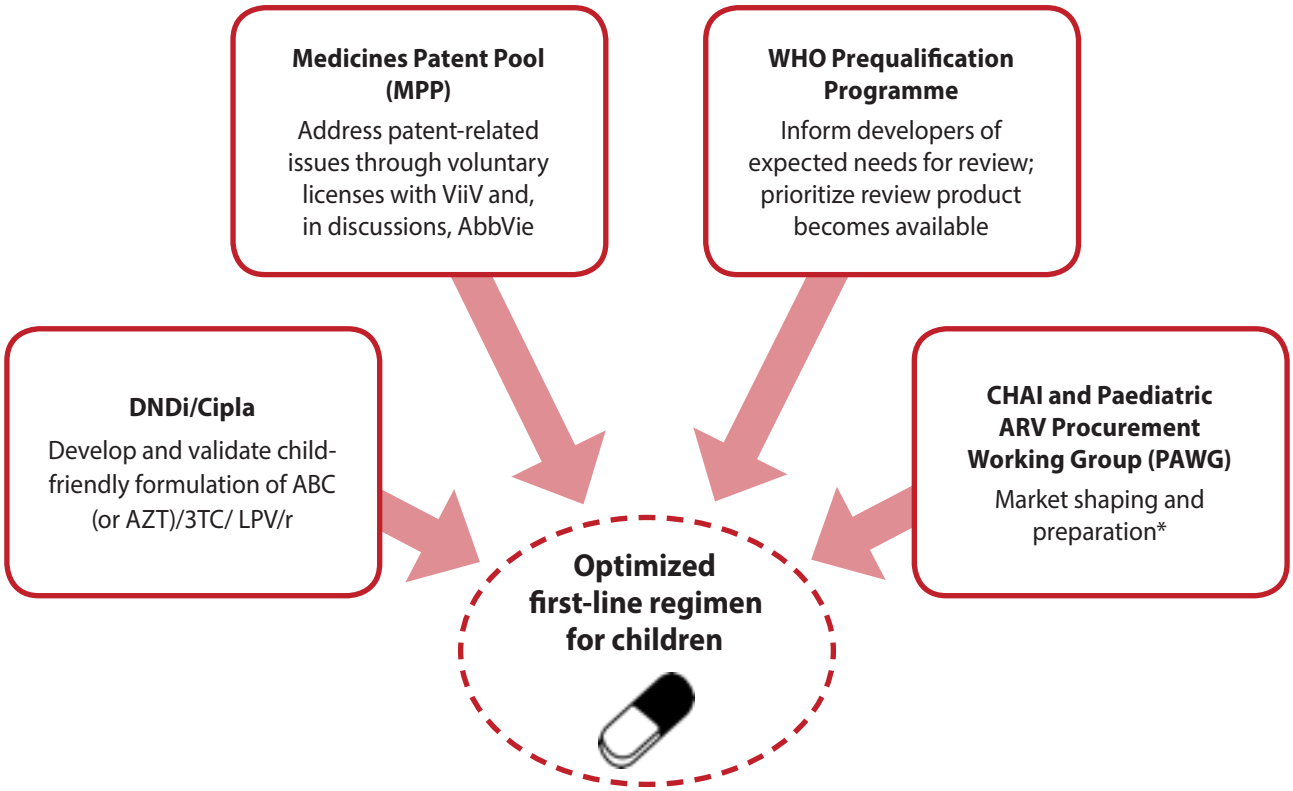
- improved access to HIV medicines for children (CHAI);
- catalysing the market for adult second-line medicines (CHAI);
- acceleration of Prevention of mother-to-child Transmission and Scale-up of Linkages to Paediatric HIV Care and Treatment (UNICEF and WHO).

Active and recently approved initiatives:

- market intelligence for APIs (William Davidson Institute);
- Medicines Patent Pool (MPP Foundation);
- preventing patent barriers in India (Lawyers Collective);
- development of child-friendly LPV/r FDCs and RTV booster (DNDi);
- innovation in ARV paediatric market access and continued ARV supply to children in Malawi, Mozambique and Uganda (CHAI);
- WHO Prequalification Programme.

UNITAID takes a comprehensive, multipronged approach to addressing market shortcomings in HIV-treatment markets. The figure below represents the UNITAID current integrated approach to shaping the paediatric ARV market in order to enable access to an optimized first-line regimen for children.

UNITAID integrated approach to shaping the paediatric first-line treatment market



*Market shaping and preparation intervention will maintain and update forecasting and continuously engage with manufacturers; support improved quantification at the country level; coordinate market space to ensure aggregation of volumes and purchasing power; ensure funding for procurement in countries not yet transitioned to other donors' funding (Malawi, Mozambique and Uganda).

Potential opportunities for ARV market interventions

Today's preferred treatment options and pipeline products require the support of new market-based interventions to attain global treatment and prevention goals. Potential interventions to increase access to ARVs can build on and leverage complementary interventions, such as those aiming to increase use of appropriate diagnostic and monitoring tools.

New opportunities for intervention to alleviate persistent shortcomings identified In the ARV treatment market are presented below. A combination of market-based approaches is generally needed, extending across market segments (e.g. adults and children), and different elements of the development and supply chain (e.g. APIs and FPPs). Section 7 of this report (Potential market interventions) provides detailed examples of the specific activities that may be conducted to take advantage of each opportunity listed below.

- Promote timely approval and access to optimal ARV regimes through early engagement and support of manufacturers and product development partnerships (PDPs), and promote further innovation by introducing reward mechanisms for optimized formulations.
- Promote market for optimized products by supporting transition from older regimens or formulations, through catalytic purchases, and payment of initial price premium associated with newer products.
- Reduce uncertainty for purchasers and manufacturers by improving ARV demand forecasting. This would enable more efficient production planning, APIs sourcing and investments in manufacturing capacity, minimizing supply vulnerability during transition to newer regimens.
- Address patent issues likely to affect the development and/or use of optimized FDCs and formulations.
- Lower the cost of production by supporting investments to increase efficiencies in synthetic and processing methods of key ARVS with potential for cost reduction.
- Consolidate demand for quality-assured products to avoid market fragmentation and unsustainable price-pressure for quality-assured products.

In addition, there is an overarching need to improve market intelligence systems to ensure adequate monitoring of marketing interventions to ascertain their impact and adapt them as needed to improve their effectiveness.

1 Introduction and methodology

UNITAID supports market-based interventions to improve access to medicines, diagnostics and preventive commodities for HIV, tuberculosis (TB) and malaria. To help identify market-based interventions, UNITAID analyses the market surrounding commodities of interest. These analyses, or landscapes, highlight critical market shortcomings, the underlying reasons for market failures and potential approaches to correcting them.

This landscape of antiretroviral (ARV) medicines examines existing regimens and treatment recommendations as well as emerging and future HIV-treatment technologies. This report aims to inform grant decision-making by the UNITAID Executive Board and its committees. It also seeks to serve as a resource for other stakeholders, global health organizations, implementers and country-level HIV programmes. The UNITAID HIV Diagnostics Technology Landscape and HIV Preventives Landscape complement this report.

This landscape has been developed from primary sources (e.g. interviews with technology developers; targeted analyses where needed) and extensive review of secondary sources (e.g. published literature; WHO reports; product developer websites; and publicly available procurement data). Data and analysis current as of the fourth quarter of 2013.

Public health problem and commodity access: These introductory sections review the HIV burden, summarizing the most recent data published by partner institutions, including the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS), and highlight the most critical issues associated with HIV treatment in low- and middle-income countries. It was prepared with support from B. Kaiser and K. Martin (UNITAID).

Technology landscape: Section 4 describes current treatment approaches, current status of the HIV medicines pipeline and strategies to optimize existing ARVs. It was prepared by P. Clayden (i-base), with support from UNITAID, as an update of the report HIV Medicines and Pipeline: Overview, 2012. Attendance at several important meetings helped inform this section, including the 2013 Conference on Retroviruses and Opportunistic Infections, the second Conference on Dose Optimisation and the PENTA Investigators meeting 2013. Interviews with trial investigators and companies, a review of the United States clinical trials registry (clinicaltrials.gov) and the United States National Library of Medicine (pubmed.gov) as well as company press statements contributed to this landscape. Information summarized and updated from the Pipeline Report (co-authored by P. Clayden, and published annually by i-Base/TAG) was a key source of information for this section; several other sections also summarize and update information from the Pipeline Report and should be consulted for further detail.

Market landscape: Section 5 overviews the current ARV market, examining the supply, demand, patent issues and price trends for finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs).

FPP analysis: P. Aylward and C. Pérez Casas prepared the market analysis with critical input from M. Auton (Global Fund). A database was generated of donor-funded ARV transactions in low- and middle-income countries, standardizing and merging information from purchase transactions obtained directly from the Voluntary Pooled Procurement (VPP) mechanism of the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and the Price and Quality Reporting System as well as the Supply Chain Management System (SCMS) and UNITAID-funded project reports. Duplicates and records with null or negative product quantities were removed from the database. The resulting dataset, which contained 32 820 records valued at over US$ 4.02 billion, was enriched with additional fields, including the World Bank historical income classifications, daily defined dose (per Médecins sans Frontières [MSF] Untangling the Web of Antiretroviral Price Reductions) and Global Fund grant data. Information on ARV approvals also was collected from the WHO Prequalification site and the FDA site, detailing approvals for use in the United States President's Emergency Plan for AIDS Relief (PEPFAR). The market analysis discusses ARV usage and costs in person-years where annual volume (in person-years) is equivalent to the total number of tablets purchased for 365 daily doses and annual costs (per person-year) equals the reported cost associated with an annual volume per patient.

API analysis: Professor J. Fortunak (Howard University, United States) prepared the API market analysis with support from UNITAID. Development of the analysis included consultation with key informants in the API industry (e.g. API manufacturers; vendors that produce advanced intermediaries for APIs; FPP vendors that purchase APIs; product development partnerships (PDPs) that focus on ARV development) as no comprehensive system or uniform methodology is in place to monitor API market patterns. In addition to WHO prequalified API producers, the analysis took into account information on APIs from companies holding Drug Master Files (DMFs) referenced in PEPFAR and WHO applications since many vendors still rely upon this process. Although useful information was derived from interviews with company representatives, some ARV API producers are now willing to provide relevant data. In addition, strategic information on API production capacity, including from the Clinton Health Access Initiative (CHAI) ARV Market Report, and information collected by the United States Agency for International Development (USAID) and the Partnership for Supply Chain Management (PFSCM) was taken into account.

Intellectual property issues for key ARVs: The analysis was prepared by K. Timmermans, with support from C. Pérez Casas, and provides an overview of the possibilities of different low- and middle-income countries to manufacture, import or use the most adapted formulations for the recommended ARV therapy regimens per the latest 2013 WHO treatment guidelines. It draws on information from the forthcoming Patents and licenses on ARVs: a snapshot, prepared by the Medicines Patent Pool (MPP) and UNITAID, and data from the MPP online document Patent Status Data-base of Selected HIV-Medicines.

Market shortcomings and market interventions: These sections review the current market challenges and the reasons behind these challenges for HIV treatment, and explore potential opportunities to intervene and shape the markets to alleviate the identified shortcomings.

Overall coordination of this report was undertaken by C. Pérez-Casas, UNITAID, and edited by M. Isbell and R. Ridzon, Ahimsa Group.

2 Public health problem

HIV remains one of the world's most serious health challenges. In 2011 (the latest year for which information is available), HIV was the world's sixth leading cause of death and the second most important cause of death in low-income countries *(1)*.

HIV/AIDS burden: Globally, 35.3 million people were living with HIV (PLWH) in 2012; a 17.7% increase since 2001. New infections and deaths, however, are both decreasing. In 2012, there were 2.3 million new infections worldwide (a 33% decrease since 2001) and 1.6 million deaths (a 30% decrease since the 2005 peak). Although global gains are encouraging, progress has been uneven. New infections continue to increase in Central Asia, Eastern Europe, the Middle East and North Africa, and AIDS deaths have not significantly declined in these regions. In addition, there are causes for concern regarding the sustainability of public health advances, including recent increases in sexual risk behaviours detected by national household surveys in several high-prevalence countries that had previously reported prevention gains *(2)*.

Sub-Saharan Africa remains the most heavily affected, with the largest number of PLWH (25 million), accounting for 70.8% of the global HIV burden and 75% of the HIV-related deaths *(2)*. Low-income, lower-middle-income and upper-middle-income countries, according to World Bank classifications, have the highest burden of HIV, together accounting for 92% of PLWH (36%, 26% and 30%, respectively) in 2011.

New HIV infections in children have decreased 52%, since 2001, to 260 000 in 2012 *(2)*. In 2012, 3.4 million children under 15 years old were living with HIV *(3)*. Without treatment, 33% of HIV-infected infants die by 12 months old and 50% by 2 years old *(4) (5)*.

Co-morbidities (co-infections and opportunistic infections, cancers and other diseases): HIV-related immunosuppression increases vulnerability to a number of potentially life-threatening opportunistic infections and cancers. In 2012, 1.1 million PLWH developed TB, accounting for 13% of all TB cases worldwide. Although it remains the leading cause of death among PLWH, TB-related deaths declined by 36% among PLWH from 2004 to 2012 *(6)*. Antiretroviral therapy (ART) reduces the risk by 65% that a person living with HIV will develop TB *(7)*; collaborative HIV/TB treatment averted an estimated 1.3 million TB-related deaths among PLWH in 2005–2012 *(2)*. Hepatitis B infection affects 2–4 million PLWH, while hepatitis C affects 4–5 million PLWH; both of which may increase the risk of liver damage and liver failure in PLWH *(8)*. Based on experience in high-income countries, it could be assumed that further expansion of ART in low- and middle-income countries would lower the incidence of opportunistic infections and HIV-related cancers.

Emerging resistance to ARVs: The emergence of HIV drug resistance could compromise the effectiveness of scaling up ART, especially in resource-limited settings. According to surveys, the prevalence of resistance to any ARV among people starting ART has increased from 4.8% (3.8–6%) in 2007 to 6.8% (4.8–9.0%) in 2010 in low- and middle-income countries *(6)*. In Uganda, a very high prevalence of resistance (11.6%) has been reported *(9)*. Based on available evidence, WHO projects that rates of drug resistance may increase.

The prevalence of transmitted drug resistance is still below 10% in all resource-limited settings studied *(10) (11)*, although available data could suggest that there is an association between higher levels of coverage of ARVs and increased prevalence (a study in Uganda indicated that each year of ART scale-up is associated with a 38% increase in the prevalence of drug resistance) *(6)*.

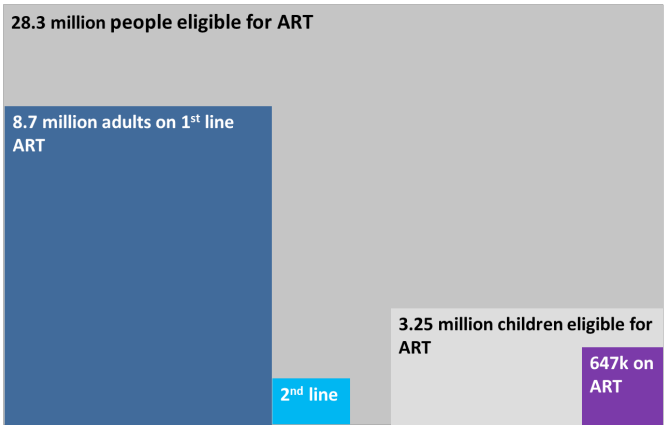
The prevalence of acquired drug resistance (developed during the course of ART) and treatment failures is low, especially during the first year of treatment. However, around two thirds of PLWH who experience treatment failure on a first-line regimen are likely to have infection with a virus that exhibits some type of drug resistance *(6)*.

3 Commodity access issues

Table 1: Treatment access and unmet needs in low- and middle-income countries at the end of 2012

Global access	**Coverage: 34% (9.7 million individuals on ART)**
	Unmet needs: 18.6 million people eligible for, but not yet receiving ART
	Median CD4 count at start of ART: below 200 cells/mm^3
	Second-line ART: 4% of people receiving ART (over 20% in the Americas region and other areas with access to viral load)
Children	Coverage: estimated at 20% (647 000 children on ART)
	Unmet needs: 2.6 million children eligible for, but not yet receiving ART
Pregnant women	62% of pregnant women received ART during pregnancy or delivery for prevention of HIV transmission to the newborn; 49% received ART during breastfeeding

Figure 1: Estimated treatment access and unmet needs for adults and children in low- and middle-income countries, end 2012

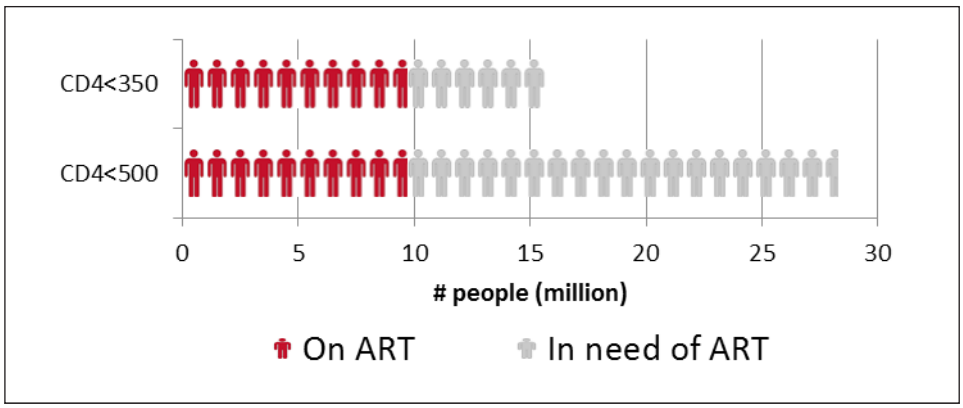


While reducing morbidity and mortality among PLWH remains the primary purpose of ART, HIV treatment also has the important secondary benefit of lowering the risk of HIV transmission (including the associated risk of transmission of drug-resistant strains of HIV). A large multisite randomized trial (HPTN 052) found that ART reduces the risk of HIV transmission by 96% among serodiscordant couples *(12)*, and recent experience has confirmed that ART scale-up is associated with substantial population-level reductions in HIV incidence *(13)*. The WHO Consolidated Guidelines for the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection *(14)*, released in June 2013, recommended earlier initiation of ART. These new guidelines increase the CD4 cell threshold for initiation of ART in most PLWH from 350 to 500 cells/mL,[1] and call for ART initiation regardless of CD4 count for certain populations (e.g. pregnant women; children under 5 years old; HIV-infected partners in serodiscordant couples; people with HIV-related TB and hepatitis B).

1 The CD4 cell count (the number of CD4 immune cells per cubic millilitre of plasma) is the standard measurement for HIV-related immune system deterioration.

As shown in Figure 2, almost 29 million people are eligible for ART with these current guidelines, nearly double the treatment target under the prior 2010 guidelines *(15)*. In 2012, 9.7 million people were being treated with ART (7.5 million on the African continent).

Figure 2: Comparison of the number of people receiving ART and those in need (based on current and previous WHO-recommended treatment guidelines)



Adult therapy: In low- and middle-income countries, ART is often initiated late in disease progression, with 20–40% starting ART with a CD4 below 100 cells/mL *(16)*; five times lower than currently recommended. Furthermore, some PLWH who initiate ART may not receive recommended regimens. Although WHO has worked to simplify regimens by sharply reducing the number of recommended first-line regimens, a median of 10 different first-line regimens were in use in 2012 among countries surveyed by WHO *(6)*.

Many countries, as first recommended by WHO in 2009, have switched patients in recent years to regimens that do not include stavudine (d4T) and yet, globally, an estimated 1.7 million people were receiving d4T-based ART regimens in 2012 *(17)*, 20% of all the adults on first-line ART according to a WHO survey *(18)*. Patients who take d4T are at risk of severe, disfiguring and life-threatening side-effects, including lipodystrophy (affecting 24–68% of patients) *(19) (20)*; peripheral neuropathy affects 31–56% of patients on d4T *(19)*; and lactic acidosis, which, while less common in resource-limited settings (< 2%), is associated with extremely high risk of mortality (15–30%) *(21) (22) (23) (24)*. Individuals receiving d4T-based regimens are up to six times more likely to switch regimens compared to those on tenofovir disoproxil fumarate (TDF)-based regimens *(6)*. Most countries are now concluding their transition to other first-line regimens.

WHO estimates that 3.6% of adult patients were on second-line regimens by the end of 2012 *(18)* (excluding Latin American countries where the proportion is higher), although this rate of utilization may not reflect actual need *(25)*. Data from more mature ART programmes and where viral load monitoring is available (e.g. South Africa), suggest that up to 14% of individuals fail first-line therapy within five years of ART initiation and need to be switched to second-line therapy *(16)*. It is expected that the number of people on second-line regimens in low- and middle-income settings will increase as viral load testing capacity increases *(14)*.

Access to third-line regimens is poorly documented, but considered to be extremely limited in low- and middle-income countries. Based on the limited available data in transactional databases, in 2012 donor-supported purchases of typically recommended third-line ARVs—darunavir (DRV), ritonavir (RTV), raltegravir (RAL), etravirine (ETR)—were equivalent to less than 1000 person-years.

Prevention of mother-to-child transmission of HIV: An estimated 58% of pregnant women eligible for ART under the earlier 2010 WHO guidelines received ART for their own health in 2012, compared to 65% coverage for adults generally. In the 21 African countries where more than 90% of cases of mother-to-child HIV transmission occur, 65% of pregnant women living with HIV received ART in 2012 to prevent transmission to newborns *(6)*. The provision in the new 2013 WHO guidelines recommend-

ing lifelong ART for all HIV-positive pregnant women (regardless of CD4 count) has increased the need for ART by 700 000 women *(6)*.

Paediatric care: Globally, 35% of infants born to HIV-positive pregnant women received a first early infant diagnostic test between 4–6 weeks old in 2012 *(6)*. Even fewer infants have repeat testing, while the proportion of postnatal transmissions is increasing. In addition, the majority of children who test HIV-positive do not return for their results *(26)*. Even with virological testing, only 30% of HIV-positive infants are promptly referred for the initiation of ART *(6)*. Overall, while access to ART among children is increasing, the coverage increase for children (11% in 2012) is much slower than for adults (21% in 2012) *(6)*. Although an updated global estimate of access is not yet available, it is known that 2.6 million children eligible for ART were not yet receiving it at the end of 2012 *(27)*, while only 647 000 children were on ART *(2)*.

4 Technology landscape

4.1 General background

Current treatment options have saved millions of lives. However, better alternatives are needed due to toxicities and monitoring requirements associated with current treatment options. Alterations of current treatment approaches, such as lower dosing to improve tolerability and fixed-dose combinations (FDCs) to improve adherence, may help address some of the limitations of current treatment options. Nevertheless, new drugs with a superior toxicity profile over drugs currently available will be needed. Toxicity and tolerability will be increasingly critical as indications for treatment broaden and more asymptomatic people with HIV are offered ART.

As described in Table 2, an ideal ARV regimen is safe, effective, tolerable and durable "so that the need for switching to a new regimen would be very rare" *(28) (29) (30)*. Unfortunately, no such regimen currently exists.

Table 2: Target product profile of an ideal ARV regimen

Safe and effective	Superior or equivalent to currently recommended drugs.
Tolerable	Minimal toxicity and side-effects.
Durable	High genetic barrier to resistance. Low PK variability. Forgiving of missed doses. Tolerable for easier adherence.
Universal	Safe and effective across all CD4 strata; in people with high viral load; in men and women; during pregnancy; across age groups and with common co-infections such as TB or viral hepatitis.
Affordable	Low intrinsic and production cost.
Simple	Convenient to use. Possible to be given in decentralized facilities or in community settings. One pill once a day (less frequently might be possible in the future). No lead-in dosing or dose adjustments when given with other common medicines. Heat-stable. Shelf life of two or more years.

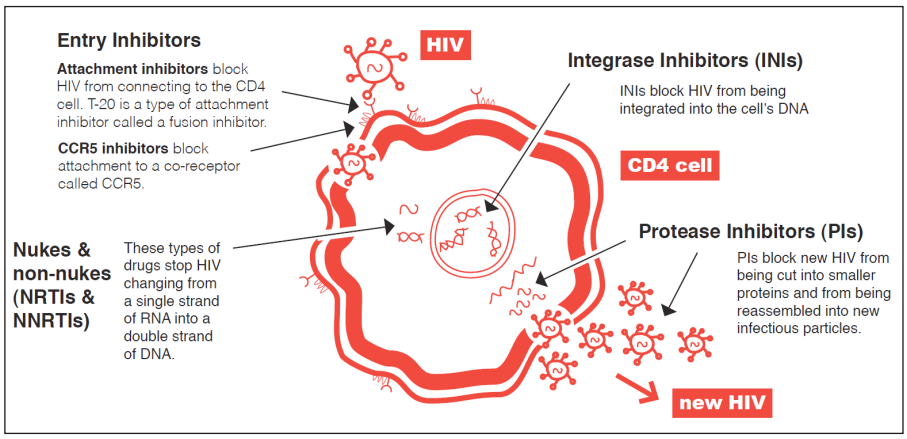
The following section reviews presently available ARVs, and describes strategies to improve their use in resource-limited settings. It also describes products in development that may improve treatment access or have a substantial effect on treatment recommendations.

4.2 Current products

4.2.1 Overview of ARV products

There are five main classes of ARVs, with each affecting a different stage of the HIV lifecycle: nucleoside (and nucleotide) reverse transcriptase inhibitors (NRTI/NtRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs); integrase inhibitors (INIs); and entry inhibitors, including different subclasses such as fusion inhibitors or attachment inhibitors (CCR5) antagonists (Figure 3). ART requires a combination of different ARVs, usually including three active drugs. In resource-limited settings, treatment programmes typically prescribe combinations with two NRTI/NtRTIs and one NNRTI. PIs are used in second-line (and more rarely first-line) regimens for adults and adolescents, but in first-line regimens for infants *(31)*.

Figure 3: HIV lifecycle—how ARVs target different stages



Until recently, only one single-agent drug, RAL, was approved in the newer INI class, but to date this drug has seldom been used due to cost constraints. It is occasionally available for use in third-line regimens. In 2012, another INI (elvitegravir/EVG), in a co-formulation with other ARVs (FTC and TDF, and the booster cobicistat/COBI) was approved by the FDA (co-formulation formerly known as Quad, now as Stribild), but also is not recommended as a preferred option, and its high price has further limited its use. On 12 August 2013, the FDA approved a third single-agent INI, dolutegravir (DTG), which has great potential for use in low- and middle-income countries.

Entry inhibitors, such as maraviroc (MVC) (CCR5 inhibitor), are rarely used. Enfuvirtide (T-20) is reserved for a small number of people infected with an extremely drug-resistant virus *(32)*.

4.4.2 WHO-recommended ARV regimens

The 2013 WHO consolidated guidelines revised and combined recommendations on the use of ARVs for HIV treatment and prevention across all age groups and populations (Table 3). The guidelines emphasize safer, simpler, affordable first-line regimens, specifically recommending use of single-tablet regimens. The 2013 guidelines made no major changes with respect to recommended second- and third-line regimens.

Table 3: 2013 WHO-recommended first-line ARV regimens (14)

First-line ART	Preferred first-line regimens	Alternative first-line regimens
Adults	TDF+3TC+EFV TDF+FTC+EFV	AZT+3TC+EFV AZT+3TC+NVP TDF+3TC (or FTC)+NVP
Adolescents (10–19 years old) ≥35 kg		AZT+3TC+EFV AZT+3TC+NVP TDF+3TC (or FTC)+NVP ABC+3TC+EFV (or NVP)
Children (3–9 years old) and adolescents <35 kg	ABC+3TC+EFV	ABC+3TC+NVP AZT+3TC+EFV AZT+3TC+NVP TDF+3TC (or FTC)+EFV TDF+3TC (or FTC)+NVP
Children <3 years old	ABC+3TC+LPV/r AZT+3TC+LPV/r	ABC+3TC+NVP AZT+3TC+NVP

Table 4 summarizes ARVs currently recommended by WHO for ART in adults and adolescents and are consequently more frequently used in resource-limited settings. Other ARVs previously recommended by WHO—notably d4T and didanosine (ddI)—are no longer recommended and are not described here.

Table 4: WHO-recommended ARVs for adults and adolescents

Compound	Class	Year of approval –adult use, FDA	Manufacturer of originator product	Comments
3TC	NRTI	1995	ViiV Healthcare	Recommended for first- and second-line. Interchangeable with FTC.
FTC	NRTI	2003	Gilead	Recommended for first- and second-line. Interchangeable with 3TC.
ABC	NRTI	1998	ViiV Healthcare	Alternative first-line for adolescents.
AZT	NRTI	1987	ViiV Healthcare	Alternative for first-line regimens. Recommended second-line (unless used for first-line).
TDF	NtRTI	2001	Gilead	Recommended for preferred first-line regimen(second-line if not used in first-line).
EFV	NNRTI	1998	Merck	Preferred NNRTI in first-line.
NVP	NNRTI	1996	Boehringer Ingelheim	Alternative to EFV in first-line.
ETR	NNRTI	2008	Janssen	Recommended for third-line.
ATV	PI	2003	BMS	To be used with booster.
LPV	PI		AbbVie	To be used with booster.
DRV	PI	2006	Janssen	Recommended for third-line. Alternative to second-line. To be used with booster.
RTV or r	PI	1996	AbbVie	Recommended as booster for PIs.
RAL	INI	2007	Merck	Recommended for third-line.

In addition, as shown in Table 5, a number of products exist that combine ARVs, although the availability of single-tablet regimens formulations of regimens recommended by WHO are currently limited to first-line treatment.

Table 5: Co-formulations of WHO-recommended ARVs: FDCs and co-packs

Compound	Class	Year of approval – adult use	Manufacturer of first product approved by FDA/WHO prequalification	Comments
Single-tablet regimens				
TDF/FTC/EFV	NtRTI/NRTI/ NNRTI	2006	Gilead BMS	Preferred first-line regimen.
TDF/3TC/EFV	NtRTI/NRTI/ NNRTI	2009	Mylan	
AZT/3TC/NVP	2 NRTI/NNRTI	2006	Aurobindo	Alternative first-line regimen.
Regimen co-pack				
AZT/3TC + EFV co-packaged	2 NRTI/NNRTI	2006	Aurobindo	Alternative first-line regimen.
Dual combinations				
TDF/FTC	NtRTI/NRTI	2004	Gilead	Preferred first-line backbone.
TDF/3TC	NtRTI/NRTI	2008	Cipla	
AZT/3TC	NRTI/NRTI	1997	ViiV Healthcare	Alternative first-line backbone.
ABC/3TC	NRTI/NRTI	2004	ViiV Healthcare	Alternative first-line backbone for adolescents.
ATV/r	bPI	2011	Mylan	Recommended for second-line.
LPV/r	bPI	2000	AbbVie	Recommended for second-line.

First-line regimens

For adults and adolescents, WHO recommends an NNRTI-based first-line regimen. The preferred option is the combination TDF/3TC (or FTC)/EFV formulated as a once-daily FDC. This option brings first-line treatment recommendations for resource-limited settings much closer to current practice in high-income countries, where once-daily TDF/FTC/EFV is the most frequently used first-line regimen.

A recent systematic review found that lamivudine (3TC) and emtricitabine (FTC) are largely interchangeable in terms of efficacy and safety *(24)*. Both are NRTIs and structurally similar, have low toxicity and are effective against the hepatitis B virus. Historically, as a result of market reasons, the use of 3TC has been greater than that of FTC as described in Section 5 of this report.

Accumulated evidence has helped alleviate earlier concerns regarding use of efavirenz (EFV) during pregnancy, with the new 2013 WHO guidelines adopting the more permissive approach that also is now recommended by such bodies as the British HIV Association *(33) (34)*. One practical concern with this recommendation is that the EFV label still states that the drug should be avoided during pregnancy, which could create confusion. The biggest shortcoming with EFV is its association with neuropsychiatric adverse events, reported to lead to drug discontinuation in 60% of people using the product according to a Danish study (compared to 3% receiving a non-EFV-based regimen) *(35)*.

TDF has been associated with renal toxicity, but the clinical importance and magnitude remains uncertain. Renal monitoring is advisable for people at high risk, although optimal monitoring parameters are unclear. Detailed information on toxicities and monitoring requirements of each of the current first-line ARVs can be found in the 2013 WHO guidelines *(14)*.

Second-line regimens

WHO recommends that second-line regimens combine a boosted, heat-stable, PI with double-NtRTI backbone. Second-line regimens are not yet available in a convenient single-tablet regimen, which is a challenge to formulate given the current high dose recommended for the PIs.

As a result of the work of CHAI through the UNITAID-funded Adult Second-Line HIV/AIDS Project, a heat-stable formulation of ATV/r was approved by the FDA in 2011 *(36) (37)*. This was the first alternative to lopinavir/ritonavir (LPV/r), and compares favourably to it, with fewer tablets and less frequent dosing (ATV/r 300/100 mg requires one pill once daily, while LPV/r 200/100 mg requires four pills per day, once or twice daily). Mylan Laboratories Ltd (hereafter Mylan) also has developed a two pill, once daily, co-packaged regimen of ATV/r with TDF/3TC, which is not yet approved by the FDA or prequalified by WHO.

The 2013 WHO treatment guidelines acknowledge the potential role of DRV in second-line therapy, but do not yet include it as the preferred option due to the high price and lack of FDC with the booster RTV. Several generic manufacturers are working to develop a heat-stable DRV/r tablet, but timelines for its marketing are unknown.

Third-line regimens

WHO recommendations are less clear with respect to third-line regimens, which remain extremely limited in low- and middle-income countries. Suggested regimens include newer drugs such as INIs (e.g. RAL) and second generation NNRTIs (e.g. ETR) combined with boosted protease inhibitors (bPIs) (e.g. DRV/r). However, these newer drugs are all extremely costly and lack either generic versions or have generic versions only recently entering the market.

Concurrent treatment of HIV and TB

Potential drug-drug interactions complicate treatment for HIV/TB co-infection, specifically in the case of second-line ART with PIs.

The rifamycin class of TB drugs (e.g. rifampicin, rifabutin and rifapentine) induces hepatic enzymes, which can lower blood concentrations of other drugs that use this metabolic pathway, including several ARVs *(38)*. Rifampicin is the most commonly used of the rifamycins and is a component of standard first-line TB treatment; however, it also is a potent enzyme inducer.

PIs and rifampicin are affected by drug-to-drug interaction, as rifampicin dramatically reduces the blood concentration of PIs. No currently available option to address this interaction is optimal. Replacing rifampicin with rifabutin allows use of all bPIs (LPV, ATV or DRV) although this approach increases the number of pills needed for TB treatment and doubles its cost (US$ 3060 for six months TB treatment) *(39)*. Increased pill burden for TB treatment, in the absence of adequate FDCs, could reduce TB treatment adherence, undermining the WHO global TB strategy. If rifabutin is not available, and rifampicin needs to be used, the 2013 WHO guidelines suggest using LPV/r for the duration of TB treatment, with an increased RTV boosting dose or a double dose of LPV/r, hence increasing cost and pill burden of the ART treatment and limiting choices as ATV cannot be similarly boosted.

Paediatric regimens

ARV options for children depend on age and weight, and whether an approved paediatric indication and adapted formulation exists. For the currently WHO-recommended first-line regimens for children under 10 years old, only one single-tablet regimen (AZT/3TC/NVP) exists, and none for the preferred regimens,

prompting programmes to prescribe combinations of different formulations or continue to use suboptimal regimens existing in more adapted and lower-priced formulations.

Adapted formulations for infants and young children who cannot swallow are urgently needed, including for first-line therapy. The IMPAACT P1060 trial found that children between 2 months and 2 years old who received NNRTI-based regimens were 20% more likely to experience treatment failure at 24 weeks than children who received regimens based on PIs, with no difference in findings based on whether the child had been exposed to nevirapine (NVP) *(40) (41)*. Although these and other findings strongly point to the wisdom of LPV/r as first-line for infants and young children, no suitable formulation of LPV/r is yet available.

In the case of children, sequencing of drugs after treatment failure is challenging, and there is a need to identify adequate options for treatment of highly experienced children (e.g. DRV/r and INIs may be useful here). DRV is not yet approved for use in children under 3 years old. In addition, ratios of DRV and the booster RTV vary for children depending on their weight and treatment experience; establishment of single ratios for adults and children (as well as recommendations for when best to use it) would simplify DRV-based regimens.

4.3 Optimization of current products

Treatment optimization is included as a critical component of Treatment 2.0, a strategic approach by UNAIDS and WHO to accelerate progress towards universal ART access and optimize use of ARVs to prevent new infections *(42)*.

For more than a decade, researchers have explored ways to optimize approved ARVs, particularly through appropriate dose reduction *(43) (44)*. Developers of new drugs often select the highest tolerated dose of a drug for testing in Phase III trials, leading to doses that may be higher than needed to achieve efficacy. There is a consensus on the need of optimizing dosage of ARVs as well as the manufacturing and formulation (including development of FDCs) for more cost-efficient delivery in resource-limited settings, as described in the statement launched at the first Conference on Dose Optimization in 2010 *(45) (46)*. Efficiencies may be achieved by reducing the amount of API, through dose reduction studies or improving bioavailability through reformulation. Reducing the amount of API may improve safety and lower drug costs as APIs represent the most costly component of generic pharmaceutical products. Dose optimization offers several strategies:

- Dose reduction: To achieve regulatory approval for a dose lower than that currently approved, fully powered non-inferiority studies (Phase III)—similar to those conducted by industry for the approval of a new drug—need to be conducted. It often requires from three to six years to generate sufficient data to file with regulatory agencies, in addition to the time for approval (about three months to one year). The estimated cost of a non-inferiority study is US$ 15–22 million.
- Reformulation: This strategy makes use of technologies and/or inactive ingredients to increase the bioavailability of a drug, permitting reduction of the approved dose. Regulatory agencies require bioequivalence studies with the approved formulation (Phase I) for any reformulation. The estimated time frame to regulatory filing is from two to three years, at a cost of US$ 2–8 million.

In addition, other strategies are available to decrease the cost of production of APIs by, for example, optimizing materials sourcing or altering the process chemistry to produce APIs more efficiently as described in Section 5.2. Regulatory authorities would only require data demonstrating equivalent stability and purity, which requires from one to two years at an estimated cost of US$ 1–2 million.

Optimization opportunities with some approved ARVs (Table 6) offer several potential advantages over current doses and/or formulations, aiming for both a cost reduction derived from reduction of APIs as well as improvement on toxicity profile and a decrease of technical challenges for co-formulating, with work under way or under discussion with several compounds *(45) (47)*.

Table 6: Approved ARV compounds with potential for dose optimization

Compound (current approved dose)	Class	Sponsor/ approach	Expected outcomes	Status
TDF (300 mg once daily)	NtRTI	CHAI; reformulation.	Approximately 33% dose reduction anticipated, to 200 mg once daily.	Under discussion.
AZT (300 mg twice daily)	NRTI	Geneva University Hospital; dose optimization – randomized clinical trial.	Approximately 33% dose reduction anticipated, to 200 mg twice daily.	MiniZID. Phase III. To be completed January 2014.
d4T (30 mg twice daily)	NRTI	Wits Reproductive Health Institute; dose optimization and comparison with TDF.	Approximately 33% dose reduction anticipated, to 20 mg twice daily.	WHCS-001. Phase III. To be completed end 2015/early 2016.
EFV (600 mg once daily)	NNRTI	Kirby Institute; dose optimization – randomized clinical trial. CHAI; reformulation.	Approximately 33% dose reduction anticipated, to 400 mg once daily. Potential additional 33% reduction by reformulation.	ENCORE 1: Phase III, completed July 2013: non-inferior. Need additional information on concomitant TB treatment and pregnancy.
ATV/r (300/100 mg once daily)	PI	HIVNAT/Kirby Institute; dose optimization – randomized clinical trial. CHAI; process chemistry.	Approximately33% dose reduction anticipated, to 200/100 mg once daily. Additional potential cost reduction by process chemistry. Additional reduction with booster dose reduction.	LASA . Phase III. To be completed early 2014. Under way.
DRV/r (800/100 mg once daily or 600/100 mg twice daily)	PI	Under discussion. Process chemistry, dose optimization and reformulation.	Anticipated 50% dose reduction, to 400/100 mg once daily. Additional reduction with booster dose reduction.	Standard of care needs to be established. Process chemistry under way.
RTV (100 mg)	Booster	Dose optimization.	Anticipated 50% reduction on boosting dose of ATV and DRV.	Under discussion.

TDF

Since the introduction of generic products, the price of TDF has dropped considerably—by more than 70% between 2006 and 2010, largely due to efficiencies in raw material sourcing and improved processing *(45) (48) (49)*. There are, however, limits to the lowest possible price for TDF due to the high milligram dose (300 mg) of current TDF formulations that limits possibilities for cost reduction.

CHAI is working on reformulation of TDF to increase bioavailability with the goal of developing a dosage form that includes a lower dose of the drug *(50)*. Reformulation of TDF may lower the daily dose to 200 mg, or perhaps even 150 mg. Discussions are ongoing in view of the potential introduction of tenofovir alafenamide fumarate (TAF) as a 10 mg daily replacement that might eventually prove to be preferable.

AZT

The standard dose of AZT was reduced (from 300 mg every four hours to 250–300 mg twice daily) after studies found similar efficacy and increased safety with the lower dosage *(51)*. India, Thailand and other Asian countries already use the twice-daily regimen of 250 mg, and Thailand is prescribing 200 mg twice daily for patients who weigh less than 50 kg. Although AZT is generally better tolerated than d4T over the long term, its toxicities (anaemia/neutropenia) remain a concern.

The ongoing MINIZID study is examining whether a dose reduction for AZT (200 mg versus 300 mg twice daily in combination therapy) reduces the incidence of anaemia. The 48-week Phase II study in 136 treatment-naïve patients in Cameroon, which will be completed in early 2014, seeks to provide proof of principle; if successful, additional research will be needed to support regulatory approval.

d4T

Dose optimization pertaining to d4T has generated considerable controversy *(52)* as WHO has strongly urged its discontinuation. With funding from the Bill & Melinda Gates Foundation, the Wits Reproductive Health Institute in South Africa is leading a Phase IIIb trial comparing 20 mg d4T twice daily to 300 mg TDF once daily in approximately 1000 patients in India, South Africa and Uganda. By measuring participants' viral load at 48 weeks, the trial seeks to determine whether d4T is non-inferior to TDF (both in regimens with 3TC and EFV) in treatment-naïve patients, and to evaluate the tolerability, overall safety and efficacy of the lower d4T dosage compared to TDF. The trial is unlikely to generate meaningful data on the long-term toxicity of d4T as the most serious d4T-related side-effects (such as peripheral neuropathy and lipoatrophy) typically emerge after long-term use. Activists in India and South Africa have protested against the trial as well as the slow phase-out of d4T in some treatment programmes.

EFV

Lowering the EFV dose could help lower the price and possibly minimize central nervous system toxicities. The recently completed multicountry ENCORE1 study found that 400 mg of EFV was non-inferior to 600 mg in treatment-naïve patients at 48 weeks *(53) (54)*. Significantly fewer patients had EFV-related side-effects (36.8 versus 47.2%, $p = 0.008$) and fewer discontinued treatment due to EFV-related side-effects with the lower dose (1.9 versus 5.8%, $p = 0.01$). It is anticipated that the ENCORE1 results could result in regulatory approval for the lower EFV dose and influence treatment guidelines, although further investigation of the impact of the lower dosage on interaction with rifampicin in cases of TB/HIV co-infection is needed.

CHAI is investigating reformulation of EFV to lower the daily dose by improved bioavailability. Researchers from the University of Liverpool are studying freeze-dried nanosuspensions of EFV to improve bioavailability to enhance antiviral activity or lower the daily dose. This group is advancing into bioequivalence studies in healthy human volunteers with their selected dosage form *(55) (56)*.

ATV/r

Dose reduction also may be possible with ATV/r. The HIV Netherlands Australia Thailand Research Collaboration, with support from the Kirby Institute *(57)*, is conducting a non-inferiority Phase IV trial among 600 virally suppressed Thai patients, comparing the efficacy and safety of ATV/r at either 200/100 mg or 300/100 mg once daily; completion is anticipated in early 2014. Although this trial is of special importance for Thailand where patients tend to have low body weight and increased risk of hyperbilirubinaemia, a known adverse event associated with ATV, results may not be generalizable beyond the study population. Favourable results in the Thai trial might justify broader research on the lower dosage. In addition, CHAI is working to optimize the process chemistry for ATV/r.

DRV/r

As WHO has yet to recommend DRV/r as a preferred option for second-line treatment, only limited efforts have focused on its optimization. There is a need to establish single ratios with adults and children as ratios of the two drugs vary depending on treatment experience and, for children, on weight. Potential

may exist to reduce the dose to 400/100 mg, particularly in PI-naïve patients, as an alternative second-line option.

CHAI is currently working on optimizing the process chemistry.

RTV

Lower boosting dose for RTV in combination with ATV and/or DRV would presumably improve tolerability, lower costs and possibilities for co-formulation. If a 50 mg heat-stable tablet of RTV could be co-formulated with either PI, then new bioequivalence studies would be needed to ensure that boosting effects were similar to those that have been achieved previously in small pharmacokinetics (PK) trials with the liquid formulation. A 50 mg RTV tablet also would be useful for paediatric dosing and co-formulations as the liquid is expensive, impractical and unpalatable and has a very short shelf life (effectively three months after transportation and distribution time) *(58)*.

4.4 Emerging products (recently approved products)

INIs

DTG

The FDA approved DTG in August 2013 for use in naïve and experienced adults and adolescents. DTG appears to have certain advantages over other INIs (RAL and EVG) as it is: approved for use in treatment-naïve patients; taken once daily at low dose (50 mg); requires no pharmaceutical boosting and is associated with no food restrictions. DTG has been included in a full-regimen FDC (572-Trii, a combination of DTG, abacavir [ABC] and 3TC) that has been submitted for approval to the FDA and the European Medicines Agency (EMA) *(59)*.

In studies of treatment-naïve patients, combinations with DTG were equivalent or superior to TDF/FTC/EFV and to combinations including RAL *(60) (61) (62)*.

Although many DTG studies have primarily enrolled patients with earlier and easier-to-treat HIV infection, DTG also has produced strong results among patients with baseline viral load > 100 000 copies/mL. Given the low-milligram required, DTG could potentially make first-line INI-based combinations a reality in both high- and low-income countries and potentially at lower cost. However, the initial price for the United States market (US$ 14 105 per person per year) far exceeds costs that would be feasible in low-income countries, underscoring the need for focused efforts to reduce its cost *(63)*.

EVG/COBI/TDF/FTC

The FDA approved the EVG/COBI/TDF/FTC four-in-one boosted INI FDC (known as Stribild, formerly Quad) for treatment-naïve people only, while EMA *(64)* extended approval to HIV-infected individuals without viral mutations associated with resistance to EVG, TDF or FTC. Its use is restricted to patients with good renal function, which is one reason United States guidelines list the combination as an alternative rather than a preferred regimen *(65)*.

As a once-daily single-tablet regimen, the product is a potentially important breakthrough. Studies in the past year have confirmed the safety and efficacy of the combination. To date, however, uptake has been limited since the United States and European approvals in August 2012 and May 2013, respectively, with its use primarily intended for treatment-naïve patients. At 96 weeks, this combination remains non-inferior to TDF/FTC/EFV or ATV/r plus TDF/FTC, and studies examining a switch to this combination in case of side-effects are ongoing.

4.5 Pipeline ARVS (adults)

A number of adult ARVs are currently in development. The list of pipeline products for adults in Table 7 is not exhaustive, but focuses on new combinations with pending regulatory applications and/or products that potentially offer advantages over existing products for use in resource-limited settings.

Table 7: Adult ARV pipeline

Compound	Company	Phase	Comments
NRTIs and NtRTIs			
TAF, tenofovir pro-drug	Gilead	Phase III	Similar safety/ efficacy to TDF with potentially reduced side-effects reported. The 25 mg dose selected for development (10 mg, FDC with COBI). Ongoing studies prioritize co-formulations including a PI FDC.
CMX157 tenofovir pro-drug	Merck	Phase I	No new data since 2008. Acquired from Chimerix by Merck in August 2012. Potential for weekly dosing.
BMS-986001 (similar to d4T)	BMS	Phase IIb	Dose-finding study compared to TDF, both with EFV+3TC, still ongoing. New animal and in vitro safety and resistance data.
EFdA	Merck	Phase I	Limited in vivo data, but encouraging in vitro potency and activity against NRTI-resistant HIV. Long half-life.
NNRTIs			
RPV (long-acting injections)	Janssen	Phase I	Ongoing studies in HIV uninfected individuals, with monthly and quarterly injections, including with S/GSK1265744. Current research focused on its potential role in pre-exposure prophylaxis, PrEP *(66)*.
Doravirine (MK-1439)	Merck	Phase II	Once-daily NNRTI that displays in vitro activity against common NNRTI resistance mutations. Mean –1.4 log VL reductions after seven days monotherapy at 25 mg dose. Dose-ranging study uses up to 200 mg.
INIs			
EVG	Gilead	Phase III	Component of four-drug FDC (Stribild). Approved in Europe in November 2013 as separate compound; FDA required resubmission in April 2013. Other studies ongoing as component of other FDCs.
S/GSK1265744 (follow-up to DTG)	Shionogi/ GSK	Phase II	No update on oral use. New in vitro data based on a monthly (long-acting) injection.
Booster			
COBI	Gilead	Phase III	Component of four-drug FDC (Stribild). Phase III data report similar efficacy/safety to RTV. Approved by EMA as individual product in September 2013; FDA required resubmission in April 2013. Ongoing studies include co-formulations of COBI with: EVG/COBI/FTC/TAF (Phase III); DRV/COBI (Phase III); DRV/COBI/FTC/TAF (Phase II); and ATV/COBI (Phase I).
Entry inhibitors			
Cenicriviroc (CCR5/2 antagonist)	Tobira	To start Phase III	Phase II results reported in March 2013 in treatment-naïve patients showed non-inferiority and better tolerability than EFV.
BMS-663068 (attachment, gp120)	BMS	Phase IIb	No efficacy update since 2011. Phase II dose-finding study versus ATV/r, each with RAL+TDF yet to report.
Albuvirtide (fusion inhibitor)	Chongquing Biotechnologies	Phase I	A single dose of this long-acting version of T-20 reduced viral load by one log copies/mL, maintained for 6–10 days. Potential for weekly dosing.

Remarks on the adult pipeline

Of the current emerging and pipeline ARVs (Figure 4), the INI DTG and NtRTI TAF appear the most promising, with the potential to replace currently recommended drugs and to be combined with other emerging ones such as DRV/r.

DTG: Although DTG has the potential to replace EFV as first-line therapy, despite nearly two years of data, it remains unclear how the drug would perform in resource-limited settings. Little information is available regarding use in women or safety during pregnancy. If used with rifampicin, a 50 mg twice-daily dosing will be required. ViiV Healthcare is planning a DTG trial in TB co-infected people and a study of DTG in women, including women who become pregnant during clinical trials.

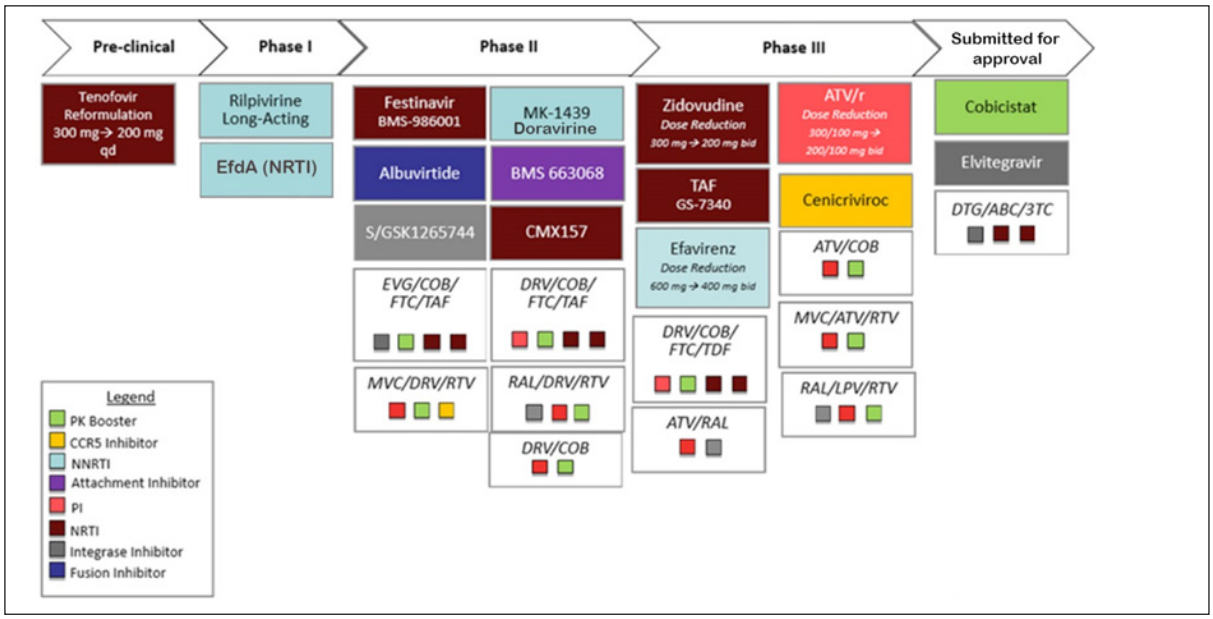
A Phase III study comparing 400 mg EFV plus FTC/TDF to DTG plus ABC/3TC in naïve patients, with sites in several African countries, is in the planning stage. This study will include people with TB co-infection. The use of DTG with DRV/r in second-line regimens could be evaluated in the second-line study currently under discussion; such a regimen has the potential to be co-formulated as a once-daily single-tablet second-line regimen, without cross-resistance to the current preferred first-line regimen.

TAF: With respect to TAF, one concern has been the absence of clear plans for development of a stand-alone TAF, or dual TAF/FTC co-formulated tablet. Although evidence has suggested potential benefits of this new pro-drug formulation of TAF for more than a decade *(65)*, efficacy data were not presented until 2011 *(65)*, by which time Gilead prioritized a co-formulation over the individual compound. Gilead appears to be considering development and testing of a dual FDC of TAF (10 mg and/or 25 mg) plus FTC (200 mg). Nearly 300 community groups and individuals have appealed to Gilead to develop and evaluate a separate formulation *(67)*.

TAF dosing will depend on results of comprehensive PK evaluations. It needs to be evaluated in the presence of NNRTIs and DTG in a timely fashion to provide data for its potential use in non-boosted generic FDCs.

In earlier stages of development: The long-acting injections of rilpivirine (RPV) and the INI S/GSK1265744 might also have the potential to change standard of care and, in turn, the market. The product profile for a long-acting regimen has not yet been established.

Figure 4: 2013 ARV pipeline in the value chain



qd = once daily
Source: P. Clayden and D. Ripin. Adapted from 2013 i-Base/TAG Pipeline Report. 2013.

4.6 Pipeline ARVs (paediatrics)

Formulations for young children in the current pipeline, except in one case, are granules, dispersible tablets or powder, some of which might be useful for low- and middle-income countries in the future. Paediatric development involves different age groups and a given ARV can be in several phases of study simultaneously depending on the formulation considered. Table 8 summarizes the pipeline of ARVs under development for children.

Table 8: Paediatric pipeline

Compound	Sponsor	Formulation(s) and dose	Status and comments
NNRTIs			
ETR	Janssen	Dispersible tablets 25 (scored), 100 mg	Approved for children 6–18 years old. Phase I/II treatment-experienced children 2 months–<6 years old, and treatment-naïve ≥2 months–<2 years old, or exposed to ARV prophylaxis; enrolling. Potentially useful for second-line regimens due to resistance profile.
RPV	Janssen	Tablet 25 mg Granules 2.5 mg base/g	Phase II, 12–<18 years old, >32 kg enrolling (PAINT–NIH, United States). Phase I/II, neonates to <12 years old, planned (IMPAACT 111).
Booster			
RTV	Cipla/DNDi	Granules	Under development (superboosting for concomitant TB/HIV treatment).
PIs and combinations			
ATV	BMS	Powder 50 mg sachet under development Capsules 100, 150, 200, 300 mg	Phase III/IIIb ongoing (PRINCE 1, includes RTV-boosted ATV), treatment-naïve and experienced children 3 months–<6 years old *(68)*. Other studies are ongoing for children up to 11 years old (Prince 2 and IMPAACT P10201–NIH, United States).
LPV/r	Cipla/DNDi	Pellets 40/10 mg (equivalent to 0.5 mL liquid)	Implementation studies 2014.
LPV/r/ABC/3TC LPV/r/AZT/3TC (4-in-1)	Cipla/DNDi	Pellets, FDC	Under development. Phase II/III studies 4Q 2014.
INIs and combinations			
RAL	Merck	Granules for suspension 6 mg/kg (100 mg sachet)	FDA-approval for use in children ≥4 weeks old (January 2014). Neonate passive PK study ongoing (neonates born to women who received RAL in pregnancy and during labour) (IMPAACT P1097). Neonates PK and safety study for prophylaxis ongoing (IMPAACT P1110) in high-risk HIV-exposed neonates from birth to 6 weeks old.
DTG	ViiV Healthcare	Granule formulation in development Reduced-strength 10 mg and 25 mg tablets also developed	Phase I/II study ongoing for treatment-naïve and -experienced children 6 weeks–18 years old (IMPAACT P1093). In a PK study, exposures from granules were moderately higher than with tablets and highest with formula milk *(76)*.
DTG/ ABC/3TC (572-Trii)	Shionogi/ ViiV Healthcare	Paediatric formulation development planned; dosing to be determined	Dependent on ongoing studies confirming DTG dose in children.

Compound	Sponsor	Formulation(s) and dose	Status and comments
EVG COBI	Gilead	EVG reduced-strength tablets and suspension in development COBI dispersible tablets for suspension	EVG PK completed, boosted RTV for children 12–<18 years old. RTV- and COBI-boosted EVG to be studied in all age groups.
EVG/COBI/FTC/TDF (Stribild)[a]	Gilead	Reduced strength tablets in development	Studies under way in treatment-naïve children 12–<18 years old; studies for 6–<12 years old planned (waiver <6 years old).
Entry inhibitors			
MVC	Pfizer/ViiV Healthcare	Suspension 20 mg/mL	Phase IV. Treatment-experienced CCR5 tropic children 2–<8 years old.

[a] There also are Paediatric Investigation Plans approved for the combination EVG/COBI/FTC/TAF, where TDF is replaced by TAF, which could be an important agent for children. The studies are not yet started. The issues of ensuring that there are data to support FDCs using TAF in un-boosted regimens are the same for children as for adults, i.e. it needs to be studied without COBI or RTV.

Remarks concerning paediatric emerging and pipeline products

Emerging products

LPV/r and combinations: The Drugs for Neglected Diseases initiative (DNDi) and Cipla (in a project co-funded by UNITAID) are developing a paediatric formulation of LPV/r in combination with the two possible NRTI dual-backbones. The formulation consists of a finite number of mini-tablets in a capsule, which is opened and could be sprinkled on soft food. PK studies in adults, children and infants *(69)* found that most parameters fell within accepted limits of bioequivalence with the new formulation, although in older children, more than 4 years old, concentrations were lower for sprinkles compared with tablets *(70)*. Caregivers found that sprinkles were more acceptable for infants, but not for older children, mainly due to the taste. Acceptability data indicate that storage, transport and conspicuousness of treatment were less problematic for sprinkles compared with syrups. The partnership is working to improve masked taste and granule formulation, which will make mixing with NRTI-backbone easier.

RAL: In January 2014, the FDA approved the use of the paediatric suspension of RAL in patients ≥4 weeks old, in addition to previous indications for the tablets to treat children 3–17 years old *(71)*. RAL approval is the first in a new therapeutic class for infants and young children that might offer certain advantages over currently available drugs. Like DRV/r, RAL has been suggested as a future option for third-line treatment for children, although, also like DRV/r, it is quite expensive and lacks generic options.

Because RAL crosses the placenta well it has the potential for use as prophylaxis against vertical transmission to infants, and PK of the drug on neonates is being studied *(72) (73)*. The follow-up INI S/GSK-1265744 and RPV, under investigation as a long-acting formulation for adults, also have provoked interest as a potential treatment of adolescents.

Pipeline

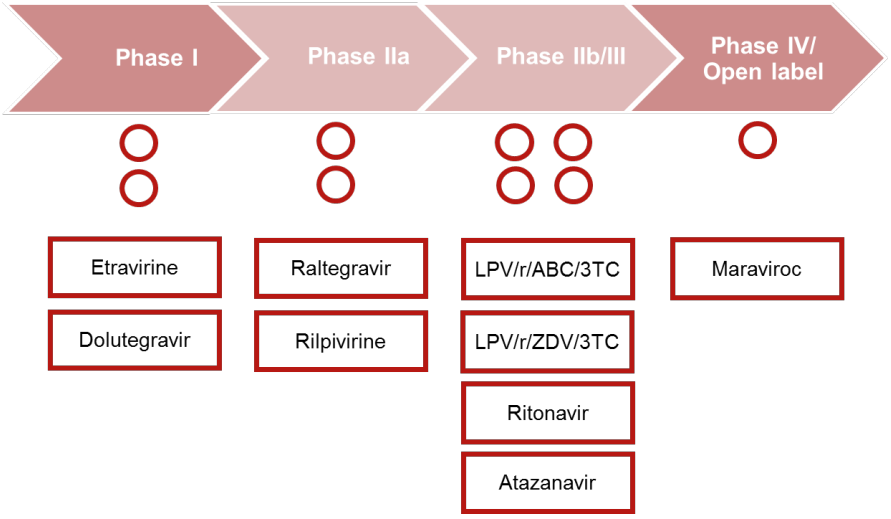
As with adults, among current pipeline ARVs in development (Figure 5), the most promising compounds for children are DTG and TAF. This area of research raises the possibility that the same anchor first-line drug might be used from infancy to adulthood.

DTG: Recently approved for use in adolescents, DTG will be studied in the youngest age group, and a granule formulation is in development. A study evaluating both tablets and granules among children between 6 and 12 years old is now enrolling. A Phase I/II trial (IMPAACT P1093) in treatment-naïve and experienced children is ongoing, using de-escalated age-bands from 18 years to 6 weeks old. Plans also have been made for a trial of a reduced strength paediatric FDC of DTG/ABC/3TC (currently under investigation for adults).

ViiV Healthcare is submitting data to support once-daily paediatric use of DTG/ABC/3TC and is working in partnership with CHAI and Mylan on a dispersible tablet FDC. They will transfer the technology and resources to the generic company for production, registration and distribution at the lowest possible cost for low-income countries *(74)*.

TAF: Although less advanced in its development, TAF may have advantages over TDF as far as bone toxicity is concerned, which could lead to further harmonization with regimens among infants, children, adolescents and adults. The potential for long-acting formulations is especially attractive for treatment of HIV in adolescents.

Figure 5: Summary of paediatric HIV pipeline



4.7 New delivery mechanisms in the pipeline

Long-acting formulations

Long-acting formulations, in monthly or weekly depot injections, are currently being studied and could radically alter the current standard of care, allowing for infrequent dosing, at least during maintenance phases of ARV treatment. Potential candidates include the NNRTI RPV and the INI GSK1265744, both in early stages of development. Studies of the two in combination are planned. CMX-157, a novel pro-drug of TDF, also has a long half-life and it has recently been acquired by Merck; so far no news has emerged regarding development plans *(75) (76)*.

Nanosuspensions

Novel nanoscale drug delivery provides a potential opportunity to improve the efficacy, safety, administration and cost of ARVs. Controlled-release nanotechnology-based formulations of ARVs could improve drugs with insoluble APIs, high pill burden, dietary requirements, side-effects, formulation difficulties, low efficacy, low bioavailability, high dose requirements and high cost *(77)*. Nanotechnology is being applied to long-acting RPV and S/GSK1265744. It also is being applied to EFV, a drug with very poor water solubility that requires high doses in order to reach therapeutic plasma concentrations after oral administration. In two recent studies, EFV nanosuspensions using freeze-drying techniques resulted in improved bioavailability *(78) (79)*. One of the studies, conducted by University of Liverpool, also found greater in vitro cellular distribution and enhanced antiviral activity using the EFV nanosuspension compared to dissolved EFV *(80)*.

5 Market landscape

This section describes the current market for ARVs, including the size and structure of the ARV industry serving low- and middle-income countries' markets and the profile of the main buyers as well as cross-cutting issues such as patents and quality for first-line, second-line, third-line and paediatric markets. For easier reading, this section approaches those market segments separately for FPPs and APIs, although they are both logically interconnected in each case.

5.1 FPPs

5.1.1 Market size

The number of people on ART has grown tremendously over the last decade. By the end of 2012, almost 10 million people in low- and middle-income countries were receiving treatment, including 1.6 million people who began treatment between 2011 and 2012 *(81)*. This represented a thirtyfold increase from 2002 and a threefold increase from 2008.

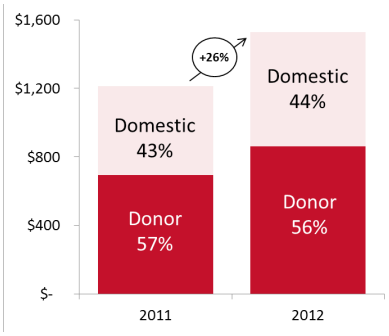
Although more than 90% of people receiving ART lives in low- and middle-income countries, this market represents less than 10% of the value of the global ARV market *(27)*. In 2012, the market for ARVs in low- and middle-income countries was estimated to be worth approximately US$ 1.53 billion *(82)*, which is large when compared with other diseases affecting these countries. For example, it is more than twice the size of the first-line public sector TB market and more than three times the size of the artemisinin combination therapy (ACT) malaria market.

Though prices of individual drug regimens have continued to decline, the increasing number of people on therapy and a shift to more effective and expensive drug regimens have allowed the market to continue its growth. CHAI estimates that the ARV market in low- and middle-income countries grew by approximately 13% from 2010–2011 and by 26% from 2011–2012 *(82) (17)*. ARV purchases by the Global Fund, PEPFAR and UNITAID grew by 6% from 2010 to 2011 and by 23% from 2011 to 2012, according to donor-procurement databases. In addition to donor-funded programmes, South Africa has a large impact on the ARV market. At the end of 2012, South Africa had over two million people on ART—20% of the global total *(83)*. South Africa's 2013–2014 ARV tender, issued in December 2012 and mostly financed with domestic resources, was valued at approximately US$ 672 million *(84)*.

5.1.2 Demand

In 2012, total funding for HIV/AIDS was estimated to be approximately US$ 18.9 billion, 53% of which was funded by domestic resources *(85)*, which have increased significantly. Funding by international donors remained relatively flat from 2008–2012 *(85)*. Within the international donor community, the Global Fund and PEPFAR are by far the largest players. In 2012, the Global Fund and PEPFAR reported US$ 456 million and US$ 386 million of ARV procurement within their respective databases. This represented approximately 56% of all ARV value procured in low- and middle-income countries. As a result, the procurement policies and practices of the Global Fund and PEPFAR have had a large impact on the market for ARVs in low- and middle-income countries. Figure 6 represents the distribution of ARV funding for the total market in low- and middle-income countries.

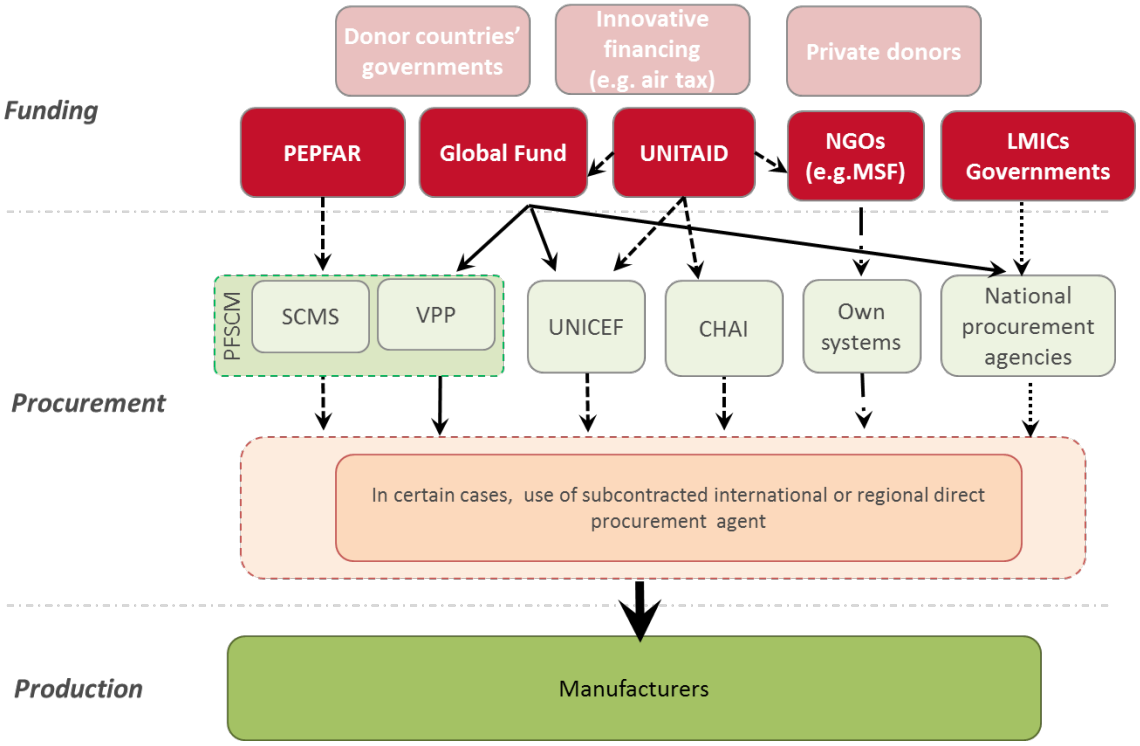
Figure 6: Estimated size of the ARV market and resources distribution (US$ millions)



Source: An overview of the ARV market (82) and UNITAID analysis of procurement databases.

Figure 7 illustrates the common procurement channels for ARVs.

Figure 7: Summarized overview of the common procurement channels for ARVs up to 2013



In 2005, USAID contracted with PFSCM, a non-profit consortium of over a dozen organizations, to create the SCMS project to pool procurement across more than 20 countries. According to USAID, this central procurement system enables countries with limited procurement capacity and smaller markets to benefit from the lower prices and consistent supply associated with bulk *(86)*.

Prior to 2009, ARVs purchased with Global Fund financing were procured by nongovernmental organizations, national procurement agencies in recipient countries and other procurement agents. In 2009, the Global Fund launched the VPP mechanism as a strategic element of market dynamics to improve the impact and performance of grants. Increasingly, the Global Fund has emphasized and reinforced the VPP mechanism and, by 2012, over one third of Global Fund financed ARVs were purchased via its VPP mechanism. In 2009, the VPP mechanism competitively selected PFSCM as its procurement agent, the same buyer as PEPFAR. By 2012, PFSCM purchased over 60% of donor-funded ARVs either via PEPFAR or the VPP mechanism, accounting for approximately 35% of all ARV procurement in low- and middle-income countries.

The Global Fund is now: (i) increasingly playing a more proactive and direct role in the sourcing and procurement of health products through earlier and closer collaboration with manufacturers; (ii) improving forecasting supported by the New Funding Model; (iii) enhancing its purchasing capability; and (iv) offering longer term contracts to drive innovation and reduce cost. An important tool in operationalizing this new approach is the VPP mechanism whereby its procurement agents will now be mainly responsible for order placement and on-time delivery rather than the selection and volume adjudication to manufacturers.

For paediatric treatment, in particular, there is an international effort to ensure that countries have the ability to procure needed regimens. As a transition from the UNITAID-funded Paediatric HIV/AIDS Project implemented by CHAI since 2006, the Global Fund is leading the Paediatric ARV Procurement Working Group and Procurement Consortium, which includes major stakeholders such as CHAI, the Global Fund, MSF, PFSCM/VPP, SCMS/PEPFAR, the United Nations Children's Programme (UNICEF) and UNITAID. Demand forecasting is aggregated across partners, shared with suppliers and quarterly orders for more than 50 countries are synchronized to ensure that even low-volume orders can be adequately served. The Consortium plans to reach out to other countries not yet part of the coordinated procurement, including some high-volume ones, as their inclusion would further reduce demand fragmentation and risks of supply in this market segment. In addition, the UNITAID Board approved in December 2013 a project, to be implemented by CHAI, to enable continuation of country support and market coordination with manufacturers in this niche.

5.1.3 Eligibility criteria on quality for procurement

International funders of HIV drugs require that purchasers adhere to their policies regarding the selection and quality assurance of health products (Table 9). PEPFAR requires that products purchased with their funds be approved or tentatively approved by the FDA, while the Global Fund and UNITAID require that products be approved by a stringent regulatory authority (SRA), including the FDA,[2] prequalified by WHO or remitted for a limited period of time by the Expert Review Panel hosted by WHO.

Table 9: Summary of main ART funders' criteria for eligibility for procurement with their funds

	PEPFAR	Global Fund	UNITAID	Domestic funding (low- and middle-income countries)
Approved by national regulatory authority	Yes	Yes	Yes	Yes
Approved (tentatively) by the FDA	Yes	Yes	Yes	–
Approved by other SRAs	–	Yes	Yes	–
Included in the WHO list of prequalified medicinal products	–	Yes	Yes	–
Temporarily accepted for procurement after positive recommendation from Expert Review Panel (ERP)	–	Yes	Yes	–

– = not applicable

As of October 2013, the FDA had issued 160 approvals or tentative approvals, including 32 approvals for full-regimen products (i.e. triple FDCs and co-packs) *(37)*. WHO relies on its own assessments and inspections as well as the evaluations conducted by SRAs. As of October 2013, WHO had issued 294 prequalification for ARVs from 31 manufacturers. The WHO prequalification list included at least 97 products that also had been approved or tentatively approved by the FDA, two products that also had been approved by EMA

2 An SRA is considered: (i) a member of the ICH (as specified on its website); or (ii) ICH Observer-European Free Trade Association (EFTA) represented by Swiss Medic, Health Canada and WHO (as may be updated from time to time); or (iii) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement—Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

and one product approved by Health Canada. Countries purchasing ARVs with domestic funds, including high-volume countries such as Brazil, South Africa and Thailand, do not necessarily require products to be on the WHO prequalification list or have approval other than by their own national regulatory authorities.

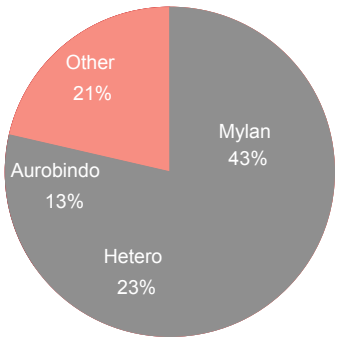
5.1.4 Supply

Across the ARV market in low- and middle-income countries, a relatively small number of manufacturers are fully active, operating as an oligopoly (Figure 8). In some markets, manufacturers are able to operate as monopolies due to patent protection and while generic products are developed and become eligible for procurement with donor funding.

Generic manufacturers play a key role in the low- and middle-income countries' ARV market. In 2012, generic producers accounted for nearly 96% of purchases financed by major donors (up from 89% in 2010). India-based manufacturers, including United States-owned Mylan, account for the majority of manufacturers supplying the Global Fund, PEPFAR and UNITAID recipients. As of October 2013, more than 75% (225) of the WHO prequalified products included manufacturing sites in India. Only four African manufacturers have products prequalified by WHO, with Aspen Pharmacare (South Africa) accounting for most of these products (12 out of 18 prequalified products manufactured in Africa), mainly producing originator products for local/regional distribution.

The concentration in the donor-funded ARV market is high; in 2012, the top four manufacturers (Mylan, Hetero, Aurobindo and Cipla) accounted for 83% of donor-funded purchases. The Herfindahl-Hirschman Index (HHI) measures the size and number of manufacturers in relation to an industry, and serves as an indicator of competition and can be used to characterize the concentration of producers, with increases in the index generally indicating a decrease in competition and an increase of market power. Markets in which the HHI is between 1500 and 2500 points are moderately concentrated, and markets with an HHI higher than 2500 points are considered highly concentrated *(87)*. In 2012, the HHI across all ARVs was 2602, indicating high concentration and hence reduced competition. The concentration of manufacturers within specific market segments such as second-line, third-line and certain paediatric regimens is considerable higher

Figure 8: Market share of top ARV manufacturers, 2012 sales value reported by the Global Fund, PEPFAR and UNITAID



Mylan is playing an increasingly large role in the market for ARVs in low- and middle-income countries. Mylan acquired the generic business of Merck and India-based Matrix labs in 2007, and has since seized significant market share in both the FPP and API markets. By 2012, Mylan, sold US$ 367 million of ARVs to donor-funded programmes, accounting for 43% of all ARV procurement and representing a volume of US$ 170 million greater than the next largest competitor. As one of three firms awarded first-line ARVs supply in South Africa's 2013–2014 ARV tender, Mylan also has a major role in the South African market.

In countries where ARVs are primarily domestically financed, such as Brazil, China, South Africa and Thailand, local manufacturers are responsible for a high percentage of the market share, except for the most recently developed ARVs. For example, with South Africa's 2013–2014 ARV tender, local manufactur-

ers accounted for 70% of the contract *(88)*, which in turn import APIs and/or FPPs. Plans for API manufacturing in South Africa are currently on hold.

Some major generic manufacturers have raised concerns about the future commercial viability of the ARV market in low-income countries, claiming that new opportunities in other therapeutic areas are making it increasingly difficult to keep production capacity allocated to low-margin ARVs. Moreover, current price pressures may discourage new market entrants, thereby exacerbating the reliance on a small number of manufacturers to supply the entire market.

5.1.5 First-line regimens

The first-line ARV market is large and growing. Of patients on ART in low- and middle-income countries, 96% are on first-line regimens *(27)*.

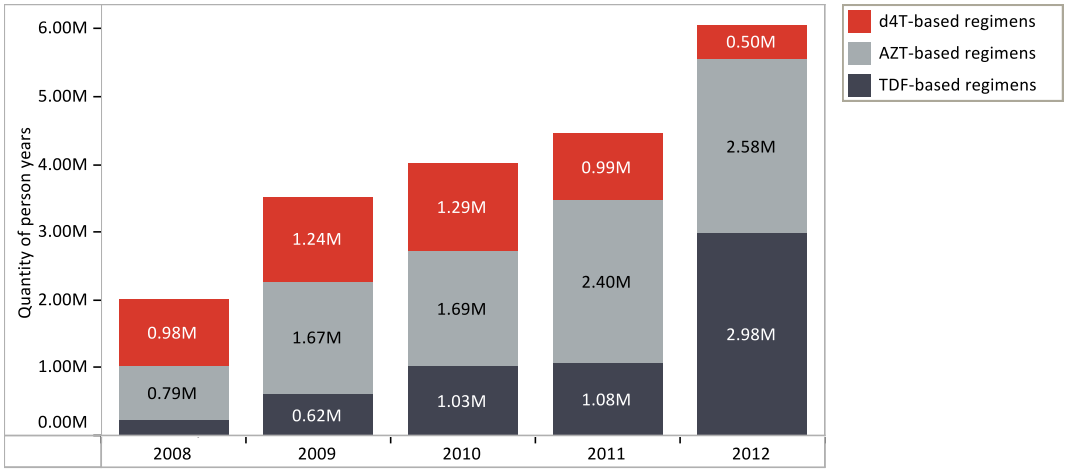
The WHO treatment guidelines have shaped demand in low- and middle-income countries and affected the ability of manufacturers to achieve economies of scale *(89)*. WHO published its first guidelines in 2002, simplified them in 2003 and updated them in 2006, 2010 and 2013. By 2012, eight regimens consisting of combinations of TDF, AZT, or d4T with 3TC or FTC, and NVP or EFV dominated the market. In the 2013 revision, WHO recommended a harmonized regimen of a once-daily FDC of TDF + 3TC (or FTC) + EFV for all adolescents and adults, including pregnant women. This harmonized regimen reflects a drastic simplification from 2006, when up to 24 regimes were included in recommendations for adults.

NRTIs d4T, AZT and TDF

In 2010, WHO formally recommended discontinuation of the use of d4T. The procurement databases reveal that by the end of 2012 most patients had been switched though more than 502 000 person-years of treatment were reported that year by donor-funded programmes in at least 21 countries (Figure 9). According to a WHO survey including all ARVs utilized in countries *(18)*, 20% of adults on first-line ART was taking regimens that included d4T at the end of 2012 (down from a previously estimated proportion of 31% at the end of 2011), while AZT-based regimens were estimated to account for 44% of first-line treatments in countries, and TDF-based regimens for 35%.

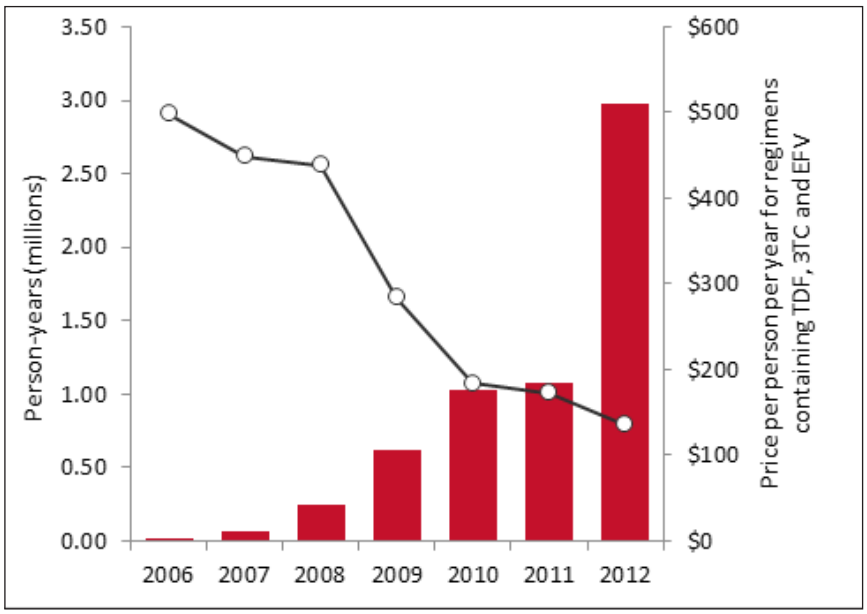
When patients are switched off d4T, there appears to be a strong preference towards TDF-based regimens (as opposed to AZT-based regimens). Among donor-supported treatment programmes in 2012, reported procurement of d4T decreased by over 488 000 person-years, while AZT and TDF volumes increased by 171 000 and more than 1.9 million person-years, respectively. At the end of 2012, donors were financing more than 2.98 million person-years of TDF-based treatment, in comparison to 600 200 in 2009.

Figure 9: Reported donor-funded procurement in person-years for adult regimens containing d4T, AZT or TDF (millions)



The market for TDF-containing regimens has changed dramatically from 2006 to 2012 (Figure 10). In 2006, TDF was included in the WHO treatment guidelines *(90)* as an optional ARV for first-line regimens *(91)*. In 2007, only one manufacturer met donor quality assurance criteria. A TDF-based triple regimen, including 3TC and EFV, cost almost US$ 500 per person per year. UNITAID and CHAI intervened to incentivize additional manufacturers to enter the market thereby stimulating competition. In 2011, the MPP, funded by UNITAID, signed a license with Gilead that enabled competition among manufacturers in more markets than was previously the case. By 2012, nine manufacturers sold TDF eligible for donor-funded procurement. Three manufacturers sold the one-tablet full-regimen TDF/3TC/EFV at a cost of less than US$ 140 per person per year. TDF volumes also increased dramatically from 2007 to 2012. TDF is now considered the preferred option in first-line combinations according to the latest 2013 WHO revised treatment guidelines.

Figure 10: Procurement volumes and prices trends for TDF, 3TC and EFV (US$)



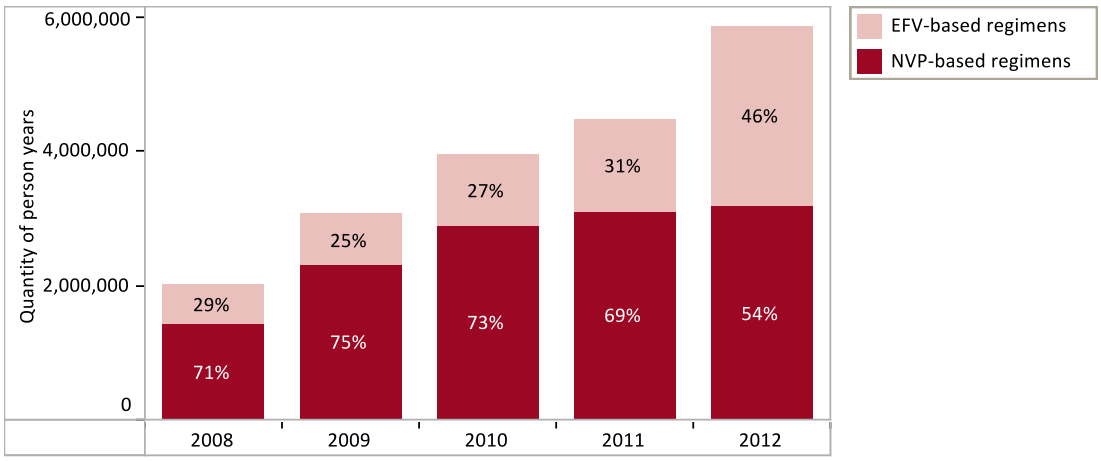
NRTIs: 3TC and FTC

Historically, the majority of people who started first-line regimens received combinations that included 3TC rather than FTC, two ARVs considered clinically interchangeable by WHO *(92)*. In 2012, 3TC was selected for use in 88% of first-line regimens in low- and middle-income countries *(18)*. The price of 3TC has historically been lower than for FTC due to its less expensive starting material, higher yields, higher demand stemming from its widespread availability in co-formulations (i.e. with TDF, AZT and ABC, whereas FTC is exclusively co-formulated in combination with TDF) and greater number of countries where combinations, including FTC, remain under patent. Nonetheless, as of October 2013, the price differential for the two recommended treatment regimens, TDF/3TC/EFV and TDF/FTC/EFV, was narrowing, especially considering the significant price reductions attained in South Africa's 2013–2014 tender. However, this will likely change as TDF/3TC/EFV from additional manufacturers receives approval by the FDA or the WHO Prequalification Programme.

NNRTIs: EFV and NVP

The use of EFV-containing regimens is increasing rapidly. By 2012, 46% of first-line regimens purchased by donor-funded programmes contained EFV (up from 27% in 2010) as shown in Figure 11. Similar proportions are found by WHO *(18)*, with a remarkable increase in EFV (35.7% for EFV versus 63.2% for NVP at the end of 2012) when surveying the use of ARVs in all low- and middle-income countries. This trend towards growing EFV use is expected to continue or accelerate with the recent WHO recommendation for EFV as the preferred NNRTI.

Figure 11: Evolution of reported donor procurement for EFV and NVP



Co-formulations

In 2012, single-tablet regimens, or triple FDCs, represented 60% of first-line donor-funded procurement volumes, with the rest being mostly the use of a two-pill regimen (consisting of a dual FDC and a third component taken separately). The uptake of one-pill TDF/3TC/EFV appears to have been hampered by a price premium that existed for this formulation. The price premium was largely due to having only a single approved product in the market for most of 2012. Two additional suppliers have since been approved. Preliminary data from 2013, however, indicate that the number of people on the triple TDF-FDC is increasing rapidly and a number of large countries, including Ethiopia and South Africa, already have transitioned to WHO-recommended triple-drug FDCs.

Competition

While the degree of competition varies for each FPP, a limited number of manufacturers are active in the market for first-line regimens. While for some older products there are up to 13 manufacturers with products eligible for donor-financed programmes (Tables 10–12), Mylan, Aurobindo, Strides, and Hetero dominate sales for most of these products. This seems to indicate that some firms may face barriers to entry that prevent them from winning market share even though they are compliant with the quality standards required by major donors. These barriers may include a lack of economies of scale, challenges in accessing APIs, different manufacturing cost structures or tender practices that award all volumes to one or two large manufacturers.

Table 10: Categorization of the markets for single-tablet regimens for first-line (triple FDCs), donor-funded purchases in 2012

Formulation	Median price per person per year (US$)	Quantity of person-years reported	Percentage of total first-line market	Number of manufacturers with products eligible for donor procurement	4 firm ratio	HHI	Concentration
AZT/3TC/NVP 300/150/200 mg	$113	1 515 882	26%	8	83%	1989	Moderate
TDF/3TC/EFV 300/300/600 mg	$146	1 169 806	20%	2 (3)[a]	100%	6969	Very high
TDF/FTC/EFV 300/200/600 mg	$176	395 689	7%	3 (5)[b]	100%	8511	Very high
d4T/3TC/NVP 30/150/200 mg	$57	417 662	7%	9	100%	6184	High
		Total	60%				

Table 11: Categorization of the markets for double FDCs used for first-line regimens, donor-funded purchases in 2012

Formulation	Median price per person per year (US$)	Quantity of person-years	Percentage of total first-line market	Number of manufacturers with products eligible for donor procurement	4 firm ratio	HHI	Concentration
TDF/3TC 300/300 mg	$63	1 086 881	19%	6	95%	3812	High
AZT/3TC 300/150 mg	$95	829 720	14%	13	76%	2215	Moderate
TDF/FTC 300/200 mg	$87	240 983	4%	5	99%	4113	High
d4T/3TC 30/150 mg	$35	84 493	1%	7	13%	4817	High
		Total	38%c				

Table 12: Categorization of the markets for single products used in first-line regimens, donor-funded purchases in 2012

Formulation	Median price per person per year (US$)	Quantity of person-years	Percentage of total first-line market	N# of manufacturers with products eligible for donor-procurement	4 firm ratio	HHI	Concentration
EFV 600 mg	$46	1 120 882	19%	11	85%	2332	Moderate
NVP 200 mg	$29	1 246 822	21%	13	94%	2907	High
		Total	40%c				

Notes for Tables 10–12:

[a] Until 4Q 2012, Mylan was the only manufacturer with TDF/3TC/EFV eligible for major donor-funded procurement, with Hetero receiving tentative approval by the FDA for its product. Since 2Q 2013, an additional product from a third manufacturer (Aurobindo) has received FDA tentative approval.

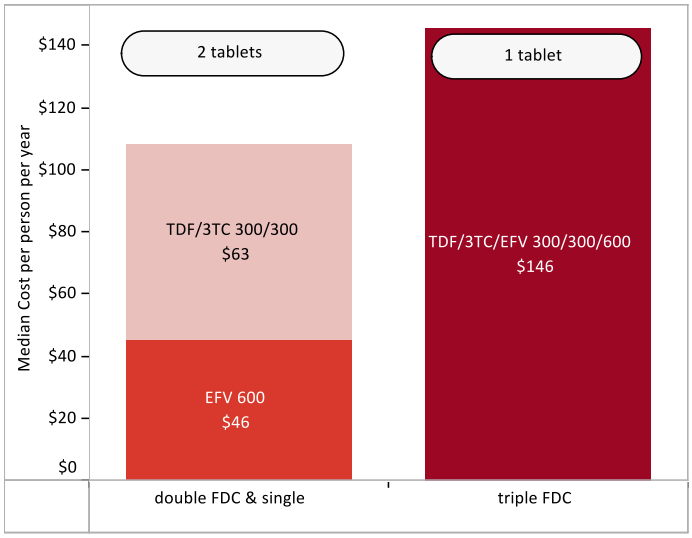
[b] Merck received FDA approval for TDF/FTC/EFV in 2006; in 2009 (Mylan) and in 2011 (Cipla) generic products became eligible for purchase by main donors. Fourth and fifth manufacturers saw their products approved in 2Q 2013 (Aurobindo) and 4Q 2013 November (Hetero).

[c] Double FDCs and single-formulation tablets are used in combination, therefore, their market shares overlap.

Price trends

The markets for triple FDC TDF-based regimens also are dominated by a small number of firms as these are the only ones that have met donor eligibility criteria. In such cases, competition is extremely limited and firms are able to extract high prices. Until 4Q 2012, Mylan was the only manufacturer in the market with a TDF/3TC/EFV FDC that met donor eligibility requirements (Figure 12). As a result, Mylan was able to charge a significant premium for this single-tablet regimen, at approximately US$ 146 per person per year, despite the fact that the separated components (TDF/3TC and EFV) could be purchased for slightly more than US$ 100, and their price was declining over time. In most competitive markets, including those for AZT/3TC/NVP and d4T/3TC/NVP, triple FDCs are priced significantly lower than other options.

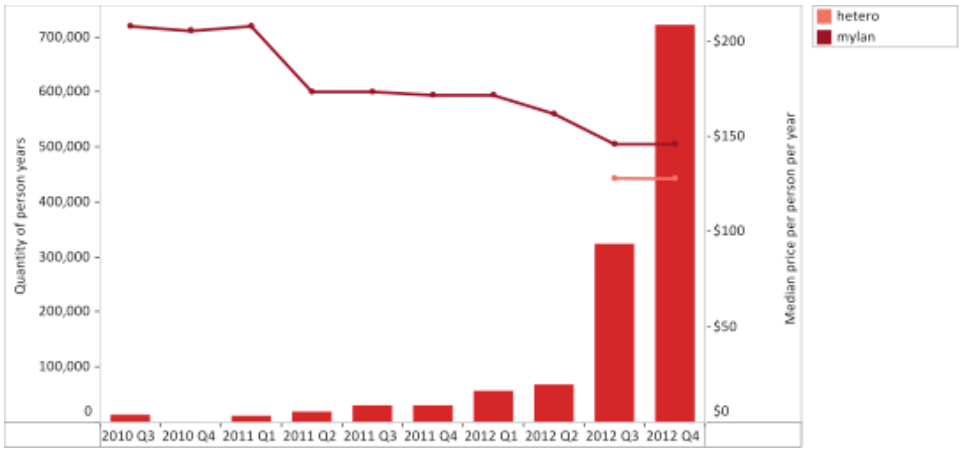
Figure 12: Price premium for triple FDC TDF/3TC/EFV, 2012 (US$)



As a result of recent approval by the FDA of TDF/3TC/EFV FDCs manufactured by both Hetero and Aurobindo, the price began to fall and by 2Q 2013, countries were achieving prices as low as US$ 128 per person per year, a decrease in price of 20% from six months earlier (Figure 13). Further price decreases are expected over the long term as uptake increases due to the WHO recommendations and additional manufacturers enter the market.

The accessibility of many products, including TDF/3TC/EFV, is often driven by price that is, in part, a function of demand and the level of competition in a market. Demand needs to be sufficient to entice manufacturers to enter the market and allow economies of scale and sustainable pricing. Once new manufacturers enter, prices tend to drop, which further increases the demand for a product, creating a positive feedback loop. TDF prices were, for example, dramatically reduced in the period 2006–2012, in part, through catalytic purchases, improvements in manufacturing processes and increased competition for supply of starting materials (as part of the second-line ART UNITAID-funded project with CHAI). The consolidation of regimens resulting from the 2013 WHO guidelines, which recommend single-tablet TDF-combinations, is expected to increase demand and encourage more manufacturers to enter the market.

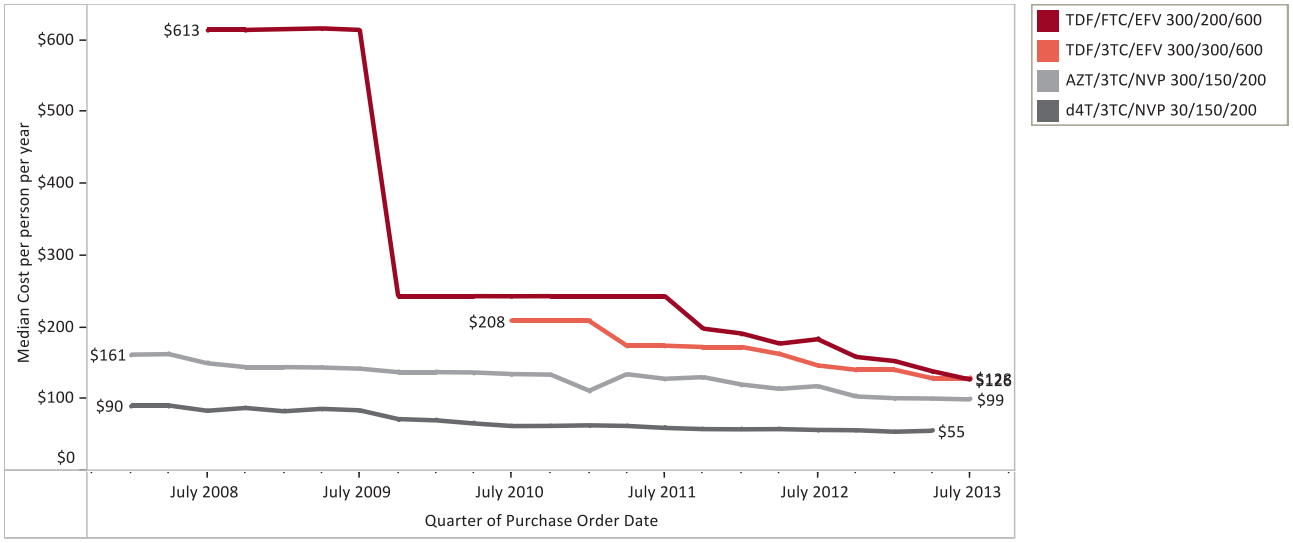
Figure 13: Evolution of reported prices and procurement volumes for TDF/3TC/EFV



Price comparison among alternative first-line regimens

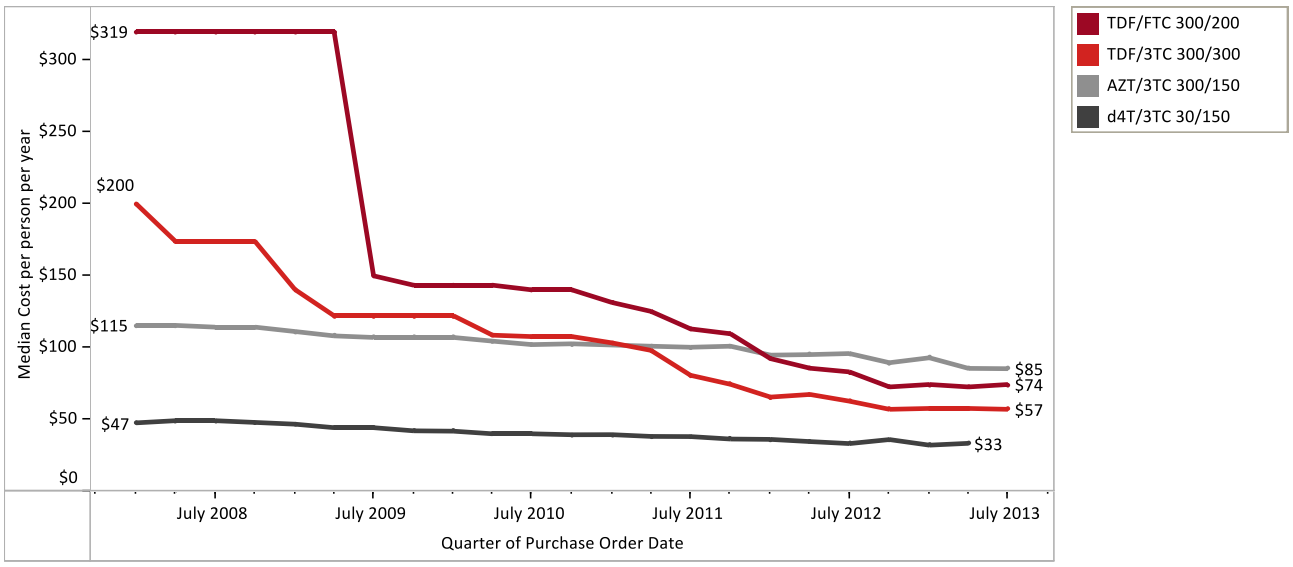
Compared to other alternative first-line regimens, the currently preferred regimens in a single-tablet formulation containing TDF, 3TC (or FTC) and EFV remained significantly more expensive in 2Q 2013 (US$ 128 per person per year) than those containing AZT, 3TC and NVP (US$ 99), with greater competition and demand. However, the price of TDF/3TC (or FTC)/EFV has declined recently as described earlier. For comparison purposes, d4T regimens are included in Figure 14, although no longer recommended by WHO.

Figure 14: Price trends: median prices for different first-line regimens in triple FDCs, 2008–2013 (US$)



In contrast with triple FDCs, double FDCs containing TDF are less expensive than AZT-double FDCs. By 2013, six manufacturers produced TDF/3TC that had been tentatively approved by the FDA and/or prequalified by WHO. Four of these manufacturers received approvals for their products prior to 1Q 2011 and the competition and increased volumes drove prices below those of AZT/3TC (Figure 15). The prices of TDF-double FDCs have continued to decline, while the prices of AZT-double FDCs have remained relatively stable since 2011. In 2Q 2013, a number of countries reported prices of US$ 57 for TDF/3TC and US$ 85 per person per year for AZT/3TC.

Figure 15: Price trends: median prices for double FDCs commonly used in first-line treatment (2008–2013)



5.1.6 Second-line ARVs

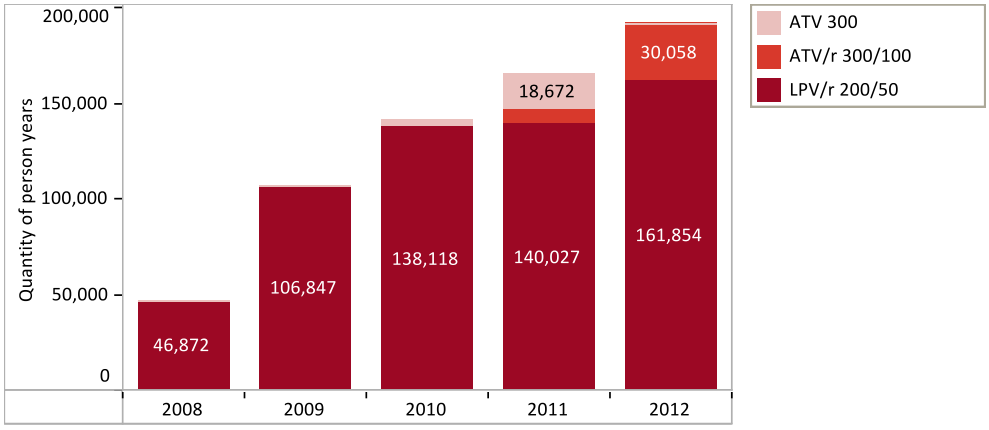
This section focuses exclusively on PIs, which are part of the WHO-recommended drug class for second-line regimens. Other ARVs used as the backbone of second-line regimens, such as AZT/3TC and TDF/3TC, were discussed in the previous section. It is expected that, as more people are initiated on the WHO-recommended TDF-containing first-line regimens, an increasing number of people will use AZT/3TC as the NRTI backbone in second-line regimens.

Market size

Although still much smaller than the first-line market, the market for second-line regimens is growing (Figure 16) and may see a jump in size over the next several years as more people in need of second-line are identified by routine viral load monitoring. For low- and middle-income countries as a whole, WHO estimates that 320 000 people were on second-line therapy in 2012 *(25)*. That year, reported procurement volumes from the Global Fund, PEPFAR and UNITAID funding were equivalent to treat over 192 000 people, representing a 310% increase from 2008. CHAI estimates that up to one million people may be on second-line ART by 2017 *(82)*.

Boosted LPV has dominated the PI market in low- and middle-income countries, accounting for 84% of donor-funded PIs procured in 2012. ATV sales significantly increased in 2011 and 2012. After the Mylan combination tablet ATV/r was tentatively approved by the FDA in November 2011, almost all volumes transitioned to the combination product; in 2012, ATV/r accounted for 30 000 person-years in the donor-funded market, and 16% of all PI purchases. CHAI expects that the ATV/r share will reach 34% in the PI adult market by 2017 *(82)*.

Figure 16: Donor-funded purchases of PIs for second-line therapy



Co-formulations

The two WHO-recommended PIs for second-line ART, LPV and ATV, are both marketed with RTV as heat-stable FDCs (see Section 5.3 for restrictions in marketing of the FDCs in some countries). A heat-stable DRV/r FDC also is under development. As of October 2013, there was no single-tablet regimen for second-line available in the market. One exception is a second-line co-pack, containing ATV, RTV and TDF/3TC, prequalified by WHO in 2011, but no transactions have been reported by donor-funded programmes yet.

Competition

The market for PIs in low- and middle-income countries has been and remains highly concentrated, with limited competition. Until 2009, AbbVie (formerly Abbott) had a monopoly on LPV/r sales within the donor-funded market. The FDA tentatively approved LPV/r by four additional manufacturers: Mylan (2009); Aurobindo (2009); Cipla (2009); and Hetero (2012). As a result, the market for PIs diversified substantially in 2009–2011 as the new entrants gained market share. Somewhat surprisingly, the concentration of PI manufacturers in the donor-funded market increased in 2012, as Cipla and Emcure both lost market share. Within the donor-funded segment, three firms, Aurobindo, AbbVie (Abbott) and Mylan, accounted for more than 99% of sales volume in 2012. In 2012, Abbott also won 100% of South Africa's 2013–2014 tender for LPV/r, which equated to annual volumes of approximately 85 000 person-years.

Mylan's ATV/r, which received tentative FDA approval in November 2011, remains the only manufacturer producing ATV/r eligible for procurement by major donor-funded programmes.

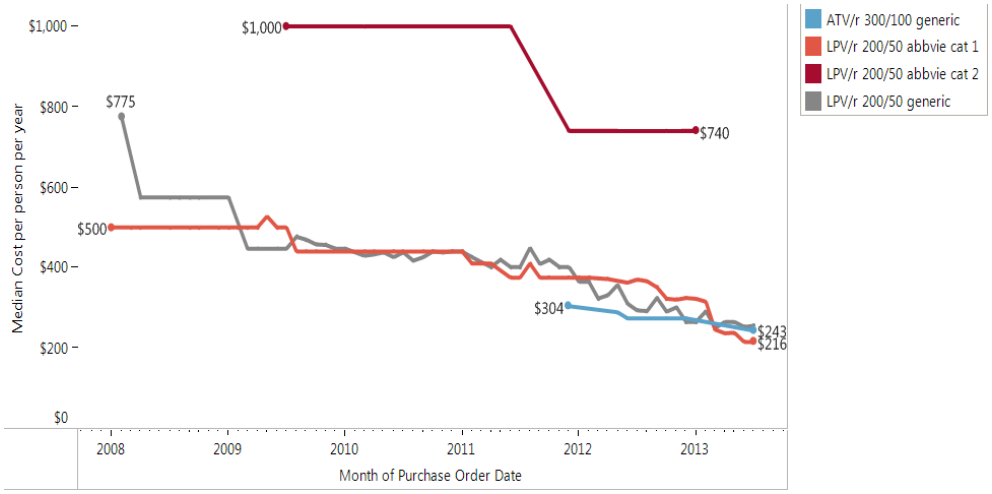
Price trends

Though the gap has fallen substantially over time, second-line regimens remain much more expensive than first-line regimens. In 2Q 2013, triple FDCs containing TDF, 3TC (or FTC) and EFV for first-line treatment were selling for US$ 128–140 per person per year, while full second-line regimens cost, at a minimum, US$ 297 per person per year (Figure 17).

Prices of LPV/r have declined by 57% in markets with generic competition. Prior to generics entering the market, AbbVie maintained a two-tiered pricing system whereby least-developed countries, as well as all countries in sub-Saharan Africa, could purchase LPV/r for US$ 500 per person per year, while most lower-middle-income countries were charged US$ 1000 per person per year. Beginning in 2008, generic manufacturers began to sell at prices below the lowest tiered price of AbbVie, leading a price reduction. By 2Q 2013, some buyers were reporting having achieved prices of US$ 215 per person per year. In addition, despite still maintaining its monopoly position in relation to patent and regulatory barriers status in many middle-income countries, AbbVie decreased its second tier price from US$ 1000 to US$ 740 per person per year in 2012.

The initial price of Mylan's ATV/r in 2011 was significantly lower (US$ 300 per person per year) than the price of LPV/r at the time. However, since 2011, the price of ATV/r has not fallen as fast as that reported for LPV/r and as a result, in 2Q 2013, the ATV/r price and the lowest price available for LPV/r were closer.

Figure 17: Reported prices for most commonly reported bPIs (US$)



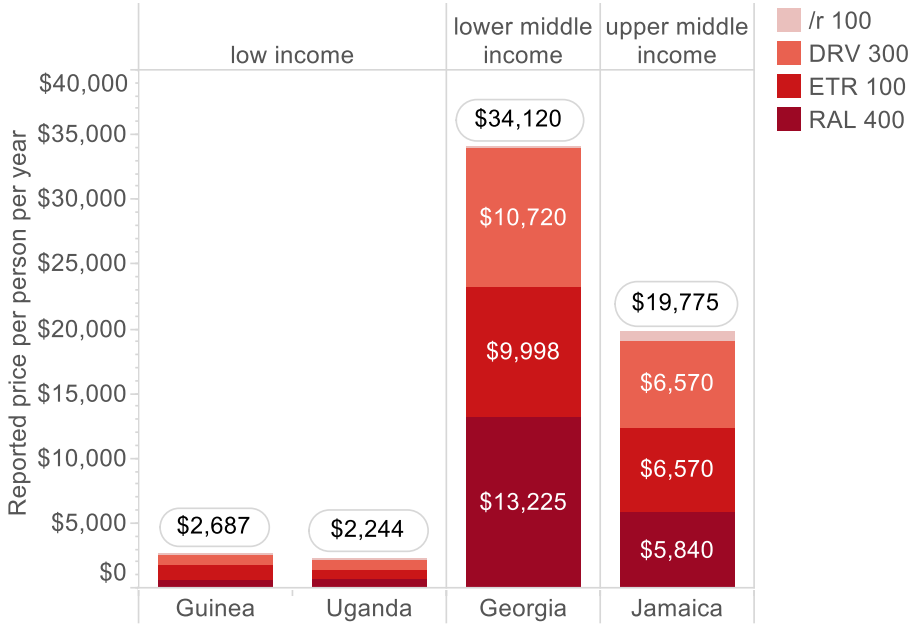
5.1.7 Third-line ARVs

Market size and prices

The market for third-line regimens in low- and middle-income countries is extremely small. The WHO recommendations for third-line ART include the combination of RTV-boosted DRV, RAL and ETR. In 2012, donor-funded procurement of these products totalled just 960 person-years for a value of US$ 1.87 million. In other countries, purchasing with domestic funds, such as Brazil, there is a significant number of people using third-line regimens.

Prices for these drugs were extremely high in the study period (Figure 18). DRV reported prices ranged from US$ 810 per person per year in Côte d'Ivoire, Rwanda and Uganda, over US$ 7000 in Paraguay, to more than US$13 000 per person per year in Georgia (considering a dose of DRV 600 mg twice daily). The price reported for the full recommended regimen (RTV-boosted DRV, RAL, ETR) ranged from US$ 2244 in Uganda to US$ 34 120 per person per year in Georgia.

Figure 18: Examples of donor-funded reported prices for third-line regimens, 2012 purchase orders (US$)



Competition

The market for third-line products is not competitive, with originator manufacturers serving as the sole source of products. In 2013, the Expert Review Panel recommended generic versions for temporary purchase of both DRV and RAL. As of October 2013, purchases of generic DRV and RAL had not yet been reported by Global Fund recipients. The uptake of third-line regimens, including generic versions, is likely to be dependent upon a number of elements, including patent and licensing issues in recipient countries as well as availability of monitoring tools and resistance testing.

5.1.8 Paediatric ARVs

Market size

The paediatric ARV market is very limited, compared to that of adults, with 7% of the global market. At the end of 2012, approximately 647 000 children were on ART, a quarter of them in South Africa. Poor access to early infant diagnosis (35%) *(93)* and a high proportion (51%) of loss-to-follow-up in children with a positive test result *(94)* contribute to explaining current limited access to treatment for children. These programmatic challenges are worsened by limited adequate infant- and child-friendly formulations despite the high number of existing formulations in this very fragmented market with over 60 formulations, including multiple formulations of the same drug for different weight-bands. Indeed, WHO estimates that 2.6 million children are eligible for treatment, but not yet receiving it, although the pace at which those children could be started on ART remains uncertain.

UNITAID-funded paediatric procurement accounted for nearly two thirds of the market between 2005 and 2012, but it is now, for the biggest part, being transitioned to the Global Fund and PEPFAR. It is anticipated that these organizations will represent a 55% and 15%, respectively, of the paediatric market once the transition is complete from 2014 onwards.

The paediatric market segment is expected to grow in the short and medium term, as additional children become eligible for treatment under the new WHO guidelines and case finding efforts improve, evolving from US$ 92 million in 2012 to US$ 182 million in 2017, and reaching over one million children *(17)*. On the other hand, according to CHAI, there are indications that the number of children on treatment has begun to flatten or decrease in some countries; several ARV manufacturers also have suggested that orders

have not amounted to anticipated volumes given historic growth rates *(82)*. This reported decrease may stem from a number of factors, including: (i) a mismatch between reporting and procurement cycles; (ii) challenges in identifying a relatively fewer number of new paediatric infections in countries that have achieved high prevention of mother-to-child transmission of HIV coverage; and (iii) decreased emphasis on case finding of HIV-positive children outside the prevention of mother-to-child transmission continuum. In addition, the rate of financing treatment for children, and inclusion in country budgets, is lingering behind that of adults.

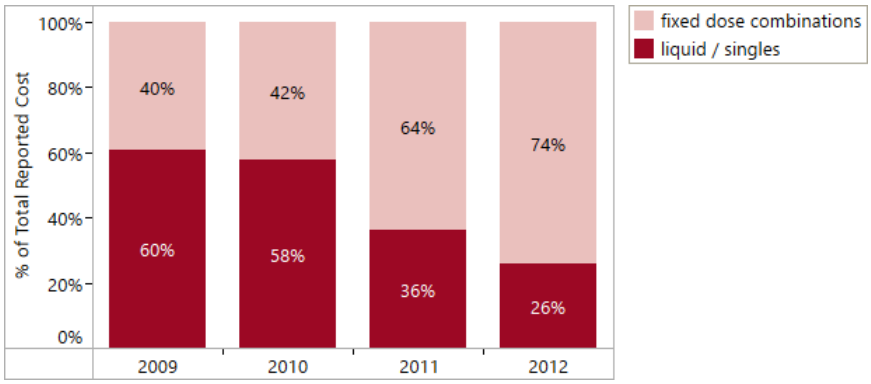
In the long run, the reduction in the number of babies born with HIV, as well as the ultimate transition of children currently on ART to adult formulations, will contribute to a reduction in the paediatric market.

Co-formulations and adapted dosage forms

In the past, the availability of FDCs, with a first dispersible tablet for first-line regimens (d4T/3TC/NVP) marketed by Cipla in 2008, meant that young children in resource-limited settings could be treated with simpler and less expensive formulations. Indeed, this market has largely been made of regimens containing d4T, with 67% of first-line paediatric patients on d4T in 2010, and 40% in 2011 *(17)*. Subsequently, newer FDCs have been produced replacing d4T with AZT, and most countries have switched to regimens containing AZT. Reported procurement for the triple FDC AZT/3TC/NVP 60/50/30 mg increased from US$ 5.7 million in 2010 to US$ 14.8 million in 2011. The work of countries and partners, led by the UNITAID–CHAI paediatric project, to promote adequate and simplified children therapy has been instrumental in aggregating demand around FDCs, although some countries still rely on a mix of syrups and single tablets, including South Africa (Figure 19).

Coordinated procurement, first initiated by CHAI within the UNITAID-funded paediatric project, and now extended and followed up by partners in the Paediatric ARV Procurement Working Group, aims to aggregate demand around a limited number of ARV formulations included on the Optimized Paediatric ARV formulary of the Inter-agency Task Team (IATT) on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children. This list, last updated in November 2013, aims to facilitate the adoption of WHO-recommended therapies by countries and to guide procurement of best-available formulations needed to meet the requirements of all paediatric age groups and weight-bands *(95)*.

Figure 19: Donor-funded paediatric market share, by value, of FDCs and single or liquid products



It is notable that the current paediatric pipeline and more recently approved drugs are mostly solid forms (tablets or granules). However, none of the four WHO-preferred first-line regimens for children exists as a single-tablet regimen. This situation contributes to perpetuating the use of less efficient (e.g. NVP-based regimens for infants) or more toxic treatments (e.g. d4T-based regimens for older children), which are marketed in child-friendly FDCs and at lower prices.

Competition

Until 2005, originator companies dominated the paediatric market. In 2011, however, the four largest generic companies controlled 88% of the market *(96)*. As shown in Figure 20, Mylan, with 44% of the donor-funded market, plays a leading role, particularly due to the AZT/3TC/NVP 60/30/50 mg market share. From 2009 to 2012, Mylan was the sole manufacturer of such an FDC product eligible for procurement by main donors. For 40% of the optimal formulations listed by the IAAT up to December 2013, when a second edition of the list was updated, only one manufacturer met the requirements of donor purchases, in most cases Cipla being the sole supplier (Table 13).

Figure 20: Donor-funded paediatric ARV sales by manufacturer, 2012

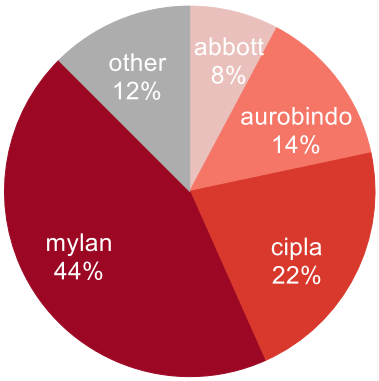


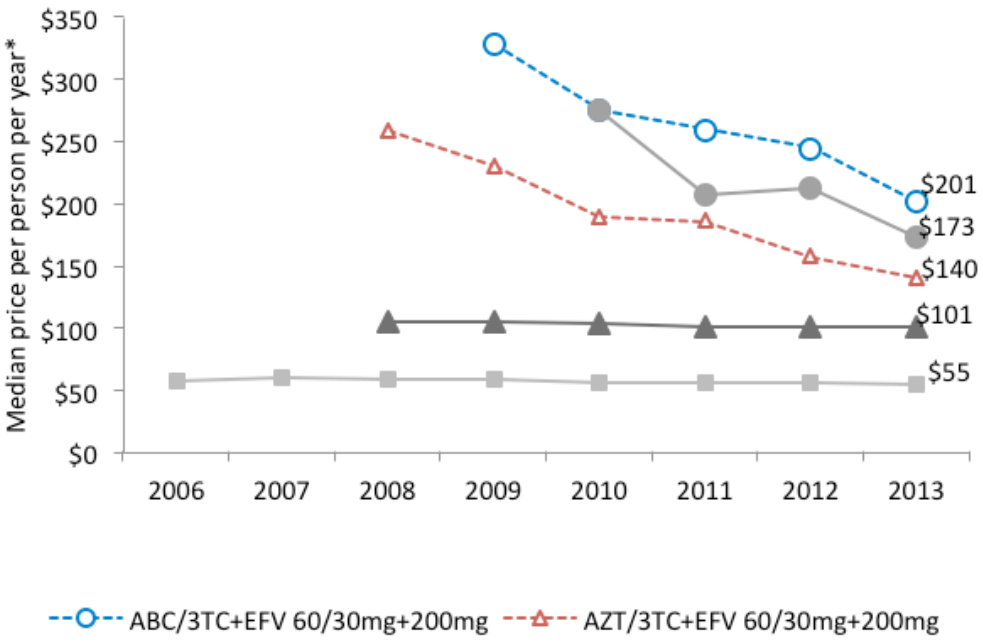
Table13: Manufacturer market share and value of the 15 formulations listed as optimal on the 2013 IATT list

Formulation	Total value reported in 2012 (US$)	Percentage of total reported value 2012	Market share of top manufacturer in 2012	Eligible manufacturers end of year 2013
AZT/3TC/NVP 60/30/50 mg	$12 162 602	40%	97%	3
ABC/3TC 60/30 mg	$3 737 917	12%	50%	3
NVP 10 mg/mL	$2 907 086	10%	52%	3
EFV 200 mg	$2 765 824	9%	83%	8
AZT/3TC 60/30 mg	$2 233 972	7%	57%	5
LPV/r 80/20 mg/mL	$1 958 039	6%	100%	2
LPV/r 100/25 mg	$1 385 626	5%	61%	3
AZT 10 mg/mL	$529 284	2%	77%	7
NVP 50 mg	$68 863	0%	100%	3
ABC/AZT/3TC 60/60/30 mg	No reported procurement			1

Price trends

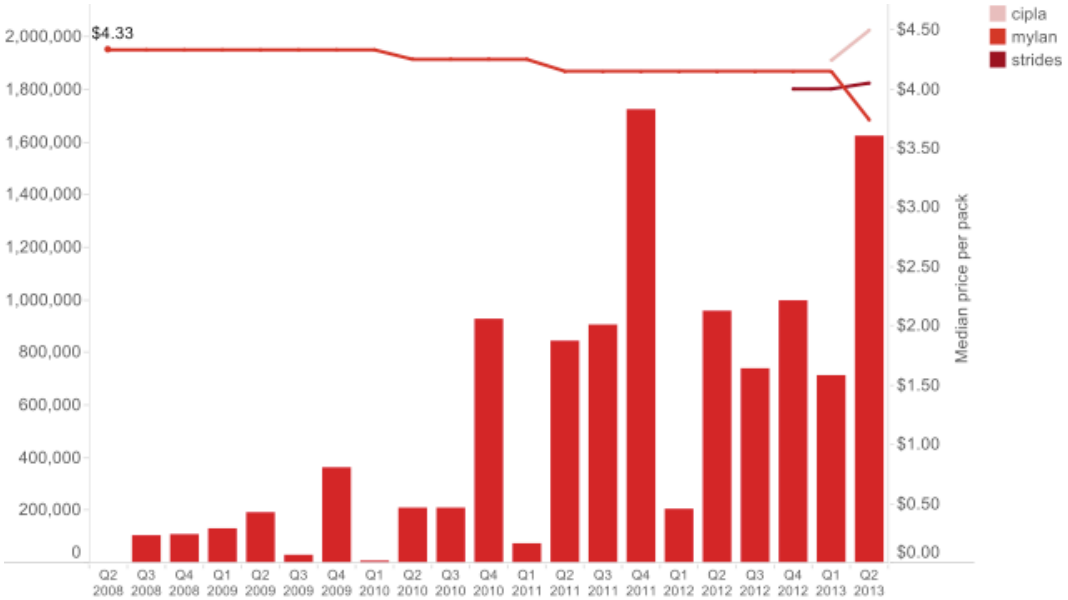
In general, prices of paediatric formulations have not changed at the same pace as those of adults, explained by the relatively small volumes and high concentration of manufacturers. As shown in Figure 21, the most commonly procured paediatric regimen, AZT/3TC/NVP 60/30/50 mg, has seen significant volume increases, but prices have remained stable. Until 2013, Mylan was the single source of AZT/3TC/NVP 60/30/50 mg eligible for donor-funded procurement (Figure 22).

Figure 21: Price trends of main paediatric ART regimens in use in countries (US$)



** Prices are calculated for a 10 kg child (recommended dosing for the 10–10.9 kg weight-band in the WHO ARV treatment guidelines).*

Figure 22: Price and procurement volume trends of donor-funded AZT/3TC/NVP 30/50/60 mg tablets (US$)



5.2 APIs

5.2.1 Introduction

The purpose of this section is to provide an overview of the API market for the priority APIs in order to further identify market shortcomings as well as potential market interventions that could prevent or mitigate price instabilities and/or inadequate ARV production levels that could threaten the treatment scale-up.

Because there are significant differences between the production of APIs and the subsequent conversion of APIs into FPPs, and because API processing is a relatively narrow and highly specialized field, a background section is included covering production, cost components, regulation, quality assurance and evaluation methods for APIs.

5.2.2 Background

Production of APIs

APIs are synthesized from simple organic molecules transformed by a series of synthetic steps in which old bonds are broken and new bonds are formed in large volumes of solvent. The synthesis has multiple steps and uses isolation, crystallization or other means to purify intermediate compounds or APIs, following certain specifications to assure consistent production of acceptable quality. A typical API process of 5–8 steps generates over 100 kg of organic waste for every kg of API produced. Recrystallization and size adjustment (milling) are critical "finishing" steps and are needed to achieve the physicochemical properties often critical to therapeutic equivalency (bioequivalence) of generic products.

In addition to particle size, the physical form (crystalline versus amorphous, and the specific crystalline packing arrangement or polymorphic form) of an API is specified to ensure FPP equivalence. RTV, for instance, is a well-known ARV for which the crystalline form II polymorph has a relative bioavailability of roughly 1% of the amorphous form.

Standards for all APIs specify rules for absolute purity (sometimes referred to as potency) as well as limitations for impurities, with not more than a 0.1% typical threshold. Impurities whose levels can increase over time from degradation of the API or the finished product (degradants) are specified and controlled differently than impurities that originate during the API production.

The resulting API, together with excipients, are processed to produce the FPP (through blending, mixing, granulation, drying, size adjustment, compression and coating rather than molecular transformations as used in API synthesis). These operations are not simple either, but generally require less expensive technology than for API production and generate only small quantities of waste. Excipients used in FPP manufacturing have a history of use in food, cosmetics and pharmaceuticals and are Generally Regarded as Safe ("GRAS").

Cost components of APIs

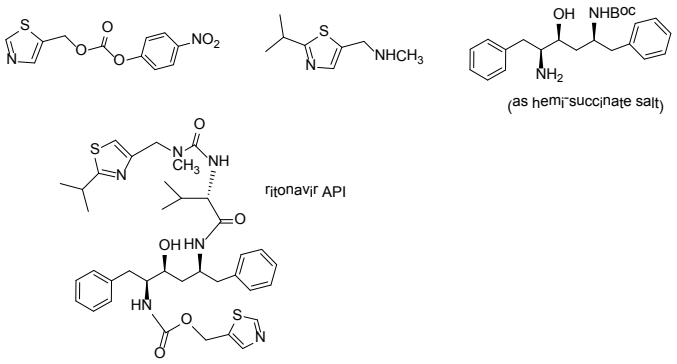
The cost of an API is most often the largest contributor to the cost of an FPP: For simple APIs with short routes of synthesis (e.g. 3TC), the cost of an API will represent a lower percentage of FPP cost than for structurally more complex APIs with longer routes of synthesis (e.g. PIs).

The main cost components of API production are starting materials and the overall yield of processing, overhead and labour associated with processing and testing and capital investment needed in equipment and facilities (which may be shared over a number of products if ARV APIs are manufactured in multipurpose).

Starting materials costs: API raw materials are often manufactured by fine-chemical manufacturers for several different purposes, most of which may not be for API production. The beginning point for carrying out API syntheses in compliance with good manufacturing practices (GMP) starts with the manufacturing firm designating and justifying the choice of API starting material(s) since access to these materials may be critical to the cost and availability of ARV APIs. As an API process approaches maximum efficiency, raw

materials costs become an increasing component of API production cost. For very efficient processes, starting materials may exceed 50% of the cost of API manufacturing. The starting materials for the synthesis of RTV API are illustrated in Figure 23.

Figure 23: RTV and starting materials



Examples of raw materials with potential to impact ARV availability or cost include the availability of 5-hydroxmethylthiazole for the production of RTV or adenine for the production of TDF, the price of magnesium (II) tert-butoxide for the production of TDF, beta-thymidine for the production of AZT and menthol as a cost contributor to 3TC and FTC.

Overhead and labour costs: Overhead and labour contributions to the cost of API manufacturing are related to the cost of skilled employees capable of carrying out GMP production and the expense of operating the manufacturing facility. The overhead and labour cost is relatively constant for a given production facility. Such costs in China and India are generally a smaller contribution to API costs than raw materials or equipment/facilities.

Equipment and facilities costs: Large-scale chemical synthesis is primarily carried out by processing individual batches of material through heating, cooling, distillation, high- and low-pressure (vacuum) filtration, drying to remove volatile organic chemicals, operation under an inert atmosphere (nitrogen), and milling to adjust particle size. Manufacturers need to implement controls to minimize employee exposure and external emissions of volatile organic chemicals and pharmaceutical solids to the environment. These safety requirements for heating, ventilation and air conditioning substantially increase the cost of building an API manufacturing facility. Companies generally amortize facilities and capital equipment over lifetimes of 20 and 10 years, respectively.

The size of a company's processing equipment often determines the limit of API production capacity. GMP requirements for cleaning, calibration and preventive maintenance effectively limit production capacity to about 80% of what could be produced if a plant were operating 24 hours a day, 7 days a week.

Economies of scale

There is a common perception that production costs of APIs decrease automatically as volume increases. This is true, with some limitations. Raw materials costs for API production are largely unaffected by volume when their primary use is for non-pharmaceutical purposes. Generalizations about the economy of scale also are affected by the number of qualified API suppliers, production capacity and the degree of capacity utilization. These limitations can be illustrated using a few hypothetical examples:

- *Demand:* Small-volume drugs are more sensitive to changes in demand than large-volume ones. An increase in demand from 10 to 60 metric tonnes/year (500% increase) will have a much greater impact on API price than an increase from 500 to 550 metric tonnes/year (10% increase).
- *Number of producers:* Although competition between multiple suppliers normally results in a price reduction, the existence of multiple suppliers has a negative impact on achievable economies of scale

in some API markets. A global demand of 800 metric tonnes/year of 3TC, for example, might easily support five major producers with annual volumes of 50–200 metric tonnes each. For much smaller demand markets such as RTV, however, even two suppliers splitting the current annual demand (less than 10 metric tonnes) could undermine achievable economies of scale. Too much competition for a limited market demand also increases the risk that suppliers will compete on price by decreasing their GMP investments, resulting in risks to the quality of APIs and FPPs.

- *Links between production capacity and economy of scale:* The maximum economy of scale depends on the capacity of a specific production facility. A company whose capacity for production is completely absorbed (e.g. 100 metric tonnes/year) has reached their maximum economy of scale, with both underutilization and overutilization of capacity resulting in cost increases. If this company is required to meet a demand of 130 metric tonnes/year, the company may need to outsource some production at a premium price, causing prices to rise over the short term. Conversely, a company with 200 metric tonnes/year of capacity must charge a higher price for 100 metric tonnes/year because the expense of their 50% unused capacity must be absorbed into this 100 metric tonnes of sales.
- *Limits to economies of scale for API production:* Equipment used for API production has practical size limits. Accordingly, the size of API batch production also has a practical limit. A company with a maximum batch size of 250 kg for API production will reach a maximum economy of scale at roughly 75 metric tonnes/year (250 kg/batch x 300 batches that can be made in a year).

Profit margins with ARV APIs and FPPs

Given the degree of specialization in the marketplace, many generic FPP manufacturers purchase some or all of their APIs from other companies. Generic producers typically target a margin of about 15–30% on API production; FPP manufacturers generally aim for a 30–50% markup.

The cost of an API typically represents roughly 60–85% of generic FPPs. This is in sharp contrast to originator companies that operate on a vastly different cost structure. The total expense distributions of originator companies for research and development (R&D), marketing, and manufacturing are 10–15%, 22–26% and 32–36%, respectively. In order to be profitable, originator companies aim to keep the total cost of an FPP (including the API) to less than 10–15% of the final price.[3]

Generic companies do not generally invest in new drug discovery, and development costs are significantly lower as product development involves "reverse-engineering" of an originator product and marketing costs for generic ARVs to low- and middle-income countries are very low to non-existent. Generic companies generally sell ARVs with a modest (15–30% or even less) profit, whereas originator companies market FPPs with a roughly 1000%, or even higher, markup over API costs in high-income markets.

Starting materials costs are roughly the same for generic and originator producers. The costs of capital investment and overhead and labour are typically much lower for generic versus originator producers, and the same is true for API costs for a variety of reasons:

- the criticality of specific ARVs in the generic market is established over a long period of time, allowing an assessment of where the highest priorities lie for the application of new technology devoted to cost reductions;
- originator companies apply "just-in-time" economics to API production, limiting the time and effort they devote to process development on any single API in order to maximize time of market exclusivity;
- originator companies do not necessarily seek the lowest possible costs for API production as they usually have a monopoly on their newer products in high-income markets.

Decreasing production cost

There are four major ways that API production costs can be significantly reduced. Many of these improvements are incremental, involve significant time and effort and may require the approval of regulatory authorities for implementation:

3 Fortunak and Sherbine, from more than 200 new chemical entities brought into development in originator companies; personal experience.

- Identify less expensive sources of starting materials for API production (improved procurement), including key intermediate/reagents made by secondary manufacturers.
- Telescope multiple steps into one step or remove purification steps no longer considered necessary; this is very commonly practised in the pharmaceutical industry.
- Discover a new synthesis that uses less expensive raw materials, has fewer steps and/or has higher overall yields.
- Switch to "continuous processing" of multiple steps in a single process. Continuous processing greatly reduces manufacturing time (overhead and labour costs) and may reduce capital investment because smaller-sized equipment can be used; reactors designed for continuous processing are known as "flow reactors", which can be used for single-step processing, and their use in the fine chemicals industry is well known. The pharmaceutical industry, however, very rarely telescopes multiple steps into flow reactors; currently no ARV APIs are manufactured in this manner.

Manufacturers of ARVs have achieved substantial reductions of API costs in dozens of cases, through improved procurement of raw materials in a competitive environment (TDF, EFV), optimized synthetic processes (TDF, FTC, NVP) and discovering new, significantly different synthetic routes for manufacturing (EFV). As an example of what can be achieved by the combination of increased volume demand, improved procurement and new technologies, the generic API cost of EFV has fallen from approximately US$ 1100 to US$ 130/kg between 2005 and 2013.

Of the other possibilities, continuous processing is increasingly being used; production using flow reactors holds great promise (to optimize the control over key production elements such as mixing, heat exchange, reaction time and solvent volumes), but is largely unproven for large-scale processing.

Quality evaluation for APIs and regulation

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the WHO Prequalification Programme are primary sources of guidance governing the production of essential medicines. These entities, along with EMA and the FDA are largely consistent in their approach to API regulation, including requirement of GMP compliance in all steps in API production. Manufacturers of generic FPPs generally purchase APIs from vendors based solely on cost considerations. This approach is perfectly valid, providing that APIs fully meet specifications and production complies with GMP requirements. Each FPP producer must evaluate the physicochemical properties of an API to assure it will be both stable and bioequivalent in their specific formulation.

The FDA has been inspecting API vendors for ARV procurement through PEPFAR for several years, both regarding GMP compliance and filing of DMFs to approve an API source for a specific FPP application. EMA has a very similar system, but FPP vendors have multiple options to get their API approved: submit API information as part of their FPP application, or refer to a WHO, FDA or EMA DMF.

Regarding WHO prequalification for a given ARV formulation, there are several ways in which the APIs used for its production can be approved, mainly by submitting: (i) a full dossier; (ii) a valid Certificate of Suitability of pharmacopoeial monographs with which the API complies; (iii) an API Master File (APIMF); and (iv) utilizing an API source that has already been prequalified.

The use of an APIMF by the WHO Prequalification Pprogramme of FPPs, in place since 2007, permits WHO access to all the information necessary for evaluating the suitability of the API in the FPP under evaluation, avoiding multiplication of assessments of one given API (one APIMF can be filed for an API used by multiple FPP producers), and lightens the workload of manufacturers and evaluators. APIMF holders reviewed as part of an FPP application are not publicly disclosed by WHO.

On the other hand, WHO prequalification of APIs, operational since October 2010, involves not only the review of the APIMF, but also an assessment of the API manufacturing site to assure adherence to GMP principles and validation of the API process. This process is independent of the prequalification of FPPs that might eventually use such an API source. The advantage of operating under the API prequalification

scheme is that prequalified API manufacturers are publicly identified on the WHO List of Prequalified APIs (as of November 2013; the list includes six ARV APIs from three manufacturing companies in Chinaand three in India).

Risks to quality with API production: API manufacturers often sell in multiple "regulatory markets": (i) those where the regulatory body is considered an SRA; (ii) those where regulatory controls are existing, but not yet included in SRA-defined territories; and (iii) those without any regulatory controls. When companies sell to multiple regulatory markets, and given the price pressure for ARVs in low- and middle-income countries, mix-ups (intentional or unintentional) and substitution of unapproved sources of APIs for those that are approved can occur, resulting in a risk of lower-quality products available in the market. Some manufacturers might produce an API to only one standard (e.g. SRA) and if a batch of API fails that standard, they might sell it to a territory where regulatory requirements are lower.

For new ARVs, an added risk comes from the absence of adequate public specifications for the physico-chemical properties (crystalline form, hydration or solvation, particle size distribution) that are normally critical to assuring bioequivalence of the final product. In the case of recently marketed products, such specifications are often not available in compendial pharmacopeia or publicly released by regulatory agencies.

5.2.3 Overview of market for first-line ARV APIs

Competition

Market concentration: Currently, 10 major suppliers dominate the ARV API market. China and India account for the bulk of raw materials, facilities and infrastructure, skilled technical staff, corporate infrastructure and regulatory experience to make APIs. Chinese-produced APIs are generally cheaper than those produced in India, when the scale being sold is the same. For ARVs no longer under patent (e.g. AZT; 3TC; ABC) and/or for which originator companies are not likely to pursue legal action against supply to low-income countries (e.g. NVP), China has become a major source of APIs. It is estimated, for example, that China supplies roughly 50% of the NVP used in FPPs. On the other hand, for newer ARVs, and due to patent status in China, India is the major supplier of APIs.

Quality-assured APIs: Table 14 summarizes generic companies that have filed United States DMFs and/or have been prequalified by WHO for APIs of ARVs used in first-line treatment. Information about manufacturers holding an APIMF is not included here as names are not publicly disclosed by WHO. Further details are included in Annex 8.1.

Table 14: Manufacturers filing United States DMFs and/or WHO prequalified APIs for common first-line ARV APIs

INN	Number of manufacturers with filed DMFs	Number of countries with manufacturers with filed DMFs	Number of APIs WHO prequalified	Countries of origin for WHO prequalified APIs
TDF	10	2	1	India
3TC	14	3	2	China and India
FTC	13	3	1	India
EFV	12	2	0	–
AZT	12	2	3	China and India
NVP	9	2	1	India

– = not applicable

There are multiple quality-assured suppliers for the four ARV APIs in the preferred first-line regimen (TDF/(FTC or 3TC)/EFV). Nearly all of these suppliers are in India, with a few located in China and other countries:

- TDF API: mostly originated in India (9 of the 10 generic manufacturers known to be SRA-approved) as it is still under patent in China;
- EFV API: India is home to 11 of the 12 manufacturers filing United States DMFs, with the EFV API patent to expire in 2014 in China;
- FTC and 3TC: with 13 and 14 manufacturers, respectively, filing United States DMFs with manufacturers mainly in China and India.

Very few sources of APIs have been directly prequalified by WHO (only one manufacturer for TDF, one for FTC, four for 3TC and none for EFV as November 2013).[4]

Capacity to supply

As the number of patients initiated on ART increases, demand for main ARV APIs and, in particular, for those in preferred first-line treatment, is expected. After a period of fluctuating demand and uncertainty during transition to newly recommended first-line treatment, adequate capacity currently exists within manufacturers of APIs having already received SRA approval of prequalification. Additional capacity will be created by new suppliers entering the quality-assured market.

A short-term challenge on sourcing API starting materials might occur during scaling-up, for example, regarding availability of the fine chemical adenine; minor demand on the TDF API market is prompted by its role in hepatitis treatment. Global EFV API manufacturing capacity of about 1700 metric tonnes/year is likely to be adequate, provided manufacturers continue to invest in ensuring that capacities match increasing demand; however, the reagent "PNE" (pyrrolidinyl-norephedrine) is likely to be limited to a larger volume demand as it is regulated as a controlled substance in China.

Following South Africa's tender in 2012, FTC has undergone a rapid change in demand growth; the availability of 5-fluorocytosine may challenge rapid scale-up of FTC production in the short term. Aside from South Africa, demand for FTC has not grown as rapidly as expected.

Price trends

The last 10 years have seen major reductions in prices for APIs used in first-line ART in low- and middle-income countries, including key products such as EFV and TDF due to decreased API production costs and increased demand and concentration of the market towards a limited number of high-volume APIs,

4 WHO list of prequalified APIs (http://apps.who.int/prequal/lists/API/2013/API_PQ-List_V15_21October2013.xlsx, accessed November 2013).

resulting in economy of scale, expansion of the market for key starting materials and additional qualified suppliers entering the market and driving competitive pricing (Table 15).

Table 15: Prices for APIs used in first-line regimens (US$)

INN	Price range per kg (2013)	Previous price API per person per year (2011)	Current price API per person per year (2013)
TDF	$270–325/kg	$61	$30–36
EFV	$130–160/kg	$29–52	$29–35
FTC	$280–360/kg	$49	$20–26
3TC	$135–145/kg	$22	$15–17
TDF/FTC/EFV		$139–162	$79–97
TDF/3TC/EFV		$112–135	$74–88

As the market matures, some factors that have driven costs down over the last 10 years are unlikely to yield further cost reductions. Additional price declines in the preferred first-line regimen APIs are likely to be more modest, particularly for 3TC or EFV APIs; with the demand of hundreds of metric tonnes/year and limited profit margins, continuing price reductions due to economy of scale are unlikely. It is likely that the most significant future reductions in prices for high-volume APIs will result from decreases in production costs through improvements to synthetic methods, and less by a decrease in the cost of starting materials, which has already been driven to quite low levels by API manufacturers.

5.2.4 Overview of the market for second-line ARV APIs

Competition

The global second-line ARV API market is heavily concentrated in India, which accounts for 9 of the 12 suppliers with United States DMFs for PIs. A manufacturer of an ATV API from China has recently filed a DMF; a DRV API manufacturer from China is included in the latest survey of APIs conducted by WHO *(97)*. The number of manufacturers filing United States DMFs and/or WHO prequalified APIs for PIs are presented in Table 16.

Table 16: Manufacturers filing United States DMFs and/or WHO prequalified APIs for PIs

INN	Number of manufacturers with filed DMFs	Number of countries with manufacturers with filed DMFs	Number of APIs WHO prequalified
LPV	5	1	0
ATV	6	2	0
DRV	3	1	0
RTV	11	4	1

Until November 2013, there were no APIs for any PI included in the WHO prequalification list, with the RTV API from Mylan making its way in the latest update in November 2013.

Production capacity

Multiple generic suppliers of LPV/r and ATV/r, the two currently recommended bPIs for second-line treatment, have either been approved or have submitted dossiers to the WHO Prequalification Programme, but current demand has been very limited. Existing capacity is likely to be sufficient to satisfy demand for RTV and LPV through 2016, although suppliers will need advance information regarding the likely effect on demand of WHO recommendations for children. Substantial underutilized capacity exists to produce the APIs of ATV as well as DRV, the latter not yet included as an optional component for second-line ART and hence with negligible demand.

LPV/r has dominated the second-line market, as already discussed, while ATV/r use is likely to grow. The impetus for a switch could depend on lower drug doses and lower intrinsic cost (300/100 mg doses of ATV/r versus 800/200 mg doses of LPV/r), in addition to more convenient (once-daily versus twice-daily) dosing.

As demand for second-line ART is marginal compared to that of first-line, there is greater room for price deductions due to economies of scale in the second-line API market. In addition, price declines of PIs may result from efficiencies in the production process of starting materials (e.g. 5-hydroxmethylthiazolefor RTV) and ongoing dose-reduction studies.

5.2.5 Overview of the market and market trends for paediatric medicine APIs

For paediatric combinations, the API supply has not been critical, due to the relatively small API volumes required for paediatric formulations. Anticipated switches in paediatric formulations due to WHO revised recommendations or market entry of new child-friendly formulations are not likely to significantly influence volume demands or jeopardize availability of any APIs, although the situation regarding LPV/r supplies needs to be monitored. Abacavir (ABC) demand has been flat from 2010 at about 8 metric tonnes/year and mostly for the adult market. Demand for the paediatric market is expected to grow, from 3 metric tonnes in 2010, to 40 metric tonnes by 2015 with paediatric treatment scale-up; the supply appears to be adequate to meet anticipated needs.

5.2.6 Overview of API-related aspects of emerging ARVs

For adult treatment, emerging clinical data from studies of the once-daily INI DGV, at 50 mg, and other ARVs such as RAL, EVG and COBI, may cause the market to move in new directions, although this is by no means certain, as discussed in Section 4.

In considering prioritization of a given ARV, cost and formulation play key roles, provided clinical and safety parameters are adequate. For example, the triple combination of TDF/FTC/RPV (300/200/25 mg) for once-daily dosing in a single tablet was approved for first-line treatment by the FDA on August 2011. It has potential practical advantages over TDF/ FTC/EFV, with the switch from EFV to RPV making sense for reasons of economics. The synthesis of RPV, fairly simple and without use of expensive starting materials or reagents, and its lower daily dose (25 mg) compared to EFV (600 mg), could lead to lower API costs. Use of RPV-based combinations, however, will be hampered by data demonstrating higher rates of viral breakthrough at 48 weeks in patients initiating therapy with a viral load > 100 000 copies/mL. Regarding TAF, with a daily dose of 10 mg, it has an advantage over TDF, dose at 300 mg daily, making TAF extremely attractive as an option to reduce cost and simplify first-line regimens.

5.3 Intellectual property issues for key ARVs

5.3.1 Background

A patent provides exclusive rights over an invention, generally for a period of 20 years from the date of application. During the patent term, the patent holder may prevent others from making, importing or using the patented product in the country where the patent was granted. Patent protection precludes generic competition for the product.

Medicines are usually subject to multiple patents, which fall into several main categories:

- The compound patent, main or basic patent: such patents cover the API and, where in force, completely block manufacture, import and use of generic versions (APIs as well as all FPPs).
- Process patents and patents on intermediary compounds in the production process: these may block manufacturing of generic products (usually for the API), unless an alternative production method can be found that does not use the patented process or intermediary.
- Formulation patents: these secondary patents vary widely. Some cover a particular dosage form (e.g. tablets containing NVP) or a particular dose (e.g. tablets containing between 5 and 100 mg of ddI); others cover a particular form of the API (e.g. NVP hemihydrate yjat is used only for liquid preparations).

It is not always immediately obvious whether or not a patent blocks generics. For instance, in case of a patent on a particular crystal form of the API, it is necessary to know whether that particular crystal form is present in the FPP. In the case of NVP hemihydrate, this patent blocks generic versions of liquid (paediatric) dosage forms, but it does not block generic tablets because the hemihydrate form is not used in tablets.

In certain cases, the patent is written in very technical language or is very broad, potentially covering hundreds or thousands of compounds. In such cases, it can be difficult to find out whether or not the patent actually covers a particular medicine. Such patents can deter generic competition as manufacturers and supply agencies might avoid taking the risk of potentially infringing a patent.

Searching and obtaining patent information for a given country is challenging. Recently, a public database of patents, created and maintained by the MPP has brought some light to this opaque area, providing information on the patent status of ARVs in 80 low- and middle-income countries.

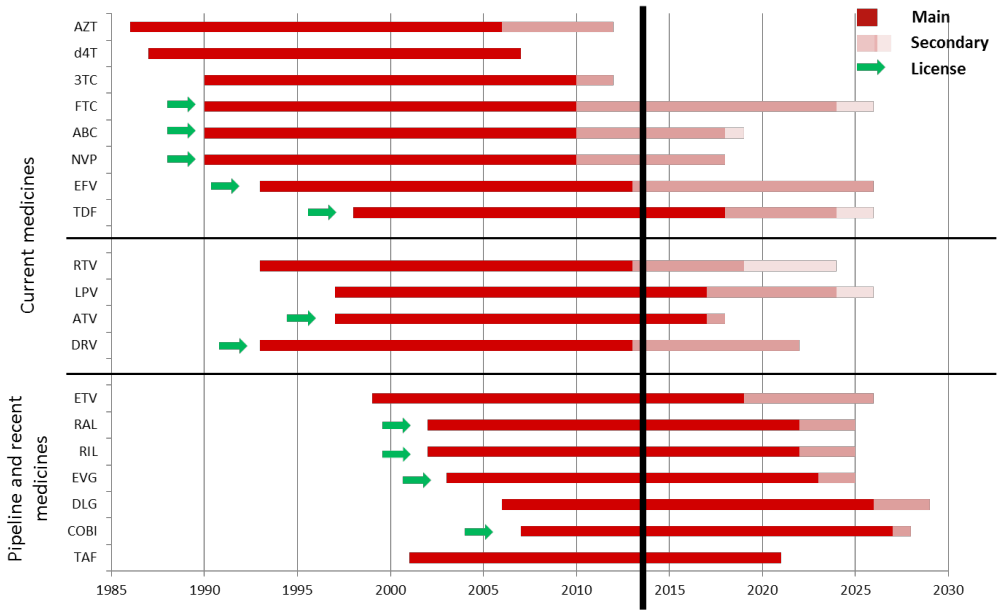
Patents affecting FDCs

FDCs can be affected by patents in different ways. A patent on any of the APIs in an FDC, or a patent on the combination of them, may block access to the (generic) FDC. For example, the patent on NVP does not just block generic NVP when marketed alone, but also blocks the FDC of NVP/3TC/AZT, including in countries where 3TC and AZT are not patented. A formulation patent on the FDC itself, similarly precludes alternative suppliers, even when each of the three APIs is off-patent. Patents related to the FDC formulation may expire a long time after the patents on the individual drugs; for example, the combination patent on PIs with RTV expires 7–11 years later than the basic patents on the individual compounds.

Patents on emerging medicines

Patents are applied for early in the R&D chain as otherwise they might not meet key criteria for patentability. Therefore, ARVs that are still in the pipeline are already patented in many countries (Figure 24).

Figure 24: Estimated patent term for most commonly used or emerging ARVs (based on international patent application) and licensing status

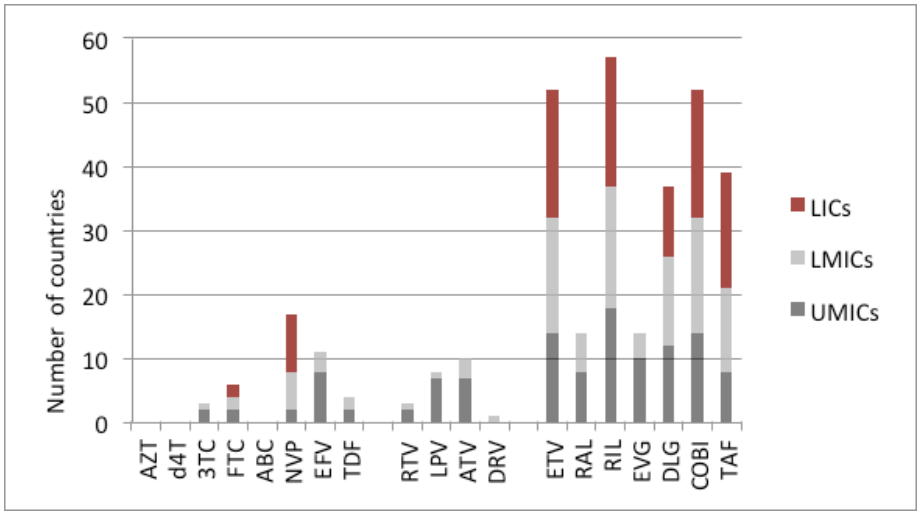


RIL = RPV
DLG = DTG

More recently developed ARVs, and those still in the pipeline, tend to be more widely patented than older products (Figure 25). This is a result of more countries putting patent systems in place and granting patents on pharmaceutical products, which many countries previously did not do, in large part a result of requirements included in the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement for most countries to have a patent system by 2000. Least-developed countries have been granted the possibility of benefiting from extra time, and currently are exempted from granting patents until July 2021.[5]

5 Extension of the Transition Period under Article 66.1 for Least-Developed Country Members, Decision of the Council for TRIPS of 11 June 2013, World Trade Organization document IP/C/64.

Figure 25: Number of countries (ordered by income level) where the main patent for selected ARVs has been granted or is pending



LIC = low-income country
LMIC = lower-middle-income country
UMIC = upper-middle-income country
DLG = DTG
RIL = RPV
Note: Information based on the information available for 80 countries in the MPP database.

Voluntary licenses

A patent holder may allow other manufacturers to make or sell generic versions of the product by granting a voluntary license, which usually sets out conditions that the sub-licensee has to comply with. Licensing terms and conditions generally specify the countries in which generic versions may be made or sold, whether FDCs can be developed, whether royalties are payable to the patent holder and quality criteria that need to be met by the licensee and other conditions. Some of those conditions can have an important impact on the market for patented ARVs. Access-friendly terms and conditions are, therefore, important to enable robust competition for ARVs. The MPP was established by UNITAID in 2010 with the mandate to negotiate access-friendly and transparent voluntary licenses with patent holders of HIV medicines. With the exception of the licenses negotiated by the MPP, the full terms and conditions of licenses are confidential.

Compulsory licenses

A compulsory license is a license issued by the government that allows the manufacture, import and/or use of a generic medicine before the patents on that medicine have expired, and without the consent of the patent holder. Compulsory licenses can be used to promote access to medicines *(98)* and allow local production or importation and use of generic versions of a patented product, and normally require that royalties are being paid to the patent holder. A particular type of compulsory license is for "government use"; such licenses are usually easier to issue, but they only allow the production, import and use of generics for public, non-commercial purposes. Royalties also are to be paid in case of "government use".

Data exclusivity

Some countries provide for a period of data exclusivity. This is a period of time during which the regulatory authority, for the purpose of registration of a generic product, is not allowed to refer to or rely on the clinical test data submitted by the originator. Data exclusivity operates independently of patents, and can block generic competition for a certain period of time, even when there is no patent, by de facto delaying the registration of generics.

The TRIPS Agreement requires countries to protect undisclosed registration data, but does not require data exclusivity as such. Nevertheless, some countries have agreed to provide data exclusivity as part of their World Trade Organization accession, or in the context of free trade agreements. Countries that already implement data exclusivity include Chile, China, Colombia, Guatemala, Morocco, Peru and Ukraine. Regulations and duration of data exclusivity vary among countries. India is currently not implementing data exclusivity, though there are concerns that it will be requested to do so, for example, in the context of negotiations for a European Union-India free trade agreement. If India were to implement data exclusivity, then there might be consequences for generic products penetration in other markets as well.

5.3.2 Patents related to key ARVs

This section summarizes the situation regarding patent and licensing status in low- and middle-income countries for the preferred formulations (in FDCs) of the WHO-recommended regimens for ART as well as key emerging ARVs. This information is limited to countries for which information is available in the MPP database.[6] As the patent status may change over time, interested readers should consult the database or the national patent office of the country concerned to obtain up-to-date information. Further details on the patent and licensing situation of individual ARVs can be found in the forthcoming publication *Patents and licenses on ARVs: a snapshot* by the MPP and UNITAID.

Patents and licenses on preferred first-line combinations

TDF: Where granted, these patents are expected to remain in force at least until 2018. Many low- and middle-income countries can benefit from the Gilead license from the MPP signed in 2011, although there are exceptions such as China and Mexico, where TDF is patented, but which are not covered by the license. Other countries not included in the Gilead licenses and where patents are not granted for this product, can either produce locally or import from Indian companies that do not have a TDF license with Gilead.

FTC and 3TC: Patents were not widely filed or granted in low- and middle-income countries, and where granted have mostly expired.

EFV: The compound patent has been granted, among others, in Argentina, Mexico, South Africa, Thailand and Ukraine. In most countries it would be expected to expire in late 2013 or 2014. Compulsory licenses have been granted in Brazil, Indonesia and Thailand, while a voluntary license is in place in South Africa.

TDF/FTC/EFV: There appear to be blocking patents, or patent applications, on one or more of the ingredients of the FDC, or on the FDC per se,[7] in Argentina, Armenia, Azerbaijan, Belarus, Brazil, China, Kazakhstan, Kyrgyzstan, Mexico, Moldova, Tajikistan, Turkey, Turkmenistan and Ukraine. In countries where these patents are granted, the manufacture, import or use of generic versions of this FDC is not permissible. In some other countries (e.g. Kenya, Tanzania and Uganda) patents have been granted on TDF/FTC, but, due to the license from Gilead to the MPP, generic versions can be imported and used.

TDF/3TC/EFV: Patents related to TDF/3TC/EFV have expired in most countries, or are included in licenses as explained above. Thus, in most countries, this FDC can be used. Notable exceptions are China, Mexico and Ukraine, where manufacturing, importation or use of this FDC may not be allowed.

Patents related to alternative first-line regimens

The main patent on AZT, d4T and NVP compounds have not been widely granted in low- and middle-income countries, and have already expired for the most part. With respect to patents on combinations of these drugs, patent holders have agreed not to enforce them (non-assert declarations) with regard to India, sub-Saharan Africa, least-developed and low-income countries where generic competition is taking place.

6 MPP Patent Status Data base (http://www.medicinespatentpool.org/patent-data/patent-status-of-arvs/, accessed October 2013).
7 Patents on the FDC per se would in most countries expire in 2024 or 2026.

Patents on PIs

RTV: The basic patent covering the compound RTV has only been granted in a few low- and middle-income countries, notably Brazil (where it is opposed), Mexico and the Philippines, and is expected to expire in 2014. However, a number of secondary patent applications have been filed or granted in low- and middle-income countries. Especially relevant is a secondary patent on a tablet formulation of RTV, either alone or in combination with PIs including LPV, ATV and DRV. This patent will not expire until 2024 and it has been granted in at least 17 low- and middle-income countries (Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Kazakhstan, Kyrgyzstan, Mexico, Moldova, Montenegro, South Africa, Sri Lanka, Tajikistan, Turkey, Turkmenistan, Ukraine and Viet Nam). It is pending in Brazil, China and India. Other secondary patents on RTV have been filed and/or granted in a number of middle-income countries. A compulsory license was issued in April 2010 in Ecuador.

LPV/r: Patents that block the manufacturing, importation or use of generic versions of LPV/r, including two formulation patents that will not expire until 2024 or 2026, have been granted in a substantial number of low- and middle-income countries, including Albania, Argentina (where it is opposed), Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Guatemala, Kazakhstan, Kyrgyzstan, Mexico, Moldova, Montenegro, Peru, Philippines, South Africa, Sri Lanka, Tajikistan, Turkey, Turkmenistan, Ukraine and Viet Nam. In Brazil and China, applications for the LPV/r patent, expiring in 2024, are pending. Applications for this patent also are pending in the Dominican Republic and India; if granted, they may block the manufacturing, importation and use of generic versions of LPV/r.

The LPV compound patent, which will not expire until 2017, is in force in Argentina, Brazil, China, Colombia and Mexico; moreover, in some of these countries additional patent applications are pending. This patent also can prevent the manufacturing and use of LPV/r.

As far as it is known, sub-Saharan countries, other than South Africa, do not appear to have granted patents that might prevent the use of generic versions of LPV/r tablets. AbbVie has not granted any voluntary licenses for LPV/r. Indonesia and Thailand have issued compulsory licenses that permit the manufacturing, importation and use of generic versions of LPV/r.

ATV/r: This FDC is manufactured as a generic product only, with Mylan having received FDA approval for this new combination in 2011 *(36)*. Patents that block the manufacturing, importation or use of ATV/r have been granted in Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Kazakhstan, Kyrgyzstan, Mexico, Moldova, Montenegro, South Africa, Sri Lanka, Tajikistan, Turkey, Turkmenistan, Ukraine and Viet Nam. These patents are generally expected to expire in 2024.

In addition, other patents that block ATV/r and that are expected to remain in force until 2017/2018 have been granted in Argentina, Brazil, China, Georgia, Indonesia, Malaysia, Pakistan, Peru and Philippines.

ATV does not appear to have been widely patented in sub-Saharan African countries; moreover, some Indian manufacturers are able to market generic ATV in the sub-Saharan African region due to an immunity-from-suit agreement from Bristol-Meyers Squibb (BMS). Patent applications are pending in Egypt, India and Thailand; if granted, they could block importation and use of generics of ATV. Brazil has negotiated a voluntary license for ATV; however, as far as it is known, it does not appear to cover ATV/r and is only for the supply of the Brazilian market.

On 12 December 2013, the MPP announced the signing of a licensing and technology transfer agreement on ATV with BMS, covering a larger number of countries (110 countries) and with improved conditions as compared with previous agreements between BMS and a few Indian companies described above.

DRV/r: This combination product is expected to be marketed in the near future by generic companies. Patents that could potentially block the manufacture, importation and use of DRV/r have been granted in Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, China, Kazakhstan, Kyrgyzstan, Mexico, Moldova, Montenegro, Philippines, South Africa, Sri Lanka, Tajikistan, Turkey, Turkmenistan, Ukraine and Viet Nam and are pending in Argentina, Brazil, India and Indonesia. They are expected to be valid until

2022 or 2024 and, where granted, may be able to block the manufacturing, importation or use of DRV/r, even though a DRV compound patent was only recently granted and expired in August 2013.

Further secondary patents or patent applications related to DRV exist in a number of low- and middle-income countries, including some in sub-Saharan Africa; their importance is not entirely clear.

In September 2010, the MPP obtained a license from the United States National Institutes of Health (NIH) for patents related to DRV. Similar agreements with other patent holders of other patents relating to DRV are not yet attained and, as a result, the patent holders would have the right to prevent the manufacture or sale of DRV in countries affected by the patents.

Complex patent situation for PIs

In many low- and middle-income countries, different patents related to PIs or their combinations are still in force and may last for another decade in some cases.

In India, the manufacture of generic versions of LPV/r, DRV/r or ATV/r is permitted, as no patent barriers presently exist. However, several applications are pending, which could impede or preclude such manufacture altogether. One of these pending patent applications covers the combination of RTV with any of the recommended PIs (ATV, DRV or LPV); if granted, it would prevent production of all three combinations (ATV/r, DRV/r and LPV/r).

This same patent for PI-combinations including RTV has already been granted in 17 countries and will not expire until 2024. In some cases, such as in Ukraine and Viet Nam, it is blocking access to these three combinations even though some of the individual components are not patented there.

In South Africa, patent barriers exist for all three FDCs. ATV and DRV may be supplied under licenses or immunity-from-suit agreements, though it is not clear whether such benefits extends to the co-formulation with RTV.

Patents related to other ARVs used in third-line

RAL: RAL is patented in a number of low- and middle-income countries, including India, with the patent expected to expire in 2022. Patents that may prevent the manufacturing, importation or use of generic versions have been granted or are pending in Albania, Brazil, China, Colombia, Georgia, India, Mexico, Montenegro, Philippines, South Africa, Turkey, Ukraine, Uzbekistan and Viet Nam. In addition, RAL-secondary patents are in place, or patent applications have been filed, in Argentina, Bosnia and Herzegovina, Costa Rica, Malaysia, Mongolia, Morocco, Nicaragua, Pakistan and Thailand. Two manufacturers have been granted a voluntary license allowing the use of a generic version in sub-Saharan Africa and low-income countries.

ETV: ETV is widely patented in developing countries, including India. The main patent is expected to expire in 2019. It precludes the manufacturing, importation or use of generic versions and has been granted in many sub-Saharan African countries (African Regional Intellectual Property Office (ARIPO) and African Intellectual Property Organization (OAPI) member countries) as well as Argentina, Armenia, Azerbaijan, Brazil, China, Eurasian Patent Organization member countries, India, Kyrgyzstan, Malaysia, Mexico, Moldova; it is pending in Indonesia and Pakistan. Albania, Mexico and Turkey have granted additional patents, expiring in 2026; applications for these additional patents are pending in Brazil, China and India. No voluntary licenses have been granted, and there are no generics on the market.

Patents related to specific paediatric medicines

In addition to information on patents already provided above, it is important to highlight the situation regarding some specific products for paediatric care, including ABC, LPV/r and their combinations, given the important role they play in children ART.

ABC: Patents on paediatric formulations and/or combinations of ABC with 3TC or FTC have been granted widely; however, many countries are included in the license of ViiV Healthcare to the MPP announced in

February 2013. As a result, generic competition in low- and middle-income countries appears to be blocked only in those countries that are not included in this license, and where relevant patents have been granted, notably: Belarus, Brazil, China, Jordan, Kazakhstan, Mexico, Peru, Turkey and Ukraine.

ABC/3TC/LPV/r: Ideally, this combination should be available as an FDC in an adequate formulation (e.g. pellets suitable for infants) to facilitate uptake of the WHO-recommended first-line regimens. Generic companies are engaged in development of such formulations combining the required ingredients;[8] nonetheless, patents on ABC and/or LPV/r (see above) can block the use of such adapted formulations for children.

AZT/3TC/LPV/r: As above, there are current efforts to develop this needed full-regimen combination in a formulation adapted to infants and young children. The main (compound) patents on AZT and 3TC have generally not been granted or have expired. Patents on the combination AZT/3TC have expired, were withdrawn or appear not to be enforced in most developing countries. However, patents on LPV/r (see above) could block the use of an adapted formulation for children.

ABC/3TC/EFV: The use of a paediatric FDC could be blocked in countries where patents on EFV are in force or in countries where ABC has been patented and that are not included in the MPP license as detailed above.

NVP liquid preparations: Patents on specific formulations of NVP (hemihydrate) may affect competition and access in, for example, China, Malaysia, Mexico, Ukraine and Viet Nam, and could prevent the use of generic versions of liquid dosage forms in these countries. This patent is expected to expire in 2018.

LPV/r, RTV and combinations (LPV/r/ABC/3TC and LPV/r/AZT/3TC): The patent status of LPV/r also can preclude, in affected countries, the importation of the forthcoming formulations for first-line ART in infants and young children that are being prepared by DNDi/Cipla. The MPP announced in December 2013 that it has entered into negotiations with AbbVie (formerly Abbott) for the use of this combination product (LPV/r) in paediatric care.

Patents related to some key emerging ARVs for adults and children

TAF: The key patent on TAF is expected to expire in 2021. It has been granted in China, India, South Africa and Ukraine and is pending in most countries in sub-Saharan Africa (ARIPO and OAPI member countries), as well as Brazil, Mexico and Viet Nam. To date, no voluntary license has been granted. The MPP is negotiating a license for TAF with Gilead.

DTG: The main patent for DTG, expected to expire in 2026, has been granted in Algeria, Armenia, Azerbaijan, Belarus, Colombia, Indonesia, Kazakhstan, Kyrgyzstan, Moldova, Morocco, Philippines, South Africa, Tajikistan, Turkmenistan and Ukraine and is pending in Brazil, China, Egypt, India, Malaysia, Mexico and Viet Nam. Where granted, this patent will block the production, importation and use of DTG and FDCs containing DTG. Patents related to the production of DTG, expiring in 2029, have been filed in several low- and middle-income countries, including China and India.

The patent holder, ViiV Healthcare, has announced a willingness to grant voluntary licenses for sub-Saharan Africa, least-developed countries and low-income countries, though no license has yet been issued. In 2013, the patent holder committed to license DTG for paediatric use to the MPP, which also is negotiating an adult license for DTG with ViiV Healthcare.

8 http://www.dndi.org/media-centre/press-releases/1514-grant-unitaid-arv.html.

6 Market shortcomings and their reasons

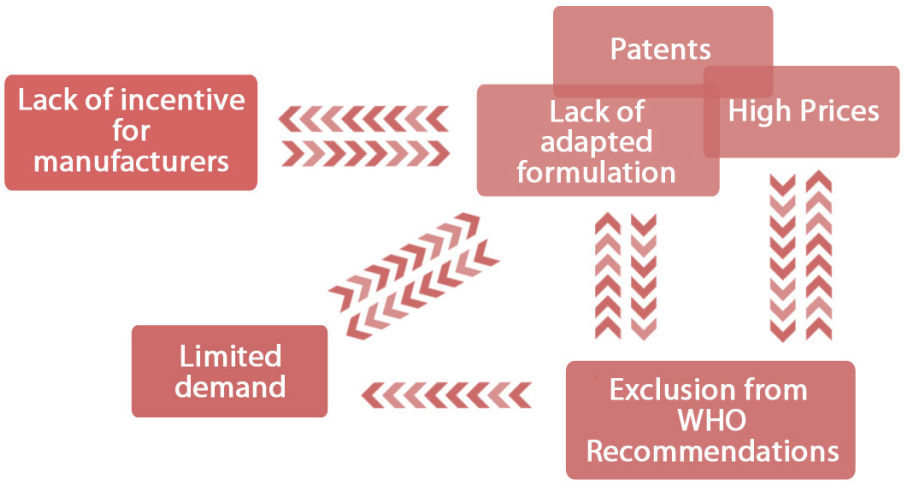
While interventions in the ARV market over the past decade have resulted in profound market and public health impact, numerous market shortcomings persist that limit access to this life-saving treatment. Major shortcomings in the ARV medicines market are summarized below, as identified through the development of this landscape. This section describes major shortcomings affecting the global ARV medicines market. Bottlenecks stemming from supply chain, health systems structure and other country-specific issues are not discussed.

6.1 Market shortcomings related to adult treatments

Availability: No ideal ART regimen exists for use in resource-limited settings. ***Reasons:*** Specific research on potential ARV products and combinations targeting the needs of low- and middle-income countries is not performed, or only with substantial delay. At a population-level standpoint, there are important differences between high- and low-income countries with respect to the needs of PLWH. In low- and middle-income countries, the HIV-infected population tends to include significantly larger proportions of women of childbearing age, children and people with TB, malaria and other co-infections. The originator companies, responsible for nearly all ARV-related innovations, almost always develop their products primarily for marketing in high-income countries, with research efforts geared to registration requirements in these countries. In addition, originator companies focus on development of combinations with products of their portfolio, or obtained through licenses and mergers with other companies, while potentially improved regimens combining other ARVS are not studied.

Adaptability: Relatively few formulations and combination products appropriate for widespread use in resource-limited settings are available, particularly second- and third-line and paediatric products. The few products that exist have tended to emerge long after initial approval of originator compounds (e.g. the FDA approved DRV in February 2008, but it is not yet marketed in co-formulation with the booster RTV to support its greater use). ***Reasons:*** Manufacturers have limited incentives to optimize current products as companies assume that revenues will be maximized through the addition of entirely new products to their portfolio, especially blockbuster drugs. In addition, ARVs often have a short lifecycle, with frequent updates of treatment guidelines and, until recently, multiple possible treatment combinations recommended for low- and middle-income countries, including for first-line treatment.

For emerging products, manufacturers typically delay investing to improve formulations and combinations due to limited early demand, which in turn closes the vicious circle impeding the potentially better-adapted regimen to be included as part of WHO-preferred treatment protocols. For example, the WHO 2013 treatment guidelines acknowledge that, even though it is in wide use in high-income settings, "currently two key factors preclude DRV/r as the preferred option in these guidelines. These include its high cost and it not being available as a heat-stable fixed-dose combination".



For some combinations and newly marketed ARVs, patent status and related market uncertainty are yet other major reasons for generic manufacturers to delay or defer investing in development of adequate formulations and FDCs.

In the case of second-line ART, a single-tablet regimen is not yet available that could enhance adherence and simplify procurement and supply-chain management. ***Reasons:*** Current market size for second-line regimens is too small to incentivize investments needed to overcome the technical challenges associated with current high doses approved for PIs. It is still uncertain how fast growth will take place for second-line regimens market.

In addition, the complexity associated with second-line ART for patients receiving first-line TB treatment has yet to be addressed. The lack of simple formulation capable of overcoming drug-drug interaction between rifampicin and PIs increases both the cost of therapy and the number of pills that patients must take. ***Reasons:*** Given the small fraction of ART people receiving second-line ART, the population in need for concomitant treatment with TB is estimated to be very low.[9] As a result, interest has been limited in searching for a solution to this complex situation.

Affordability: Although sharp reductions in ARV prices have made possible the dramatic expansion of ART over the last decade, affordability remains challenging, especially for newer drugs.

First-line therapy: Current preferred first-line regimens are more expensive than historical ones, adding a high burden to donors and countries' already constrained budgets. Regarding available single-tablet regimens, and although prices of TDF-triple FDCs have sharply declined in recent months (20% decrease in the first six months of 2013) the difference with AZT-triple FDCs remains substantial. As of 2Q 2013, AZT-triple FDCs were 23% less expensive than the lowest-price reported for TDF-triple FDCs. The price increment for TDF-triple FDCs is even greater (55%) compared with d4T-triple FDC regimens that were previously being used by most of the population in need in low- and middle-income countries. In addition, in 2012, the preferred single-tablet regimens were almost US$ 50 more costly than the equivalent regimen in two separate tablets. ***Reasons:*** As the market has been disaggregated across different options previously recommended in WHO and countries' guidelines, the full price reduction for TDF-related APIs and final products has yet to be realized. In the absence of demand, competition and generic penetration in the market was limited for TDF-based products. Six years elapsed from the original regulatory approval of TDF in 2001 to the first generic approval by the FDA in 2007, while the first generic triple FDC-containing TDF emerged only in 2009, three years after the FDA had approved the originator combination. Those first generic entrants have benefited from a quasi-monopolistic situation, leading to high and static prices.

High prices associated with limited competition remain a cause for concern in certain countries despite the emergence of competitors in other countries. Excluded from the existing licenses for the current preferred first-line products, at least 14 countries, mostly middle-income countries, have blocking patents or patent applications in place, valid until 2024–2026 on one or more of the ingredients of the combination therapy TDF/EFV/FTC. However, only a handful of countries remain affected by patents relating to the combination of TDF/3TC/EFV.

Second-line therapy: Increased competition has led to sharply lower prices for PIs. Nevertheless, costs associated with PIs have caused the total price of second-line regimens to remain more than double the lowest price available for first-line products. The price differential is much greater in countries where generic PIs cannot be purchased, and where the originator tiered price is almost three times greater than prices available for low-income countries. ***Reasons:*** Limited volumes for PIs and the uncertainty of future demand and market growth have helped keep PI prices high. Competition has been limited and slow, with one originator company having dominated the PI market for many years.

In the case of LPV/r, nine years elapsed between approval of the originator and the first generic compound. The ATV/r market is still dominated by a single (generic) producer. Regarding DRV, it is not yet recom-

9 Assuming that there are between 110 000 and 550 000 people co-infected with HIV and with active TB disease (99), that all of them are on ART per current WHO guidelines and that 6% of them are on second-line ART *(100)*, then the potential number of people taking both treatments concomitantly ranges from 6600 to 33 000 people.

mended formally for second-line therapy by WHO; a generic product was listed as temporarily eligible for procurement by the Global Fund and UNITAID, following Expert Review Panel recommendations, in 2013.

Patents that preclude competition for bPIs are common in middle-income countries, limiting the potential market for competitors in the countries where demand for second-line ART is greater (such as South Africa). To date, generic PI makers perceive little incentive to invest in marketing their products in patent-free low-income and least-developed countries.

Tiered pricing schemes, in the absence of competition, have resulted in considerable high-price premiums. In the case of LPV/r, for example, in countries outside Africa or not least-developed countries, AbbVie prices the product either on a case-by-case basis or with a price premium, resulting in prices nearly three times greater than the price available in sub-Saharan Africa (US$ 740 per person per year versus US$ 265). Except for South Africa, AbbVie does not have market exclusivity in African or least-developed countries, and generic competition can take place.

Third-line therapy: According to reports from the small number of low- and middle-income countries that have used Global Fund financing to purchase third-line regimens, prices range between almost US$ 2500 per person per year in low-income countries to over US$ 30 000 in middle-income countries. ***Reasons:*** Extremely low demand and limited competition characterize this market. Tiered pricing schemes have resulted in substantial price premiums in the few countries where demand is growing (albeit timidly). In the case of RAL, for instance, Merck is offering sub-Saharan African and low-income countries a price of US$ 675 per person per year, compared to reported prices over US$ 13 000 in lower-middle-income countries using Global Fund financing.

RAL and ETR are widely patented, including in India; and, in the case of ETR, also in sub-Saharan Africa. The RAL Indian patent will expire in 2022, while ETR patents will expire no sooner than 2019 (and later for secondary patents). Current licenses are limited. For example, the RAL license only permits generic distribution in low-income and sub-Saharan countries, where the drug is barely used.

To date, one generic RAL and one DRV product are temporarily permitted for procurement with donor funds (i.e. Global Fund and UNITAID) based on Expert Review Panel recommendations.

Emerging products: Prices for new emerging products are high in the absence of competition and demand (e.g. DTG price for the United States market is over US$ 14 000 per person per year). ***Reasons:*** New product formulations and combinations might not be appropriate to facilitate rapid adoption in low- and middle-income countries. With prices unrelated to cost of production, the increase on demand in low- and middle-income countries is limited, and products remain of marginal use. New and pipeline ARVs are normally subject to wider patent protection than older ARVs in use in low- and middle-income countries, and originators benefit from market exclusivity for these products in an increasing number of countries, including low- and middle-income countries. For example, DTG is patented in many developing countries, mostly middle-income countries, including India. The patents will expire in 2029. The TAF patent is being granted in India and South Africa, and is pending in many other countries. The patent will expire in 2021. Even when voluntary licenses are available their stipulations may hinder competition and not result in optimized price reductions in all cases.

Quality: As treatment is scaled up, the risk that products of substandard quality gain market share may increase. ***Reasons:*** Overstretched manufacturing capacities for certain products while the market rearranges to meet increased demand, and downward cost pressures may induce companies to be less vigilant with respect to quality assurance. The door to quality variations according to price is further widened by differences in the quality assurance policies and eligibility criteria for procurement by donors and countries purchasing with domestic funds. Less costly APIs appear to be accounting for a substantial portion of price reductions attained in some nationally funded procurement, while information on API quality is not readily available. WHO prequalification for APIs, a mechanism that can increase the transparency on information on API quality, is relatively new and there are as yet few WHO prequalified APIs for key ARVs.

Delivery: As countries transition to new recommended regimens, there could be an increased risk of drug shortages, especially in small-volume countries. For example, the Global Fund has reported lead times for orders of TDF combinations increased by two to four months during 2Q and 3Q 2013 as demand increased in anticipation of the imminent WHO change in recommendations for first-line regimens. PSFCM recommends planning for lead times of at least six to eight months for major volume deliveries of FDCs containing TDF. ***Reasons:*** For key preferred regimens, especially during the period of transition after changes in the WHO and countries' guidelines, demand may temporarily exceed the production capacity for APIs and FPPs. Peaks in demand due to large volume countries' orders (e.g. Malawi and South Africa) have the potential to destabilize a constrained market. Market instability may be exacerbated by uncertainty regarding financing availability as well as challenges associated with aligning funding cycles with the transition to more expensive regimens. Failure to inform manufacturers of forthcoming changes in recommendations for treatment protocols may delay the necessary rearrangement of the market to ensure adequate and timely deliveries, including modifications of production plans, API sourcing and regulatory filing of products according to new recommendations.

In some countries, access to adapted formulations and FDCs that only exist as generic products can be restricted due to patent issues (e.g. ATV/r or NVP tablets for oral suspension). Increased pill burden and use of formulations not adapted for children in resource-limited settings undermine adherence and increase procurement and supply management challenges. ***Reasons:*** Patent status in certain countries, mostly middle-income countries, impedes the use of improved dosage forms already available through generic producers (e.g. ATV/r-related patents block its use in 23 countries, including South Africa). Complex licensing strategies from different companies, and the absence of key licenses (e.g. RTV in combination), do not enable production or selling of an FDC in all license-territories.

6.2 Market shortcomings related to paediatric medicines

Availability: Of 29 ARVs approved for adults by the FDA or EMA, 5 are without paediatric indication and only 10 are approved for use in children under 2 years old. A long time-lag exists between adult and paediatric approval, as paediatric clinical trials typically launch long after adult trials. ***Reasons:*** Despite incentives and penalties from regulatory agencies designed to ensure that children benefit from treatment advances for adults, the disincentives to develop, test and manufacture paediatric ARVs are considerable. There are complexities inherent in evaluating the pharmaceutical safety and efficacy of a new drug in children, including challenges to identify sufficient numbers of children to be enrolled in the trials, while the level of expected revenues is quite low. The ARV paediatric market accounts for 7% of the total ARV market and is confined to low- and middle-income countries as demand is negligible in well-resourced countries where paediatric HIV has been virtually eliminated. Generic firms operating in the low- and middle-income countries' ARV market, on the other hand, lack the capacity to sponsor the necessary trials.

Adaptability: Efforts to ensure children's access to HIV treatment suffer due to the lack of child-friendly formulations, notably for WHO-recommended priority ARVs. The 2013 WHO guidelines highlight the urgent need for development of 11 child-friendly formulations, and none of the currently preferred regimens by WHO for paediatric first-line treatment is available as a FDC (ABC/3TC/EFV, LPV/r/ABC/3TC and LPV/r/AZT/3TC). The absence of key paediatric formulations perpetuates use of less efficient NVP-based regimens for infants, or more toxic treatments d4T-based regimens in the case of older children, as these options are less costly and marketed in child-friendly formulations. ***Reasons:*** Companies have few incentives to invest in the development of paediatric formulations. Expected revenues are limited in this comparatively small market, and companies confront technical challenges in developing suitable formulations for all age groups, while they bear major risks given the short product lifespans.

Affordability: Recommended first-line therapy in infants and children under 3 years old, including PIs, is twice the annual cost of the first-line regimen for adults at US$ 250–350 per child annually, compared to adult TDF-based regimen at US$ 128–140. The cost also is higher for countries purchasing syrups. ***Reasons:*** The API cost for PIs is higher than other ARV classes used in first-line therapy for adults. In addition, as the paediatric market represents low value and is highly concentrated, paediatric products have seen

lower price reductions compared to adults. Supply chain costs are greater for the liquid formulations still used for treatment in the youngest age group.

Quality: There are complex relays on regulatory approval pathways for paediatric products and combinations. ***Reasons:*** There are challenges for pharmaceutical companies in identifying the requirements for evaluation of FDCs when dosing ratios differ from adult comparator combinations. Lack of harmonization between WHO weight-bands and United States and other SRAs age-bands add complexity and delay the entry of child-friendly formulations.

Delivery: Contrary to WHO recommendations, few children start on HIV treatment prior to 18 months old. Small countries, and those with low HIV prevalence among children, do not meet manufacturer volume requirements for production if ordering individually and consequently confront increased lead times (up to nine months) and drugs shortages. Supply risks also exist for non-priority products needed only at low volumes in each country. ***Reasons:*** The paediatric ARV market is quite fragile. As countries other than South Africa, and several others, tend to have a relatively small number of children receiving ART, it is difficult for each of them individually to satisfy the minimum batch size (typically about 6000 packs, though it can be as large as 50 000). Where individual orders fail to reach the minimum batch size, manufacturers often delay orders until combined with others to satisfy the minimum size requirement. Current coordinated efforts for increasing the security of supplies by main stakeholders do not yet include high-volume countries such as Ethiopia, India, Kenya and South Africa. In addition, given the often limited shelf life of ARV products (24 months), current procurement practices requiring a high proportion of shelf life (up to 85%) still available at the time of arrival to the country is challenging.

7 Market interventions

7.1 UNITAID interventions to date

From its inception, UNITAID has supported ARV-related market interventions and has worked with stakeholders at the international and national levels to address ARV market shortcomings.

UNITAID interventions in the ARV market to date

(implementing partner noted in parentheses)

Previous UNITAID interventions:

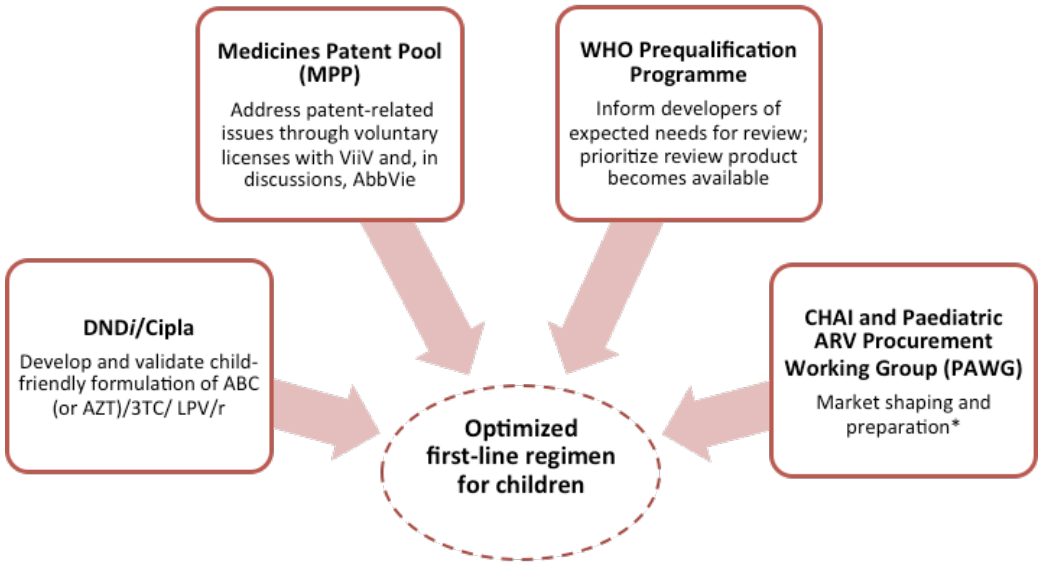
- improved access to HIV medicines for children (CHAI);
- catalysing the market for adult second-line medicines (CHAI);
- acceleration of Prevention of Mother-to-Child Transmission and Scale-up of Linkages to Paediatric HIV Care and Treatment (UNICEF and WHO).

Active and recently approved initiatives:

- market intelligence for APIs (William Davidson Institute);
- Medicines Patent Pool (MPP Foundation);
- preventing patent barriers in India (Lawyers Collective);
- development of child-friendly LPV/r FDCs and RTV booster (DNDi);
- innovation in ARV paediatric market access and continued ARV supply to children in Malawi, Mozambique and Uganda (CHAI);
- WHO Prequalification Programme.

UNITAID takes a comprehensive, multipronged approach to addressing market shortcomings in HIV-treatment markets. Figure 26 represents the UNITAID current integrated approach to shaping the paediatric ARV market in order to enable access to an optimized first-line regimen for children.

Figure 26: UNITAID integrated approach to shaping the paediatric first-line treatment market



*Market shaping and preparation intervention will maintain and update forecasting and continuously engage with manufacturers; support improved quantification at the country level; coordinate market space to ensure aggregation of volumes and purchasing power; ensure funding for procurement in countries not yet transitioned to other donors' funding (Malawi, Mozambique and Uganda).

7.2 Potential market interventions

Today's preferred treatment options and pipeline products require the support of new market-based interventions to attain global treatment and prevention goals. Potential interventions to increase access to ARVs can build on and leverage complementary interventions, such as those aiming to increase use of appropriate diagnostic and monitoring tools.

This section suggests new opportunities for intervention to alleviate persistent shortcomings identified In the ARV treatment market. Opportunities are not necessarily exclusive to UNITAID and may fall within the mandate and expertise of other market actors. A combination of market-based approaches is generally needed, extending across market segments (e.g. adults and children), and different elements of the development and supply chain (e.g. APIs and FPPs).

- **Promote timely access to optimal ARV regimes through early engagement and support of manufacturers and PDPs, and promote further innovation by introducing reward mechanisms for optimized formulations.** Interventions might include:
    i. supporting manufacturers and PDPs for required clinical trials in low- and middle-income countries to demonstrate additional benefits of combination regimens of emerging and promising ARVs (e.g. new ARV regimens not included in originator companies' studies such as TAF/3TC/DTG, new paediatric combinations) or studies of dose-reduction of priority ARVs;
    ii. supporting manufacturers and PDPs for the development of optimal formulations and FDCs (e.g. single-pill TAF/3TC/DTG; FDCs including dose-reduced EFV once outstanding clinical questions are resolved; heat-stable DRV/r tablet for adults and children, ABC/3TC/EFV for children);
    iii. establishing reward systems for first manufacturers bringing to market optimized products (e.g. priority FDCs such as DRV/r or dose-reduced ARVs), or in niche areas, through advanced purchase commitments (e.g. infant ARV market) to reduce financial risks for the manufacturers.

  In all cases, there is the need to prioritize the regulatory and WHO review and prequalification of optimized products, prompting their inclusion in WHO guidelines, and country registration after WHO prequalification or SRA approval.

- **Promote market for optimized products by supporting transition from older regimens or formulations, through catalytic purchases and payment of initial price premium associated with newer products.** These interventions might be needed to support countries' move towards newly recommended treatments, including roll out of optimized ARVs (e.g. FDCs containing DRV/r for second-line, or ABC/3TC/EFV for children) and emerging regimens (e.g. TAF/3TC/DTG).
- **Reduce uncertainty for purchasers and manufacturers by improving ARV demand forecasting. This would enable more efficient production planning, APIs sourcing and investments in manufacturing capacity, minimizing supply vulnerability during transition to newer regimens.** Interventions may include:
    i. gathering information on domestically-funded transactions, including in the analysis procurement cycles and timelines;
    ii. modelling changes in ARV demand potentially resulting from guideline revisions and approval of newer ARVs, and timely share of information with manufacturers.
- **Address patent issues likely to affect the development and/or use of optimized FDCs and formulations (e.g. TAF/3TC/DTG, DRV/r, LPV/r pellets).** Interventions may include:
    i. supporting the use of pro-public health and transparent voluntary licenses, such as those obtained through the MPP, for those key ARVs not yet included in such licenses (e.g. DTG, TAF, LPV/r, RTV) or only partially (e.g. DRV/r, RAL);

ii. encouraging countries to utilize TRIPS flexibilities (including governmental or compulsory licenses) where relevant to enable competitive procurement of specific FDCs and formulations (e.g. LPV/r-containing FDCs for infants in South Africa);

iii. enhancing countries' capacities to prevent patent (e.g., supporting pre-grant patent oppositions) and data-exclusivity barriers (e.g. increasing information on trade agreements).

Efforts should still be paid to increasing patent information transparency by publishing patent landscapes and maintaining public databases such as that of the MPP.

- **Lower the cost of production by supporting investments to increase efficiencies in synthetic and processing methods of key ARVS with potential for cost reduction.** This may include targeted investments to optimize API production of high-cost/high-volume ARVs (e.g. PIs).
- **Consolidate demand for quality-assured products to avoid market fragmentation and unsustainable price pressure for quality-assured products.** Potential opportunities may include leveraging purchasing power of the main buyer and alignment between major donor purchasers such as the Global Fund and PEPFAR and government purchases, including high-volume countries purchasing with their own funds (e.g. Brazil, Thailand, South Africa); engaging with API manufacturers to increase the number of APIs that are stringently reviewed and included in the WHO Prequalification Programme in order to decrease time to prequalification of final ARV products; and support technologies to verify drug quality at the point of care in low- and middle-income countries.

In addition to the potential market interventions suggested above, there is an overarching need to improve market intelligence systems to ensure adequate monitoring of marketing interventions to ascertain their impact and adapt them as needed to improve their effectiveness.

8 Annexes

8.1 First- and second-line ARV API suppliers

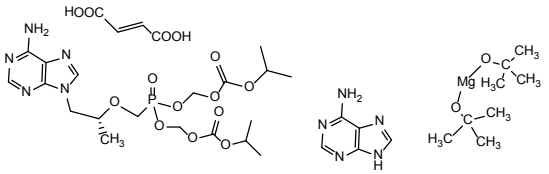
Table 17: Manufacturers of first-and second-line ARV APIs filing United States DMFs and/or prequalified by WHO

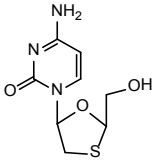
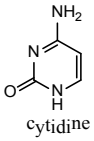
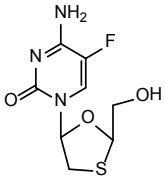
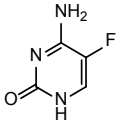
	TDF	EFV	FTC	3TC	NVP	AZT	ABC	d4T		LPV	ATV	RTV	DRV
India													
Arch Pharmalabs				•									
Aptuit Laurus P.	•	•	•										
Aurobindo	•	•	•	•	•	•	•	•		•		•	
Cipla	•	•	•	•	•	•	•	•			•		•
Cydmax Pharma		•											
Dr. Reddy's							•			•		•	
Emcure	•	•	•								•	•	
Hetero	•	•	•	•		•	•			•		•	
Kreative Organics												•	
Lupin			•				•				•	•	•
Macleods	•	•	•										
Matrix (Mylan)	•	•	•	•	•	•	•	•		•	•	•	•
Ranbaxy	•	•	•	•	•	•		•		•	•	•	
Sequent Science	•	•			•	•		•					
Sibra Pharma		•		•		•		•					
Vitalife (ArchPharma L.)				•	•	•		•					
China													
Auhui Biochem				•									
HEC Pharma Co.						•							
Lonzeal Pharma				•									
Matrix Xiamen						•							
Shanghai Desano C.	•	•	•	•	•	•		•			•	•	
Shijiazhuang Lonzeal			•	•									
Xiamen MChem Labs					•								
Zhejiang Huahui			•		•								
Others													
Apotex, Mexico				•			•						
Finorga, France												•	
Fidia, Italy			•									•	

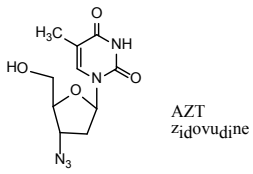
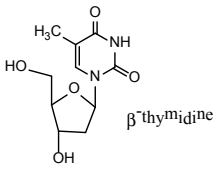
Note: Black dots indicate that the manufacturer has filed a United States DMF; dark boxes indicate WHO prequalified APIs.

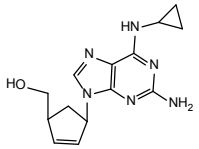
8.2 Summary cards for key APIs

NtRTIs and NNRTIs

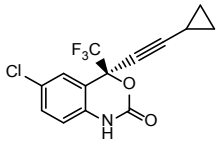
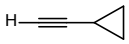
	TDF
API price range	2013: US$ 270–325/kg 2011: ~US$ 400/kg
API price per person per year	2013: US$ 30–36 2011: US$ 61
API price as % of treatment price	70% of treatment price per person per year for the lowest price generic FPP (54% for the average price of generic TDF FPP)
API and main intermediates	 TDF tenofovir disoproxil fumarate adenine magnesium (II) tert-butoxide
Affordability	The full impact of optimization of procurement for starting materials and increases in process manufacturing efficiencies (48) has now been largely incorporated into the market; future API price decreases will likely be less than in prior years, in spite of volume increases. Dose-reduction trials are ongoing to establish the clinical equivalence of ARV regimens containing reduced doses of TDF from 300 mg to 200 mg daily dose.
Delivery	Capacity is estimated at roughly 880 metric tonnes/year. In late 2010, low- and middle-income countries experienced long lead times, and even stockouts of TDF-based formulations. Indian generic manufacturers responded promptly by increasing their in-house API capacity for all products and ramping up production to meet increased demand. As a result, estimated TDF manufacturing capacity in India now stands at 70–75 metric tonnes/month, up from 12 metric tonnes/month in 2010.
Quality	The majority of TDF API manufacturers are situated in India, with 14 Indian manufactures having filed United States DMFs. There is currently only one manufacturer already prequalified by WHO, also situated in India.

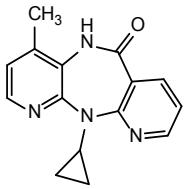
	3TC
API price range	2013: US$ 135–145/kg 2011: ~US$ 190/kg
API price per person per year	2013: US$ 15–17 2011: US$ 22
API price as % of treatment price	71% of treatment price per person per year for the lowest price generic 3TC FPP (38% for the average price of generic 3TC FPP)
API and main intermediates	 3TC lamivudine  cytidine
	FTC
API price range	2013: US$ 280–360/kg 2011: ~US$ 425/kg
API price per person per year	2013: US$ 20–26 2011: US$ 49
API and main intermediates	 FTC emtricitabine  5-fluorocytidine
Affordability	The difference in price between APIs for FTC and 3TC is decreasing. Substitution of the more expensive 5fluorocytidine in FTC for cytidine in 3TC results in significant API price differential. However, this difference is largely offset by the difference in daily dosage requirement, with 3TC dosed at 300 mg, while FTC at 200 mg. The 2012 South African tender, opting for TDF/FTC/EFV greatly changed the FTC API landscape, causing a large scale-up in volumes and substantially falling prices. Prices might continue to fall as Gilead has offered their licensees a Technology Transfer package for a modified synthesis of FTC that may decrease API pricing even further.
Delivery	Eleven manufacturers of FTC and 3TC have filed United States DFM, the majority of which are situated in India and some in China. FTC and 3TC APIs are manufactured by the same synthetic process; FTC uses 5-fluorocytosine rather than cytosine as a raw material. There are currently no supply shortages of FTC or 3TC APIs. Because FTC and 3TC APIs are manufactured by the same synthetic process (although FTC uses 5-fluorocytosine rather than cytosine as a raw material), manufacturing capability for FTC can be expanded by those already producing 3TC, provided adequate regulatory approval is obtained.
Quality	There are four sources of APIs already prequalified by WHO for 3TC (two from China and two from India), while only one for FTC (from India).

	AZT
API price range	2013: US$ 250/kg 2011: US$ 310–370/kg
API price per person per year	2013: US$ 54 2011: US$ 66
API as % of treatment price	77% of treatment price per person per year for the lowest price generic AZT FPP (71% for the average price of generic AZT FPP)
API and main intermediates	 AZT $z_{id}ovu_{di}ne$  $\beta^{-}thy^{m}i_{di}^{ne}$
Affordability	Prices had been influenced by the sharp increase on demand in past years, as d4T was switched off and TDF was less available, leading to decreased availability of raw materials and increased price, in particular β-thymidine, the critical intermediate for AZT production that is available from either fermentation technology or chemical synthesis. Prices are currently moving slightly downwards and will remain stable or slightly decrease in future; competition from multiple suppliers is heavy and Chinese generic competition is helping move prices down.
Delivery	Market share will decrease as a consequence of new WHO treatment recommendations. However, as not all those already on AZT-containing regimens will be switched, and given its use on second-line therapy, an important demand for AZT API will continue to exist in the near future (e.g. demand in 2013 estimated at about 800 metric tonnes). Adequate capacity exists for quality-assured AZT API production (at least 1100 metric tonnes).
Quality	There are currently three API sources prequalified by WHO, two from China and one from India.

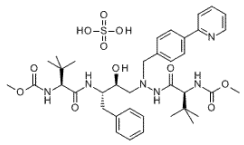
	ABC
API price range	2013: US$ 675–850/kg
API price per person per year	2013: US$ 142–179
API as % of treatment price	95% of treatment price per person per year for the lowest price generic ABC FPP (79% for the average price of generic ABC FPP)
API and main intermediates	 ABC $a_b$acav$_i$r
Affordability	Because volume demand has been low, reliable API cost projection is not available.
Delivery	Demand for adult regimens is expected to remain essentially flat at about 8 metric tonnes or to decrease; however, it is projected as a major component in paediatric treatment (2011 projection of 3 metric tonnes rising to 40 metric tonnes by 2015). This projection is dependent upon guidelines and the widespread uptake of new paediatric co-formulations and may not manifest until 2016. There are presently only three registered (WHO, FDA) suppliers of the API, with capacity to meet a demand of 40 metric tonnes/year.
Quality	There are currently no API sources prequalified by WHO for ABC.

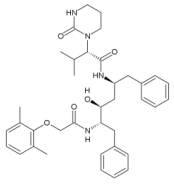
NNRTIs

	EFV
API price range	2013: US$ 130–160/kg 2011: US$ 130–240/kg
API price per person per year	2013: US$ 29–35 2011: US$ 29–52
API as % of treatment price	74% of treatment price per person per year for the lowest price generic EFV FPP (64% for the average price of generic EFV FPP)
API and main intermediates	 EFV efavirenz  CPA cyclopropylacetylene
Affordability	The cumulative effects of multiple cost reductions for EFV raw materials and synthesis routes are still being incorporated into FPP prices, with a slow decrease from 2011, demonstrating that it does take some time for improvements in manufacturing costs to be fully implemented. Median price of EFV from 2010 to 2012 went approximately from US$ 240/kg to ~US$ 180/kg (25% price reduction), and has now further reduced to ~US$ 130/kg (54% reduction between 2010 and 2013). In addition to cost reductions stemming from production process modifications, demand has grown and price is stabilizing to compete with the lowest available vendor costs in 2012. The South Africa tender has been awarded at a much lower EFV cost level than before. A dose-reduction trial showed clinical equivalence of a reduced daily dose of EFV from 600 mg to 400 mg, and complementary studies are needed. Moving to this lower dose would decrease not only the price per pill, but also the volumes of API required.
Delivery	The majority of EFV API manufacturers are situated in India, with 10 Indian manufacturers and 1 Chinese manufacture having filed United States DMFs. Catering to existing demand levels, there are currently no supply shortages of EFV APIs with a claimed total global capacity of 1500 metric tonnes/year. Demand will clearly increase, in detriment of NVP, while the global supply capacity of EFV is predicted to be adequate to withstand this demand increase. The additional production capacity is likely to be met by new and existing suppliers, especially as patents expire on these drugs, increasing the likelihood of significant additional competition from Chinese suppliers.
Quality	There are currently no API sources prequalified by WHO for EFV.

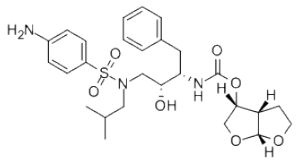
	NVP
API price range	2013: US$ 140–150/kg
API price per person per year	2013: US$ 20–22 2011: US$ 26
API as % of treatment price	71% of treatment price per person per year for the lowest price generic NVP FPP (64% for the average price of generic NVP FPP)
API and main intermediates	 NVP nevirapine
Affordability	Efforts to develop and introduce a new API synthesis that will reduce the cost of NVP API are known to be ongoing; the potential impact this may have on the per kilogram and person-year cost of NVP-containing treatments cannot be calculated with a high degree of confidence at this time.
Delivery	The majority of NVP API manufacturers are situated in China and India, with six Indian manufacturers and three Chinese manufactures having filed United States DMFs. If the new 2013 WHO treatment guidelines are rapidly adopted by countries, then the volume of demand for NVP may sharply decline.
Quality	There are currently two API sources prequalified by WHO for NVP.

PIs

	ATV
API price range	2013: US$ 1100–1400/kg
API price per person per year	2013: US$ 121–154 2011: US$ 187
API as % of treatment price	62% of treatment price per person per year for the lowest price generic ATV FPP (ATV is now available as a generic product in co-formulation with RTV)
API and main intermediates	
Affordability	At a daily dose of 300 mg, combined with 100 mg of RTV, the per person per year cost of boosted ATV is theoretically substantially less than for 800/200 mg LPV/r. At an API cost of US$ 1200/kg, the per person per year cost of ATV is less than that of LPV. Aggressive pricing in the LPV/r market has led to almost equalization of price, with a difference in the range of 15–30% lower for ATV API.
Delivery	At about 5–6 metric tonnes, the uptake for ATV has been significantly less than predicted, despite its advantages including the lower cost versus LPV/r. Capacity is more than adequate to provide at least 25 metric tonnes/year.
Quality	There are currently no API sources prequalified by WHO for ATV.

	LPV
API price range	2013: US$ 600–625/kg
API price per person per year	2013: US$ 175–183 2011: US$ 234
API as % of treatment price	LPV is not a standalone product and is always marketed with RTV
API and main intermediates	
Affordability	There are two significant raw materials cost inputs for making LPV. One of them is the "Boc-Core" that is used to manufacture both LPV and RTV. This has stabilized at a cost of about US$ 300/kg. Rising volume demand for the tetrahydro-pyrimidinone (other expensive raw material input) for LPV also has caused its price to decrease.
Delivery	Demand is expected to be about 100 metric tonnes in 2013. There are four United States DMFs filed for the API. This seems adequate to both ensure capacity and to generate cost competition.
Quality	There are currently no API sources prequalified by WHO for LPV

	RTV or r
API price range	2013: US$ 800–850/kg
API price per person per year	2013: US$ 29–31 for 100 mg once daily 2011: US$ 29–52 for 100 mg once daily
API as % of treatment price	35% of boosting dose price per person per year for the lowest price offered by originator company, valid in least developed countries and all African countries (16% for the generic RTV)
Affordability	One of raw materials needed to manufacture RTV is "Boc-Core", which also is used to manufacture LPV. This has stabilized at a cost of about US$ 300/kg. Companies that produce both LPV and RTV have a significant cost advantage. It is likely that the internal pricing for these companies is substantially less than the purchase price on the API market, as reflected in prices of FPPs available on the market.
Delivery	Demand is expected to be about 30 metric tonnes in 2013, inclusive of use in both LPV/r (26 tonnes) and all other uses. With seven DMFs filed in the United States, current supply seems capable of covering increased demand.
Quality	There is currently one RTV API source prequalified in November 2013 by WHO. The physical form (crystalline Form I rather than Form II) of the API is important to control closely to ensure FPP equivalence. Form I is converted to amorphous material during formulation, but this is not the case for the Form II polymorph.

	DRV
API price range	2013: US$ 1800–1900/kg
API price per person per year	2013: US$ 526 at 800 mg once daily US$ 788–832 at 600 mg twice daily
API as % of treatment price	97% of treatment price per person per year at 600 mg twice daily for the lowest price offered by originator company, valid in least developed countries and all African countries (72% for the price of generic FPP at 800 mg once daily)
API and main intermediates	
Affordability	Pricing is very uncertain due to the law (2–3 metric tonnes) volume demand.
Deivery	With five DMFs filed in the United States, capacity to produce is presently much larger than demand as this product is still a reserved one for third-line according to current treatment recommendations from WHO mainly due to cost, the unavailability of a co-formulation with RTV for dosing convenience and a twice-daily dosing regimen.
Quality	There are currently no API sources prequalified by WHO for DRV.

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