

HIV, TUBERCULOSIS AND MALARIA MEDICINES LANDSCAPE

**PROGRESS REPORT ON EMERGING ISSUES
AND POTENTIAL OPPORTUNITIES TO IMPROVE ACCESS**

JANUARY 2012

UNITAID Secretariat
World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
T +41 22 791 55 03
F +41 22 791 48 90
unitaid@who.int
www.unitaid.eu

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the UNITAID Secretariat in preference to others of a similar nature that are not mentioned. All reasonable precautions have been taken by the UNITAID Secretariat to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind either expressed or implied. The responsibility and use of the material lies with the reader.

This report was prepared by UNITAID's Market Dynamics Team with input for HIV/AIDS from: Polly Clayden and Simon Collins at HIV iBase; Joseph M. Fortunak at Howard University, US; James P. Sherbine, Independent Consultant; and Mario Vitoria at the World Health Organization. For tuberculosis from: Kaspars Lunte, Global Drug Facility; Jean Michel Caudron, Independent Consultant; Elizabeth Gardiner and Melvin Spigelman at the TB Alliance; Claire Wingfield and Javid Syed, who were assisted by Grania Bridgen, Martina Casenghi, Polly Clayden, David McNeeley, and Hallie Rozansky at TAG; and Christian Lienhardt at the World Health Organization. For malaria from: Colin Boyle, Paul-Francois Cossa, Yasmine Hamri, and Mathieu Lamiaux at the Boston Consulting Group; Win Gutteridge, Independent Consultant; Renia Coghlan at Medicines for Malaria Venture; and Ian Bolton at TropMed Pharma Consulting. Additional assistance was provided by Daniel Hulls, Nebojsa Novcic, and Hardeep Kaur at Cambridge Economic Policy Associates. All reasonable precautions have been taken by the authors, contributors, and reviewers to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader.

UNITAID is hosted and administered by the World Health Organization.

TABLE OF CONTENTS

Executive Summary	1
Background and purpose	1
HIV market overview.....	1
Tuberculosis market overview	2
Malaria market overview	3
Summary and next steps.....	3
1. Background and purpose	5
1.1 Background	5
1.2 Purpose	6
2. HIV	7
2.1 Public health problem and commodity access issue	7
2.2 Antiretroviral market trends.....	8
2.3 Current and future trends in medicines development.....	12
2.4 Antiretroviral market shortcomings and their reasons	12
2.5 Emerging opportunities	14
3. Tuberculosis	17
3.1 Public health problem and commodity access issue	17
3.2 Market landscape.....	17
3.3 Current and future trends in medicines development.....	19
3.4 Tuberculosis market shortcomings and their reasons.....	20
3.5 Emerging opportunities	23
4. Malaria	25
4.1 Public health problem and commodity access issue	25
4.2 Artemisinin-based combination therapy market trends	26
4.3 Current and future trends in medicines development.....	28

4.4	Malaria medicines market shortcomings and their reasons	29
4.5	Emerging opportunities	31
5.	Summary and next steps	33
5.1	Summary	33
5.2	Next steps.....	33
Annex 1.	HIV tables and figures	35
Annex 2.	Tuberculosis tables and figures.....	37
Annex 3.	Malaria tables and figures	40

Executive Summary

Background and purpose

At the 30-31 March 2011 UNITAID retreat, the Secretariat presented a framework for strategic prioritization of UNITAID investments to maximize UNITAID's public health and market impact. The Board approved the strategic framework, which included, among other things, landscape analyses to map current and future trends in disease burden, product development, and market evolution for preventatives, diagnostics, and medicines used in HIV, tuberculosis (TB), and malaria.

The landscape analyses are one part of an exhaustive reform to lay the prioritization framework and develop evidence and intelligence needed for action. The purpose of this paper is to provide a **progress report** to the Board on the Secretariat's work to develop medicines landscapes for HIV, TB, and malaria.

UNITAID projects have positively shaped many markets, with a focus on niches where extensive market shortcomings resulted in limited or no access to treatment in low-income countries prior to UNITAID. Without UNITAID's support, many key markets would be substantially smaller and more fragmented, medicine prices would be higher, and fewer adapted products would exist. **Many market niches are "healthier" than five years ago. However, some markets remain sluggish,** despite substantial investment.

Markets are dynamic in nature. As markets evolve, efficiencies are gained, but new shortcomings also arise. This report describes the evolution of UNITAID's market niches and describes some current market shortcomings and the reasons for these shortcomings. It provides preliminary views on **additional opportunities** for UNITAID to **create new markets, catalyse markets for underutilized products, and address market inefficiencies** towards increased access to medicines. In these times of financial crisis, the role of UNITAID in improving medicine affordability while at the same time promoting innovation is critical.

HIV market overview

The HIV treatment market has rapidly expanded and matured since 2005, with **growth to 7 million people on treatment** and an almost **five-fold increase in donor funding** by the end of 2011. Ambitious global goals include the doubling of the number of people on treatment to **15 million by 2015**. However, current funding commitments are unclear, threatening global access goals and creating market uncertainty.

Major trends affecting the first-line treatment market include the **phasing out of stavudine in favour of safer tenofovir- and zidovudine-based regimens**. While prices for these newer treatments remain high, they have fallen considerably in recent years and continued price reductions are expected as global volumes increase.

Expanded **access to CD4 and viral load testing** will help to optimize the impact of HIV treatment, with viral load playing a critical role in scale-up of second-line treatment. The market for

lopinavir/ritonavir, preferred in second-line treatment, has improved dramatically with UNITAID support, including addition of new manufacturers and formulations, and substantial price decreases. The November 2011 WHO Prequalification and Food and Drug Administration **approval of the first heat-stable atazanavir/ritonavir** combination offers the first real alternative to lopinavir/ritonavir in second-line treatment and shows promise in significantly reducing the cost of treating individuals who fail first-line treatment.

A **strong transition process for the current UNITAID paediatric project is critical** to maintaining the gains achieved in this fragile market. Much work remains to secure market stability, encourage uptake of existing dispersible formulations outside UNITAID programmes, and ensure that critical missing formulations are developed and brought to market. Expanded access to Early Infant Diagnosis will help to grow the demand for paediatric HIV medicines.

Early considerations for **potential new UNITAID interventions** include: securing the active pharmaceutical ingredient supply, targeting new opportunities in the paediatric and second-line niches, creating incentives for development of WHO high priority “missing” HIV medicines, and continuing to build more sophisticated market intelligence to monitor trends and impact.

Tuberculosis market overview

The **first-line tuberculosis (TB) medicines market for drug sensitive TB remains sizable and mature**, and the global target to halve death rates for tuberculosis is likely to be met by 2015. Unfortunately, the global target of halving the number of new cases by 2015 is unlikely to be met. Also, there are **continuing challenges in the paediatric and second-line TB medicines markets**, which are characterised by **high prices for second-line medicines, and low demand in both paediatric and second-line niches**.

In the first-line market, **non-quality assured (QA) medicines predominate**. Whereas donors often require purchase of QA medicines with their funds, first-line TB treatment is often funded by local governments who do not impose QA requirements on medicines purchased with their funds. The end result is a fractured market with numerous non-QA producers supplying medicines to government purchasers and private sector outlets, and other QA producers supplying medicines on the donor-funded market.

Second-line TB medicines can be up to 100-times higher than first-line medicines. The second-line TB market remains small, in part because of poor access to drug sensitivity testing (DST) diagnostics. However the recent release of the GeneXpert diagnostic offers the first opportunity to improve TB diagnosis in decades.

In the paediatric market, a lack of **appropriate FDC formulations** is driven by a lack of demand for paediatric treatment in national programmes, low access to diagnostics, and uncertainties around the ideal dosing for a paediatric FDC formulation.

While there have been no new medicines for TB for some time, there is hope on the horizon. **Two new second-line medicines** will likely be launched over the next few years. Unfortunately, there is a **limited focus on paediatric medicines development**, which significantly lags adult formulations. The brightest hope lies in **dramatically improved regimens that are due to emerge in the three to five year** time frame.

Early considerations for **potential new UNITAID interventions** involve: expanding market intelligence; strengthening links between medicines and diagnostics efforts; increasing the market share of quality-assured medicines; securing supply of active principle ingredients and medicines for second-line treatment; exploring coordinated interventions with key high-burden countries; developing a 'centre of excellence' for paediatric medicine development; and preparing markets for rapid introduction of new medicines as they emerge from the pipeline.

Malaria market overview

Scale-up of artemisinin-based combination therapy (ACT), the WHO-recommended treatment for uncomplicated *P. falciparum* malaria, has increased dramatically. Whereas only 11 million ACT treatment courses were purchased in 2005, **an estimated 287 million ACT treatments were purchased in 2011**. The global ACT market has also seen considerable increases in the number of new WHO-prequalified manufacturers, and better medicines and formulations. Still, **ACTs are underused in the private sector** and are considerably more expensive than non-ACT medicines. Where ACTs are used, they are often misused to treat non-malaria fevers. The **scale-up of rapid diagnostic tests for malaria is critically needed to promote rational use of ACTs** and prevent artemisinin resistance. The global malarial medicine **pipeline shows more promise than ever before**, with the majority of products being developed with support from the Medicines for Malaria Venture.

Several key market drivers will influence the evolution of the malaria medicines market going forward: (i) availability and stability of Global Fund and AMFm funding; (ii) malaria control efforts resulting in fewer global malaria cases and more countries entering malaria elimination phases; (iii) increased use of rapid diagnostic tests to differentiate malaria and non-malaria fevers; (iv) supply and price of plant-derived artemisinin, the active ingredient in ACTs; (v) market introduction of semi-synthetic artemisinin; and (vi) market entry of new, improved, cost-effective ACTs tailored for use in specific indications and populations.

There are a number of areas where **potential new UNITAID interventions** could have a considerable impact, including: (i) Support market entry and uptake of new, cost-effective antimalarial medicines coming out of the pipeline (ii) promote more rapid and extensive uptake of intravenous artesunate for the treatment of severe malaria in children; (iii) continue working towards introducing more clarity into ACT demand forecasting (including market intelligence in non-donor funded markets) and stabilising the artemisinin supply market; and (iv) establish better market intelligence for private sector and government-funded medicines.

Summary and next steps

Work on medicines landscapes will continue over the next few months and be finalized before the next Board meeting. At the same time, the Secretariat will continue other prioritization efforts, including: coordination of information from landscape analyses, market intelligence systems, and project intelligence; additional methods development and studies to estimate UNITAID's market and public health impact; incorporation of newly generated tools and information into UNITAID's strategy and project management activities; and proactive communication and dissemination of UNITAID's approaches and results.

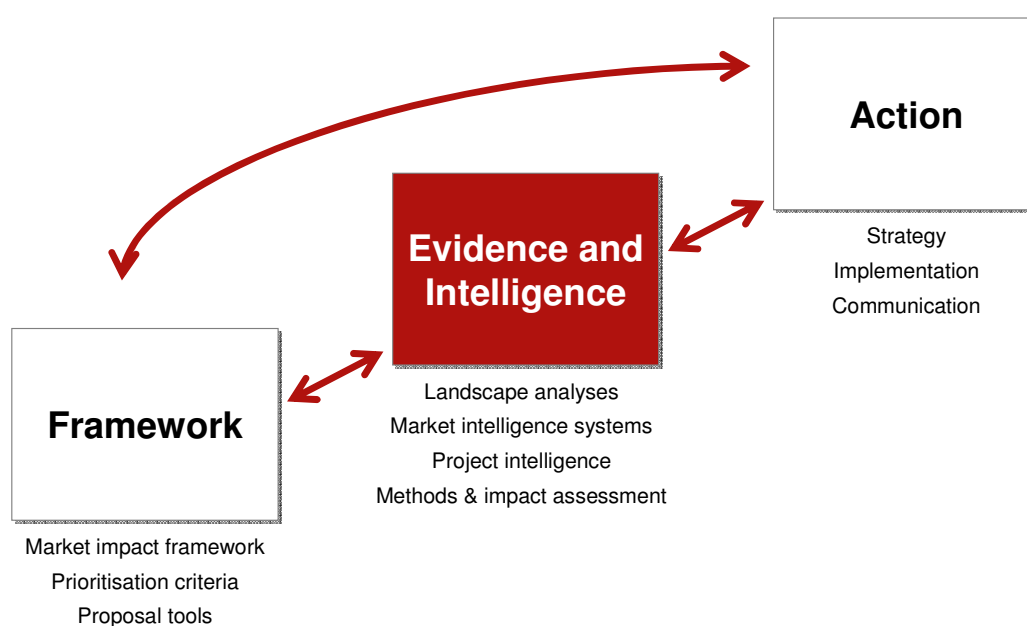
1. Background and purpose

1.1 Background

At the 30-31 March 2011 UNITAID retreat, the Secretariat presented a framework for strategic prioritization of UNITAID investments to maximize UNITAID’s public health and market impact. The Board approved the strategic framework, which included, among other things, landscape analyses to map current and future trends in disease burden, product development, and market evolution for preventatives, diagnostics, and medicines used in HIV, tuberculosis (TB), and malaria.

The landscape analyses are one part of an exhaustive reform to lay the prioritization framework and develop evidence and intelligence needed for action (Figure 1.1).

Figure 1.1: UNITAID building blocks to action



Progress on landscape analyses

The Secretariat started work on the Diagnostic Landscapes for HIV, tuberculosis, and malaria immediately after the March 2011 Board retreat. The first annual HIV Diagnostics Landscape was published shortly thereafter, and the semi-annual update was published in October 2011. Draft outputs of the TB and malaria diagnostic landscapes were presented at the July 2011 Board meeting and have since been finalized, with publication anticipated over the next few weeks. **All diagnostic landscapes are now on schedule for regular annual publication and semi-annual update.**

The diagnostics landscapes have already proven to be useful resources both within and outside of UNITAID. The draft landscapes were posted as supportive materials for the UNITAID call for Letters of Intent (LOIs) to promote the uptake of diagnostic technologies. The landscapes also served as a vital resource for the Secretariat during the LOI screening. The fact that **all manufacturers, products, organizations, and initiatives presented in LOI submissions were well documented in the landscape reports** provided reassurance that the landscapes were capturing the key players and activities in these markets.

The utility of the HIV Diagnostic Landscape in particular has been noted by the World Health Organization (WHO) HIV Department, academics, governments, global health organizations, and industry. The HIV **landscape report itself creates opportunities and incentives for developers**, who can now easily compare progress and timelines for their products against others. This transparency may result in improved products as developers can easily see what improvements are needed to place their product ahead of competing diagnostics. One developer reported the HIV landscape analysis played a critical role in obtaining venture capital support for ongoing development of their pipeline diagnostic product.

Building on the success of the diagnostic landscapes exercise, the Secretariat began work in June 2011 to develop the medicines landscapes for the three diseases. The medicine landscapes are being prepared by the UNITAID Market Dynamics Team, supported by relevant expert consultants. The methodology to date has involved:

- Initial desk research to identify and analyse existing information;
- Review of existing market research and analysis;
- Identification of unavailable but required market research and analysis; and
- Key informant and expert interviews.

The Secretariat is closely following ongoing work of other organizations to avoid duplication of effort and to ensure new information is incorporated into the landscapes in a timely manner. The Secretariat has focused initial efforts on systems to **monitor real-time advances in the development and approval of pipeline medicines** as well as approaches to better monitor the **active principle ingredient (API) markets and production capacity of API suppliers**.

1.2 Purpose

The purpose of this paper is to provide a **progress report** to the Board on the Secretariat's work to develop medicines landscapes for HIV, TB, and malaria. **This Board update report is not the Medicines Landscape Report**. The landscape reports are extensive and comprehensive reports derived from several existing and new research activities. This Board paper aims to extract key preliminary findings from landscape analyses and present them to the Board through the lens of the UNITAID Market Impact Framework. It is intended to give the Board a general overview of our current understanding of **access and market trends**, the **role of UNITAID in the evolution of key markets**, and **emerging potential opportunities for UNITAID support**.

Structure and content of the paper

As noted above, this progress report provides an update on emerging content in each of the disease areas, drawing on initial consultants' reports developed to date and work by the Market Dynamics team at the Secretariat.

The remainder of the report is structured as follows:

- **Section 2** provides initial findings from the **HIV medicines landscape**.
- **Section 3** provides initial findings from the **tuberculosis medicines landscape**.
- **Section 4** provides initial findings from the **malaria medicines landscape**.
- **Section 5** provides a **summary and key next steps**.

2. HIV

2.1 Public health problem and commodity access issue

Trends in HIV disease burden

Approximately **34 million people are living with HIV**, 95% of whom live in low- and middle-income countries and in particular, Sub-Saharan Africa. Among **2.5 million children living with HIV**, 2.3 million live in Sub-Saharan Africa. The number of new HIV infections acquired per year has remained stable across most of Sub-Saharan Africa in recent years, but dramatic increases in the number of new HIV infections are observed across countries in the Middle East, North Africa, Eastern Europe, and Central Asia. The number of people living with HIV is expected to increase over the coming years, due in part to the growing reduction in AIDS-related deaths resulting from antiretroviral therapy scale-up.

Trends in World Health Organization HIV Treatment Guidelines

World Health Organization (WHO) Treatment Guidelines are strong drivers of the global ARV market. Countries have recently or are still in the process of adopting the 2006 WHO recommendations to **move away from stavudine-based first-line regimens towards better, but more expensive tenofovir (TDF)- and zidovudine (ZDV)-based first-line regimens.**

Fewer countries have adopted 2010 WHO treatment recommendations to initiate treatment at earlier stages of disease. Specifically, the WHO now recommends beginning treatment with CD4 cell count ≤ 350 , compared to earlier recommendations to begin treatment when $CD4 \leq 200$. Some researchers estimate the **2010 WHO recommendations to initiate treatment at earlier stages of disease result in approximately a 50% increase in the number of people eligible for treatment.**

Trends in treatment access: Goals and progress

Given recommendations for earlier treatment initiation, it is estimated that **18.3 million people living with HIV in low- and middle-income countries will be in need of treatment by the year 2015.** The United Nations General Assembly High Level Meeting on AIDS in June 2011 resulted in a Political Declaration on HIV/AIDS **with a goal to provide treatment to 15 million people by 2015.** While substantial gains in treatment coverage have been made in recent years, only **40%, or 7 million people, are actually receiving treatment among the 16 million in need of treatment.** Treatment 2.0, a new initiative launched by WHO and UNAIDS, provides a "framework for catalysing the next phase of treatment, care, and support". Treatment 2.0 offers an umbrella under which UNITAID and other organizations can contribute across five main work areas aiming to: "optimize drug regimens, provide access to point-of-care diagnostics, reduce costs, adapt delivery systems, and mobilize communities".

2.2 Antiretroviral market trends

Overall growth in the antiretroviral market

Prior to the establishment of the Global Fund in 2002, the global antiretroviral (ARV) market for low- and middle-income countries was limited to a few countries (e.g., Brazil, Thailand, etc.) providing ARVs through government-sponsored programmes. The market was very small and dominated by innovator ARV manufacturers charging very high prices for ARVs. The unprecedented global funding and numerous interventions over the past ten years have resulted in the establishment of a competitive generic ARV market. **The total value of the ARV market in 2010 was estimated at US\$ 835 million**, consisting of US\$ 659 million for adult first-line ARVs, US\$ 95 million for adult second-line ARVs, and US\$ 81 million for paediatric ARVs. This represents a **4.5-fold increase** over the **US\$ 188 million donor-funded ARV market in 2005**. Seventeen manufacturers created 82 quality-assured formulations in 2005, compared to 26 manufacturers and 274 formulations in 2011.

As the market for ARVs continues to grow, there is concern that **insufficient supply of active pharmaceutical ingredients (APIs)** may limit treatment scale-up for some key medicines. Access to the required volumes of APIs is not expected to be a significant issue for most medicines; however, there is risk that the current global capacity for some key APIs may be exceeded (Annex 1, Table A1-1). The rapid growth of TDF from 2010-2015, in particular, is expected to be a challenge for the market.

First-line antiretroviral market trends

Prices for many first-line regimens have lowered substantially in recent years. Prices for older WHO-recommended d4T/3TC/NVP regimens decreased from US\$ 132 to US\$ 79 from 2005 to 2010, while prices for newer WHO-recommended regimens of TDF/3TC/EFV and ZDV/3TC/NVP decreased from US\$ 339 to US\$ 200 and US\$ 174 to US\$ 140, respectively, from 2007 to 2010. UNITAID facilitated the entry of the new HIV/AIDS medicine TDF into numerous low- and middle-income country markets since its inception. By creating demand and reducing the price of tenofovir by more than 70%, more than one million people today have access to this new generation medicine.

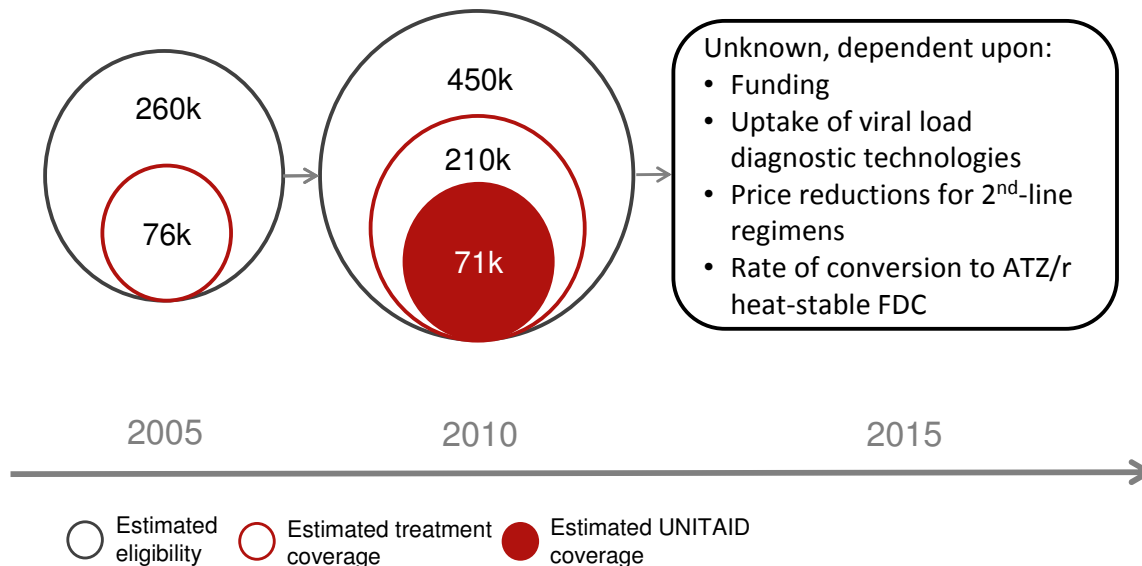
Second-line antiretroviral market trends

A dramatic shift in the second-line market occurred in 2006 with the launch of the UNITAID project and the release of the first heat-table fixed-dose combination (FDC) ARV (LPV/r). Prior to 2006, all ARVs for second-line treatment required refrigeration, a factor that limited use in most resource-limited settings. By 2010 there were two WHO prequalified manufacturers producing six heat-stable FDC formulations for second-line treatment.

The number of people receiving second-line treatment increased nearly three-fold from 2005 to 2010, with UNITAID accounting for roughly one third of people on treatment in 2010 (Figure 2.1). The UNITAID project accounted for 57% of total market volume for LPV/r in 2008. Over the course of the project, UNITAID has achieved price reductions of more than 50% for second-line ARVs. The November 2011 WHO Prequalification and Food and Drug Administration approval of the first heat-

stable atazanavir/ritonavir (ATZ/r) FDC offers the first FDC alternative to LPV/r in second-line treatment and presents opportunities to significantly reduce the cost of second-line treatment.

Figure 2.1: Market evolution of second-line antiretrovirals



Paediatric antiretroviral market trends

The paediatric market, virtually non-existent before UNITAID, has exhibited dramatic growth over the past several years. In 2005, most paediatric ARVs were produced by innovator companies in single-component solid and liquid formulations. By 2010, there were five 2-in-1 and four 3-in-1 generic paediatric FDCs in solid and dispersible forms, most (67%) of which were produced by one quality-certified generic manufacturer. During this time period, the number of children receiving treatment increased more than seven-fold with UNITAID accounting for 80% of children on treatment in 2010 (Figure 2.2). Over the course of the project, UNITAID has achieved price reductions of 49% for paediatric ARVs. The UNITAID project accounted for 97-100% of total market volume for all solid and dispersible paediatric FDCs purchased with donor-funds in both 2008 and 2009. Approximately 85% of the children benefiting from UNITAID support are now on FDCs, up from 69% in 2009 and 48% in 2008.

Figure 2.2: Market evolution of paediatric ARVs

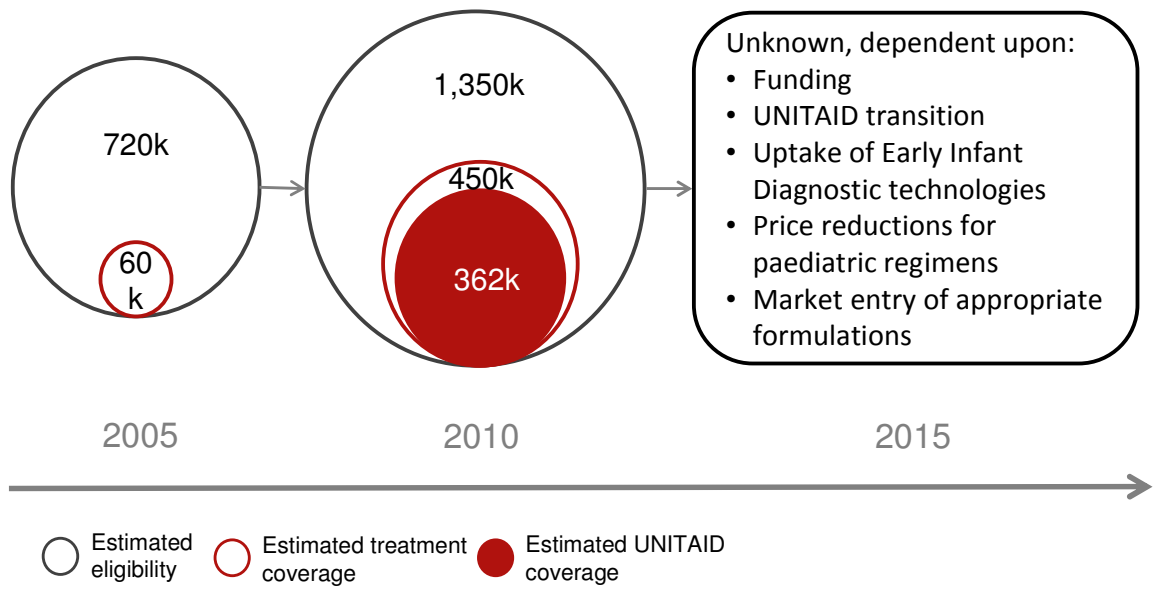


Table 2.1 Key highlights of HIV antiretroviral market trends

Pipeline

While the pipeline reveals many promising new medicines in the medium to long-term, the short-term opportunities lie in improved regimens (with existing medicines) and dose-reduction of existing medicines

First-Line ARV Market

- **Mature market** with active price competition.
- Prices for **TDF and ZDV** are currently high, but will decrease naturally as global volumes increase.
- **Expanded access to new CD4 technology** should optimize impact of first-line ART.

Second-Line ARV Market

- **Market for LPV/r has improved dramatically** with UNITAID funds, including addition of new manufactures and formulations, and price decreases; however, **second-line prices still double those of first-line.**
- **ATV/r offers a new opportunity** to shift the second-line market toward a regimen with greater promise of price reduction than others in its class.
- Expanded access to **new viral load technology** should improve impact of second-line.

Third-Line ARV Market

- **No real market established for third-line ARVs** due to high prices and unavailability of viral load testing.
- Expanded access to **new viral load technology** should improve impact of third-line.

Paediatric ARV Market

- Market **created by UNITAID**, including addition of new manufacturers and formulations, and price decreases.
- **Transition mechanism is critical to maintain UNITAID gains**, future paediatric scale-up may not keep pace with the need without continued investment, robust forecasting, and coordinated procurement.
- **Market will continue to grow** over the next few years, and then taper off as advancements in PMTCT are realized and current paediatric cohort grows older.
- Expanded access to **new Early Infant Diagnosis technology** should improve impact of paediatric ARVs.
- Still in need of **more ARVs with paediatric indication** and still in need of **four key paediatric ARV formulations.**

2.3 Current and future trends in medicines development

The **2011 adult ARV pipeline appears promising**, with at least 12 novel single ARV agents and FDCs in phases 2 and 3 of development and 3 existing products in phase 3 study for dose optimization (Annex 1, Figure A1-1). Important products further along in the pipeline include:

- **Dolutegravir** (previously GSK1349572), a once-daily integrase inhibitor, is a key pipeline compound for use in multi-drug resistant patients, is expected to be a strong second-line medicine (replacing the thymidinic component or the entire NRTI backbone), and could eventually be used in first-line treatment (possibly replacing efavirinz [EFV] or combined with RPV as an NRTI sparing regimen);
- **Cobicistat**, a pharmacokinetic booster with similar boosting efficacy and side effects compared to ritonavir, without residual direct antiretroviral activity; and
- **Quad** (elvitegravir/cobicistat/tenofovir/FTC), a once-daily single pill integrase FDC with the potential to improve patient options.

Dose reduction studies for existing medicines could result in **decreased prices for ATV/r** (US\$ 355 to US\$ 125 per person per year), **ZDV** (US\$ 89 to US\$ 60), **and EFV** (US\$ 63 to US\$ 42 [400 mg] or US\$ 31 [300 mg]).

While there are some promising developments in **the paediatric pipeline** that overcome the current insufficient range of child-friendly formulations, the pipeline **appears less promising than that for adults** (Annex 1, Figure A1-2). There are some recent advances:

A paediatric investigational plan has been developed for **dolutegravir**;

Cobicistat and **Quad** development plans were given a positive opinion by US and EU regulatory agencies;

The **rilpivirine** development plan will proceed with granule formulation;

The dossier for boosted **darunavir** for treatment-experienced children aged three to six years has been submitted to US and EU regulatory agencies; and

Raltegravir will be studied in neonates, first in a passive pharmacokinetic study and then dosed directly.

2.4 Antiretroviral market shortcomings and their reasons

While the interventions of UNITAID and other global health organizations have resulted in profound market and public health impact, there are still numerous market shortcomings that limit access to HIV treatment. Examples are provided in Table 1.1, reflecting the findings of UNITAID research and short-term priorities from the London WHO ARV Drug Optimization Meeting in April 2011. The UNITAID Secretariat will continue to work closely with WHO as they develop medium- and long-term priorities to ensure consistency across the UNITAID strategy and WHO priorities.

Table 2.2 Current ARV market shortcomings and their reasons, by niche

Market Shortcoming	Description of Market Shortcoming	Reasons for Market Shortcoming
First-Line Adult		
Affordability	Newly-recommended ARVs (TDF & ZDV) up to two times more expensive than d4T	High API and production costs for TDF & EFV. Higher global volumes needed for further price reduction. Lack of competition for WHO-preferred regimen of TDF/3TC/EFV (one FDC manufacturer).
Delivery	Future demand for some APIs (TDF, EFV, ZDV) may be greater than available supply	Country adoption of WHO-recommended new first-line regimens may create demand that exceeds volume and production capacity of API suppliers. No global forecast to communicate to API suppliers.
Second-Line Adult		
Affordability	Second-line regimens are 2 to 3 times more expensive than first-line	High API and production costs for LPV/r. Insufficient volumes of ATV/r to drive price down. Lack of competition for ATV/r (one FDC manufacturer).
Delivery	Insufficient uptake of second-line ARVs	Unavailability of viral load testing to identify when second-line is needed High prices. Side effects. Lack of incentives for manufacturers to register ARVs.

Table 2.2 continues on the next page.

Table 2.2 Current ARV market shortcomings and their reasons, by niche (continued)

Market Shortcoming	Description of Market Shortcoming	Reasons for Market Shortcoming
Third-Line Adult		
Affordability	Third-line is several times more expensive than first-line	High cost for API and production. Insufficient volumes to drive price down.
Acceptability	No darunavir/ritonavir FDC available	Lack of incentive for investment given low volumes.
Delivery	Practically no uptake of third-line regimens	High prices. Unavailability of viral load testing to identify when third-line is needed. Unclear WHO guidance on third-line. Lack of incentives for manufacturers to register ARVs.
Paediatric		
Availability	Few safe & effective medicines approved for use in children	Few incentives and funder for paediatric HIV research.
Acceptability	Missing formulations: TDF/3TC/EFV FDC; LPV/r dispersible; AZT/3TC dispersible; RTV 25mg	Few incentives for investment in development of paediatric formulations.
Delivery	Little uptake of paediatric FDCs outside UNITAID programme; Scale-up slower than demand outside UNITAID programme	Lack of awareness of paediatric FDC availability and price. Little research on clinical benefit of paediatric FDCs. Supply chain difficulties in managing paediatric FDCs. Unavailability of Early Infant Diagnostic tests for infants.

2.5 Emerging opportunities

Based on an initial data collection, analyses, and discussions with key stakeholders, the following potential opportunities have emerged:

Secure API supply for antiretroviral medicines: Develop market intelligence on API markets to identify suppliers, production capacity, cost structures, intellectual property issues, and relationships between API suppliers and finished product manufacturers. Support upstream API production expansion where needed through incentives such as: (i) guaranteed, low-interest loans to support

expansion of capacity for current producers and/or market entry for new producers; and/or (ii) guaranteed volume and pricing for purchases for a limited number of years after investment.

- **Decrease prices and increase access to second-line treatment:** Following WHO Prequalification and FDA approval of ATV/r FDC in November 2011, catalytic interventions could be launched to shift the second-line market from LPV/r to ATV/r. With lower production costs, timely switching could result in potential cost savings of more than 40%.
- **Protect paediatric market and further catalyse paediatric treatment scale-up:** Work is needed to ensure the UNITAID gains in the paediatric market are protected and that paediatric scale-up continues at the same rate. Additional work is needed to encourage uptake of paediatric formulations outside of UNITAID-funded countries. Work could include continued support for commodity purchases and coordination in order to meet growing number of children eligible for treatment and scale-up of appropriate FDCs.
- **Create incentives for continued development of formulations and registration for WHO high priority "missing" ARVs, particularly for paediatric treatment:** Examples of incentives include: (i) offering a "X-prize" reward for manufacturers who are first to develop and register a missing formulation; and (ii) providing or coordinating financing for manufacturers facing late-stage market-entry hurdles.
- **Generate and share regular market forecasts at API and final product levels:** Collect, analyse, and share market forecasts that present both the supply and demand estimates for adult and paediatric niches. Improved transparency could minimize market uncertainty for developers and manufacturers and help to stabilize markets. This becomes increasingly important as levels of future funding are unclear.

The feasibility and potential impact of these and other opportunities will be further investigated in the forthcoming landscape for HIV medicines.

3. Tuberculosis

3.1 Public health problem and commodity access issue

Trends in tuberculosis disease burden

While one-third of the world's population is infected with tuberculosis (TB), only a small portion will develop active disease. In 2010, an estimated 8.8 million people developed active tuberculosis, resulting in 1.4 million deaths. Most cases of active disease are in adults; however, an estimated 10–15% of TB cases occur in children. **Tuberculosis is concentrated in specific countries, with 22 high-burden countries accounting for 80% of the global tuberculosis burden.** While new cases of TB have been declining globally, incidence has flat-lined in critical geographies, such as South East Asia (mostly driven by India). **In sub-Saharan Africa, TB rates increased during the 1990s before stabilizing around 2005, with HIV coinfection as the largest driver of new cases** in that region. Finally, drug resistance is a significant public health issue. In 2009, 3.3% of all new TB cases were multi-drug resistant (MDR-TB), and it is estimated that 75% of MDR-TB cases are now the result of person-to-person transmission.

Snapshot of the WHO treatment guidelines

The **current treatment regimen for drug sensitive tuberculosis (DS-TB) is long: 6-month treatment with four first-line medicines. Treatment for MDR-TB with second-line medicines is even more complex.** Second line treatments **take 18 months or more**, often involve injectable medicines, and are associated with severe side effects.

Trends in treatment access: goals and progress

In 2006, the World Health Organization's (WHO) Stop TB Partnership launched *The Global Plan to Stop TB*; the plan was updated in 2011. It was developed as a roadmap to scale up prevention and treatment in support of Millennium Development Goal 6 to halt or reverse the TB epidemic by 2015. The plan aims to **reduce TB new cases and death rates by 50% by 2015 over 1990 figures. However, the goal of halving TB cases by 2015 is unlikely to be achieved globally.**

3.2 Market landscape

Snapshot of the current TB medicines markets

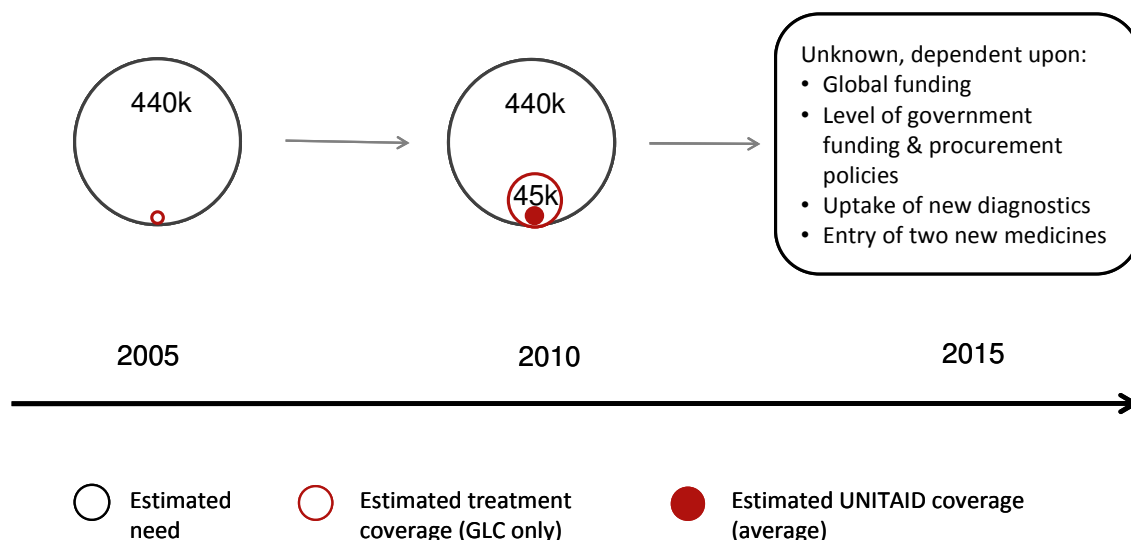
The **global tuberculosis market for first-line medicines is estimated to be approximately US\$ 261–418 million**, representing more than 5 million treatments per year. It consists of a mix of public and private markets, the mix of which varies by country. Volumes are high, with **non-quality-assured (QA) medicines making up the majority of the market.** The dominance of non-QA medicines is due to procurement practices by countries using domestic financing. These country procurements use different QA standards than institutional purchasers.

The public sector in high-burden countries is increasingly using WHO-recommended fixed-dose combination (FDC) formulations. The situation in the private sector is more varied, and the use of loose tablets predominates in some markets. Increased use of FDC formulations is important in reducing inappropriate prescribing practices.

Second-line TB medicine market trends

The markets for both second-line and paediatric products are considerably smaller than the first-line market. While the second-line market has grown significantly over the last 5 years, it remains small in comparison to total need (Figure 3.1). As new TB diagnostics are increasingly scaled-up, it is expected that more MDR-TB cases will be detected. This could significantly increase the size of the second-line market.

Figure 3.1: Market evolution for second-line TB medicines



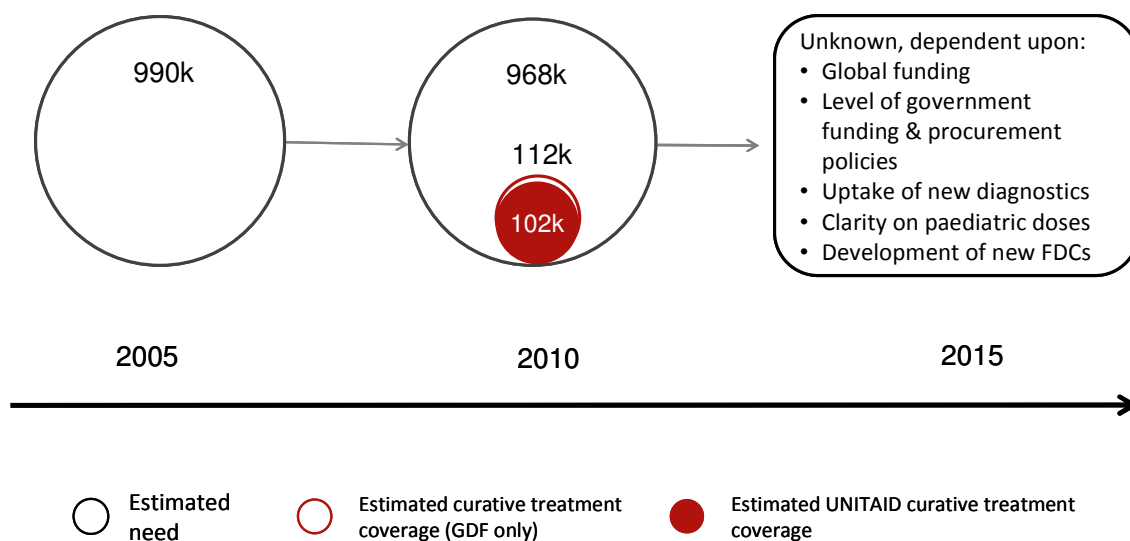
While a treatment course with quality-assured first-line medicines costs US\$20 to US\$40, a course of quality-assured, second-line medicines can cost more than US\$2,400.

Donor funding for second-line TB medicines is likely to be limited, and focused on low-income countries. As a result, middle-income countries drive expansion of their second-line medicine programmes using domestic financing and do not always require purchase of QA medicines with their funds. This could result in asymmetrical growth in the non-QA market compared to the QA market.

Paediatric medicine market trends

Prior to UNITAID's intervention in 2007, there was effectively no paediatric TB medicines market. While UNITAID's intervention has driven significant growth in the market, almost 90% of need is still unmet (Figure 3.2).

Figure 3.2: Market evolution of paediatric TB medicines



Current fixed dose combination (FDC) medicines available on the market are not aligned with updated 2010 WHO paediatric treatment recommendations, which increased the recommended dosages for all four first-line medicines.

3.3 Current and future trends in medicines development

Many of the medicines for TB have been in use for over 40 years and suffer from a number of shortcomings. Overall, research and development (R&D) efforts in TB **aim to develop shorter, more effective regimens for the treatment of DS-TB and MDR-TB**. This includes both through efforts to shorten existing regimens, and research on entirely new products and regimens. An overview of the development pipeline is included in Annex 2-1. At a high level, there are three waves of progress expected over the short- to long-term:

- Next two years: More effective second-line medicines.** Two novel second-line medicines are expected to reach the market via an accelerated regulatory process. These medicines are a step-wise improvement over current second-line medicines. A clear transition pathway from clinical trials to country adoption is essential. While steps have been taken to better understand this issue by WHO and others, a clear path forward has not yet been established.
- Next five years: Shortened regimens.** Shortened regimens using fluoroquinolone antibiotics for first-line treatment, and a shortened regimen for second-line treatment are expected to reach the market. These shorter regimens could represent a substantial breakthrough in TB treatment. A decreased length of treatment is expected to impact both adherence to treatment and cost of treatment for first- and second-line treatment.
- Next 10 years: Effective, short-course treatment for DS and MDR-TB.** Entirely new regimens, effective for both DS-TB and MDR-TB, are expected to become available, resulting in simpler, cheaper, and better treatments for tuberculosis.

Table 3.1 Key highlights of TB market trends

<p><i>First-Line TB Market</i></p> <ul style="list-style-type: none"> • Mature, generic market. • High volume, low price. • Varied mix of public and private markets. • High use of fixed-dose combinations in the public sector of most high burden countries. • Significant use of domestic financing for the purchase of products. • High market share for non-quality-assured medicines, compared to international standards (linked to domestic procurement). <p><i>Second-Line TB Market</i></p> <ul style="list-style-type: none"> • Primarily generic market. • Low volume, high price. • UNITAID financing has achieved gains: contributed to scale-up and a greater number of suppliers, and reduced lead times. • Increasing access to new diagnostics should increase the number of people requiring treatment. • Constrained donor funding may drive greater use of domestic financing in middle-income countries. • Risk that market share for non-quality-assured medicines will increase. <p><i>Paediatric TB Market</i></p> <ul style="list-style-type: none"> • Market created by UNITAID including the addition of suppliers and the prequalification of products. • Market still heavily dependent on UNITAID financing. • FDC formulations are currently inappropriate (do not match dosing in revised guidelines). • Need to diversify and amplify financing and demand (to move towards transition), but this cannot take place without formulation modifications.

Improvements in paediatric treatment are expected to trail behind innovations in adult treatments. It is worth noting that one of the novel compounds under development has submitted a paediatric plan to the European Medicines Agency (EMA). Targeted efforts to reduce the lag between adult and paediatric approvals will likely significantly improve outcomes for children with TB.

3.4 Tuberculosis market shortcomings and their reasons

While UNITAID’s interventions have helped create markets in the underserved niches of second-line and paediatric medicines, there remain significant market shortcomings in TB medicines. Examples of these are detailed in Table 3.1.

Table 3.2 Current TB medicines market shortcomings, by niche

Market shortcoming	Description of market shortcoming	Reasons for market shortcoming
First-line adult (DS-TB)		
Quality	Low market share of quality-assured medicines	Country purchases, with domestic financing, make up a large share of the market. Procurement processes for country purchases do not typically require the same quality assurance standards as international procurement agencies. Private sector also makes up a large share of the market and there is limited regulation to ensure quality standards in the private sector.
Delivery	Inappropriate use in the private sector	Lack of national regulatory standards and enforcement. Marketing by manufacturers of a variety of drug dosages and combinations not recommended by WHO.
	Country supply shortages/stock-outs	Inadequate national planning and global forecasting. Financing volatility and procurement cycle mismatch. Weak supply chain management.
Second-line adult (MDR-TB)		
Affordability	High prices for quality assured regimen (driven by Capreomycin, PAS, and Cycloserine)	Small market size that results in a limited number of finished product and API suppliers. Complexity of production and additional burden of quality assurance standards. Loss of subsidized pricing for Capreomycin, Cycloserine.

Market shortcoming	Description of market shortcoming	Reasons for market shortcoming
Delivery	Global supply shortages	<p>Small market for products driven by limited economies of scale. Leads to a restricted number of manufacturers (particularly of API), and supply insecurity.</p> <p>Volatile demand with lack of forecasting. No incentives for manufacturers to supply these markets.</p>
	Country supply shortages/stock-outs	<p>Inadequate national planning and forecasting.</p> <p>Financing volatility and procurement cycle mismatch.</p> <p>Weak supply chain management.</p>
	Low country uptake	<p>Lack of access to diagnostics as initial step in driving demand.</p> <p>Lower priority in national treatment programme.</p> <p>High costs of treatment.</p>
Paediatric		
Availability	FDCs do not exist in appropriate dosages	<p>Revised WHO paediatric treatment guidelines in 2010 increased recommended dosages for four first-line medicines. Manufacturers report unwillingness to develop new FDC dosages, due to small, unattractive markets and concerns regarding changes in guidelines.</p>
Delivery	Country supply shortages/stock-outs	<p>Inadequate national planning and global forecasting.</p> <p>Weak supply chain management.</p>
	Low country uptake	<p>Lack of access to diagnostics as initial step in driving demand.</p> <p>Lower priority in national treatment programme.</p> <p>Lack of appropriately formulated medicines.</p>

3.5 Emerging opportunities

Based on initial data collection, analyses, and discussions with key stakeholders, the following potential opportunities have emerged:

- **Improve market share of quality-assured products** by engaging with high-burden, middle-income countries to align country procurement standards with international procurement standards, setting up incentives to do so where needed. Doing so will allow countries to use their substantial market power for better prices and supply security for QA products in all countries.
- Develop a comprehensive “**centre of excellence**”, focusing on **paediatric TB medicine development**.
- **Facilitate rapid new product and regimen adoption and scale-up**, developing guidance and support to register new products and quickly introduce new and improved products and regimens into national treatment programmes.
- **Increase the supply reliability for medicines and their active principle ingredients**. More work is needed to estimate and consolidate global demand, understand incentives and production capacity of suppliers, and triangulate the supply and demand for these markets.
- **Develop mechanisms to obtain market intelligence for medicines supplied through government and government channels**. A dearth of information exists on the size and nature of these markets. The ability to improve these markets relies on a clear understanding of issues and drivers.
- **Ensure linkage between momentum in diagnostics and medicines markets**. The greater use of new diagnostic tools must be matched with adequate supply of second-line medicines. Access to diagnostics appropriate to new medicines and new regimens as they reach the market will be essential.

The feasibility and potential impact of these opportunities will be further investigated in the forthcoming landscape for tuberculosis medicines.

4. Malaria

4.1 Public health problem and commodity access issue

Trends in malaria disease burden

Malaria control and case management are leading to a reduction in the number of malaria cases and malaria deaths. Approximately **225 million malaria cases occurred in 2009**. The malaria burden is highest in sub-Saharan Africa, which accounts for 90% of worldwide deaths and where one in five childhood deaths is caused by malaria. In 2009, an estimated **781,000 people died of malaria, 85% of whom were children** under the age of 5 years. There is **substantial variability in malaria disease burden across countries**. While a few countries have reported recent increases in the number of malaria cases, many countries have seen reductions of more than 50% for confirmed malaria cases, and some countries have actually eliminated malaria.

Trends in World Health Organization Malaria Treatment Guidelines

WHO-recommended malaria treatments vary according to the type of malaria (e.g. *P. falciparum*, *P. vivax*, *P. ovale*, etc.) and the endemic level of the region (e.g., high transmission, low transmission, etc.), and the severity of infection (Annex 3, Figure A3-1). The recommended treatment for uncomplicated *P. falciparum*, the malaria type with the greatest burden and mortality rates, is **artemisinin-based combination therapy (ACT)**. Despite growing resistance to non-artemisinin therapies, they are still recommended under certain circumstances: chloroquine for *P. vivax* in areas without significant resistance, quinine for women in the first and second trimesters of pregnancy, and sulfadoxine pyrimethamine (SP) for intermittent preventive treatment for pregnant women and infants (IPTp and IPTi).

The most substantial shift in the WHO Guidelines is the 2010 recommendation to use **diagnostic tests to confirm malaria cases prior to treating them with an anti-malarial medicine**. This represents a major change in treatment strategy. WHO advice prior to 2010 was to presume that all fevers were malaria to be treated with antimalarial medicine. This paradigm shift resulted from the introduction of inexpensive, quality-assured rapid diagnostic tests and the downward trend in malaria cases. As the number of new malaria cases decreases, there is increasing need to differentiate a malaria fever from a non-malaria fever. Much work is needed, however, to change established practices around malaria diagnosis and treatment.

Other notable changes in WHO recommendations include the addition of one new ACT (dihydroartemisinin-piperaquine) and the April 2011 WHO recommendation to use **intravenous artesunate** in preference to intravenous quinine for the treatment of **severe *P. falciparum* malaria in children**.

Trends in treatment access: Goals and progress

In 2011 the Roll Back Malaria Partnership published **new objectives for 2015** that reflect continued progress in malaria control: to **reduce global malaria deaths to near zero; reduce global malaria**

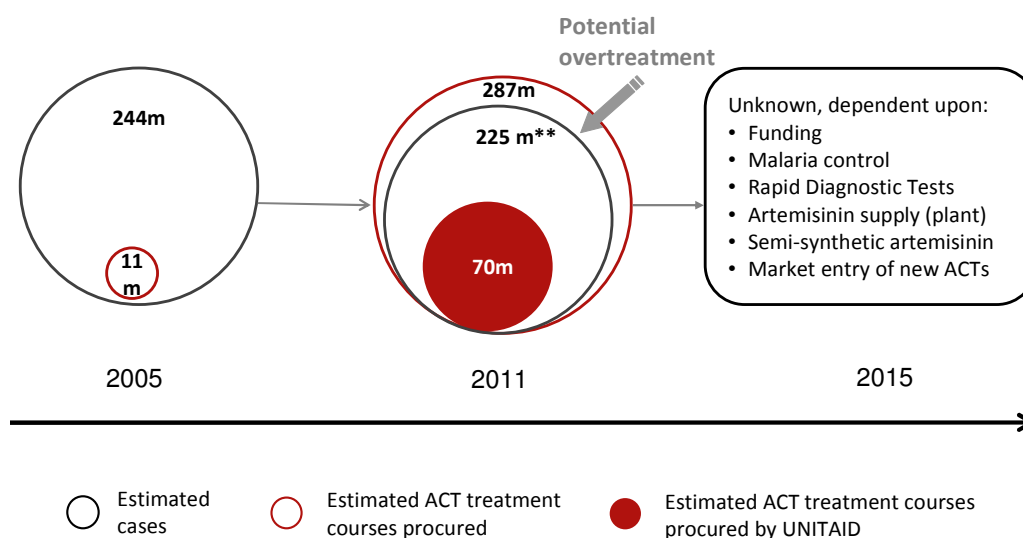
cases by 75% (from 2000 levels); and to eliminate malaria in 10 new countries (since 2008) and in the WHO European Region. Improving access to diagnostic testing and appropriate treatment for confirmed cases is essential for meeting these objectives. While significant advances have been made in these areas, challenges still remain. For example, in 2010 ACT-based commodities represented **less than 40% of the market share** for antimalarial treatments in Africa. In the **private sector**, where the vast majority of antimalarial medicines are sold, **microscopy and RDTs are less widely available** than in the public sector and the **medicines in stock are usually not the recommended ACTs**.

4.2 Artemisinin-based combination therapy market trends

Overall growth in the artemisinin-based combination therapy market

Considerable efforts have been made in the past decade to scale-up access to artemisinin-based combination therapies (ACTs) (Figure 4.1). External expenditure on malaria control has **increased from USUS\$ 35 million in 2000 to USUS\$ 1.5 billion in 2009**, of which 31% (USUS\$ 460 million) was treatment related. UNITAID investments in malaria treatment have included over USUS\$ 100 million for the scale up of ACTs (USUS\$ 65.4 million for the ACT scale-up initiative, USUS\$ 1.3 million for ACT treatments in Liberia and Burundi, and USUS\$ 21.5 million for ACT purchased as part of Global Fund Round 6); USUS\$ 130 million to support the Global Fund-led Affordable Medicines for Malaria project (AMFm); and USUS\$ 9.3 million for assuring artemisinin supply.

Figure 4.1. Market evolution of artemisinin-based combination therapies (ACTs)*



Artemisinin-based combination therapy market trends

In the past few years there has been a rapid increase in the volume of ACT treatments funded by global donors, from 11.2 million in 2005 to 217 million in 2010. **Demand is expected to increase to 295 million ACT treatments in 2012** (Annex 3, Figure A3-2). Over the longer term, however, advances in malaria control and increased use of rapid diagnostic tests should result in decreasing ACT demand.

There are currently seven WHO-prequalified ACT manufacturers producing 11 relevant ACT formulations compared to only one product in 2005¹. Especially compelling are advancements in paediatric, dispersible ACT formulations. While donor-funded malaria programmes have adopted the use of newer child friendly malaria formulations, uptake outside donor-funded programmes remains very low. The WHO estimated 25 countries were still allowing undesirable artemisinin monotherapies to be sold by 39 manufacturers in November 2010.

The market for WHO-prequalified ACTs, a primarily donor-funded market, has historically been dominated by one ACT made by one manufacturer. But recently new ACTs, formulations and manufacturers have emerged and market share is shifting amongst new and old players. The non-prequalified ACT market is heterogeneous and consists of a large number of local and global manufacturers selling to local governments and private markets.

- Within AMFm countries, preliminary results suggest that ACT prices have decreased. In Kenya and Ghana, the first countries to receive co-paid drugs, the retail prices of ACTs in the private sector have decreased by 50% and 89%, resulting in median retail prices of approximately US\$ 0.33 and US\$ 1.32, respectively. However, ACT prices remain substantially higher than non-ACT prices in AMFm countries and ACT prices remain unaffordable in non-AMFm countries (Annex 3, Figure A-3).
- Market uncertainty around ACT demand and the supply of artemisinin, the key active principle ingredient of ACTs, have recently resulted in sharp increases in artemisinin prices (Annex 3, Figure A3-4) which then lead to higher ACT prices. Because artemisinin is derived from a plant, long lead times are needed to grow, harvest, and extract artemisinin needed for production of the final ACT product. The entire planting, harvesting extraction, and final product production typically takes about 14 months. A semi-synthetic version of artemisinin is currently under development and expected to enter the market in 2012-2013, although uptake for the actual manufacture of final products will be gradual. The need for plant-derived artemisinin will remain for the near future.

Several key market drivers will influence the evolution of the malaria medicines market going forward: (i) availability and stability of Global Fund and AMFm funding; (ii) malaria control efforts resulting in fewer global malaria cases and more countries entering malaria elimination phases; (iii) increased use of rapid diagnostic tests to differentiate malaria and non-malaria fevers; (iv) supply and price of plant-derived artemisinin; (v) market introduction of semi-synthetic artemisinin; and (vi) market entry of new, improved, cost-effective ACTs tailored for use in specific indications and populations.

¹ WHO Prequalification Programme (<http://apps.who.int/prequal/>).

Table 4.1 Key highlights of malaria medicines market trends

- Not all malaria is the same. There are several types of malaria, each of which requires a specific type of treatment.
- Not all ACTs are the same. The malaria medicines **pipeline is more promising than ever**. New ACTs coming out of the pipeline are increasingly differentiated from existing ACTs. New antimalarial medicines are less expensive and can be used to treat many types of malaria with fewer doses.
- The **quality-assured ACT-market is primarily a donor-funded market**. This market has increased dramatically in terms of absolute volume of ACT treatments procured, number of WHO-prequalified manufacturers and products, and price decreases.
- Government-funded and private sector markets remain large. These markets are characterized by non-quality-assured medicines and continued use of dangerous monotherapies. ACTs remain unaffordable in the private sector outside of AMFm.
- **Semi-synthetic artemisinin will emerge in 2012-2013** and provide some supply security and ACT price stability. Still, additional work is needed to ensure the continued cultivation of artemisinin plants as the new semi-synthetic gradually gains market share. Incentives may be needed to encourage supplier uptake of the semi-synthetic product.
- Demand for ACTs is expected to grow in the short term, driven primarily by increased demand from the private sector in AMFm countries. In the **medium term, ACT demand is expected to plateau and eventually decline as the number of malaria cases decreases as a result of control efforts and scale-up of RDTs**.
- Careful market monitoring and active market management will be needed as the number of malaria cases continues to decline. Different approaches and tools will be needed as countries progress towards malaria elimination.
- No real market has been established for intravenous artesunate to treat severe malaria due to high price relative to intravenous quinine.

4.3 Current and future trends in medicines development

The global malaria medicine pipeline is more extensive than it has ever been, with the majority of products being developed with support from the Medicines for Malaria Venture (Annex 3, Figure A-5). In particular, the following products show high potential for public health and market impact:

- **Dihydroartemisinin/piperaquine FDC** (Euratesim®): First antimalarial to receive European Medicines Agency approval (October 2011). Approved and WHO-recommended for both **uncomplicated *P. falciparum* and *P. vivax* malaria** that offers an **inexpensive, once a day dosing** (for three days).
- **Pyronaridine/artesunate FDC** (Pyramax®, Registration by a stringent regulatory authority (SRA) expected in 2012): Approved for use in both **uncomplicated *P. falciparum* and *P. vivax* malaria** that offers and **inexpensive, once a day dosing**. A **paediatric formulation** is also under development.

- **Tafenoquine** (Phase IIb/III): The only molecule in the pipeline with published activity against *P. vivax* hypnozoites. The long half-life would **reduce the treatment period from 14 to 2-3 days** and thus improve treatment compliance.
- **Azithromycin+chloroquine tablets** (Phase IIb/III): A potential **replacement for SP for IPTp**, it may have activity against SP-resistant parasites and simultaneous activity against bacterial sexually-transmitted diseases.
- **OZ439** (Phase IIa): A fully synthetic peroxide which could provide an alternative to artemisinin derivatives. It **might be active in a single dose**, which would dramatically improve treatment compliance.

4.4 Malaria medicines market shortcomings and their reasons

While the interventions of UNITAID and other global health organizations have resulted in profound market and public health impact, there are still numerous market shortcomings that limit access to malaria treatment. Examples are provided in Table 4.1, reflecting early findings of UNITAID research and discussions with key stakeholders.

Table 4.2 Current malaria medicines market shortcomings and their reasons

Market shortcoming	Description of market shortcoming	Reasons for market shortcoming
Availability	No alternative to primaquine for follow-up <i>P. vivax</i> treatment	Newly approved ACTs for <i>P. vivax</i> are limited to one or two treatment courses per year. More research needed to ascertain safety with repeated dosing.
	No alternative to SP for intermittent preventive treatment in pregnant women	Little research on alternatives to date. Too soon to know if azithromycin+chloroquine studies will prove effective.
Quality	WHO-prequalified ACTs represent only 42% of total ACT market in Africa	Few incentives for additional producers to apply for WHO PQ. Preference for local producers who are unable to invest in upgrades to achieve WHO PQ.
Quality	Existence of counterfeit and substandard products (e.g. quality failure rate of 28.5% for all anti-malaria treatments)	Lucrative business. Insufficient local quality control and awareness.

Market shortcoming	Description of market shortcoming	Reasons for market shortcoming
Affordability	High ACT retail prices compared to non-ACTs	High API and production costs. Mechanisms to promote ACT price competition have not been optimized.
	High intravenous artesunate retail prices	Only one prequalified product. Insufficient global volumes for economies of scale. Little incentive for new manufacturers to produce.
Acceptability	No single dose ACT treatment for malaria	Research by MMV ongoing but product not yet available.
	Few ACT FDCs appropriate for use in many Asian countries	Mefloquine + artesunate used in areas of observed ACT resistance not produced as a FDC. Few incentives for manufacturers to develop.
Delivery	Slow uptake of new, cost-effective ACTs coming out of the pipeline	Many ACTs are developed by small companies with no global pharma partner which limits or delays registration, marketing and sales in countries.
	Low market share of ACTs overall (< 40% of antimalarial market in Africa)	Higher costs and more complex dosing regimens than conventional monotherapies.
	High use of dangerous artemisinin monotherapies outside of donor-funded malaria programmes (7-13% products sold AMFm countries)	Countries have not banned or enforced bans for monotherapy sales. Manufacturers generate substantial revenue from sales. Low awareness of associated risks.
	Stock outs of quality-assured ACTs in the public sector	Unknown demand and unpredictable supply. Weak supply chain management systems.
	High rate of ACT overuse for non-malaria fevers	Insufficient use of diagnosis tools (e.g. RDTs). Lack of awareness of new WHO recommendations.
	Low uptake of intravenous artesunate for severe malaria	Difficult for countries to change treatment guidelines. Lack of awareness. High prices.

4.5 Emerging opportunities

Based on initial data collection, analyses, and discussions with key stakeholders, the following potential opportunities have emerged:

- **Support market entry and facilitate uptake of new, cost-effective ACTs coming out of the pipeline** (e.g. dihydroartemisinin/piperaquine FDC, pyronaridine/artesunate FDC, tafenoquine, OZ439, azithromycin + chloroquine). This could include interventions to support registration and demand generation, identification of global pharma partners to support registration and marketing, safety studies to support repeated dosing indications, and other activities to promote rapid uptake once products are available and recommended by WHO.
- Promote more rapid and extensive uptake of intravenous artesunate for the treatment of severe malaria in children.
- **Continue work on ACT forecasting and artemisinin supply monitoring.** The convergence of many factors will continue to create market uncertainty over the next several years. Ongoing work to estimate global ACT demand and match that to artemisinin and ACT supply is critically needed to ensure supply security and affordable prices.
- **Support the development of a more structured and reliable artemisinin upstream supply chain** following efforts pursued by the Assured Artemisinin Supply System (A2S2) initiative to overcome uncertainties and resulting costs related to the production and sourcing of raw artemisinin.
- **Stabilize artemisinin prices and supply** through the creation of a price bank which would act as a global stock management entity using stock buffers to compensate demand/price soar.
- **Support the adoption of semi-synthetic artemisinin.** Specifically, incentivize manufacturers to adapt their production processes to the use of semi-synthetic artemisinin and help them through the WHO prequalification process.
- **Tailor funding for ACTs to maximize impact.** Commission studies on lessons learned from AMFm, including best subsidy structures to promote price competition, better assessment and matching of countries' real needs to purchases, assessment of efficiency/ impact of potential first line buyers, and bundling co-payment of ACTs with rapid diagnostics tests.
- **Ensure appropriate use of ACTs and minimize resistance** through accelerated scale-up of RDTs and improved monitoring of estimated needs and consumption volumes.
- **Improve market intelligence for non-donor funded markets.** Create mechanisms to collect and synthesize national-level data on the need, supply, and use of malaria medicines (ACTs and non-ACTs) in order to better understand the private sector and government-funded channels.

The feasibility and potential impact of these and other opportunities will be further investigated in the forthcoming landscape for HIV medicines.

5. Summary and next steps

5.1 Summary

This paper provided a progress report on the development of HIV, tuberculosis, and malaria medicines landscapes recently commenced by the UNITAID Secretariat. A substantial amount of work has already been accomplished within a short space of time, including:

- **Creation of systems to regularly monitor and report progress in product pipelines.** This tracking will support strategic planning and investment decisions that allow UNITAID to prepare and quickly intervene to support rapid uptake of emerging products with strong public health impact.
- High level **mapping of market evolution and UNITAID's relative position in these markets.** This work, combined with other data collection efforts, is needed in order to tell the "UNITAID story" and then quantify UNITAID's market and public health impact through robust analytic studies. Understanding what has worked well and what has not will support decision-making within UNITAID but also generate evidence for use by other organizations adopting market approaches for public health.
- Identification of critical issues **affecting the markets for active pharmaceutical ingredients (API).** Analyses of API markets and production capacity have been largely overlooked to date but are critical to ensuring pricing and supply stability in the market.
- Preliminary insights on key **market shortcomings** in each of the respective disease markets, the **reasons** behind them, and **potential opportunities for UNITAID** and others to intervene.

5.2 Next steps

As noted in Figure 1. in the Background and purpose section, these medicines landscapes are part of the **Evidence and Intelligence** stepping stone towards **Action**. The landscapes are one piece of a much larger body of work to implement the recently approved UNITAID prioritisation framework.

The work on the landscapes is progressing at a good speed. There is, nevertheless, still work to be done in both developing the landscapes as well as building up the other aspects of **evidence and intelligence resources**, including:

- **Market Intelligence Systems.** Work on integrating existing market intelligence systems into the ongoing monitoring of markets and product pipelines by UNITAID is currently underway. The expectation is that these tools, when developed, will provide considerable utility to UNITAID in early 2012.
- **Project Intelligence.** Further work is required to create better links between landscape analyses, Market Intelligence Systems and intelligence that is obtained from projects. Partners hold critical information which could be better utilised and the Secretariat will prioritise this coordination in 2012.
- **Methods and impact assessment.** Impact assessment can only be undertaken once relevant data and methods are available. The work done to date on both intelligence gathering and development of methods to measure market and public health impact has started to provide

the required resources to take this forward. For example, work on the public health impact of GeneXpert (TB diagnostics) and second-line HIV medicines has already been conducted and work to estimate public health impact of diagnostics is planned with outputs expected in time to support Board decision-making on diagnostic proposals.

Development of evidence and intelligence is needed for UNITAID **Action**, including:

- **Strategy development.** New information and tools emerging from this large body of work will regularly feed into implementing the current strategy. They will also be used by the Advisory Group on Funding Priorities when they deliberate to discuss priority market niches for UNITAID. Finally, they will provide critical inputs into the new 2013 to 2015 strategy, development of which will begin in January 2012.
- **Implementation.** New information and tools can also support project selection and implementation. Proponents and the Secretariat made use of landscape analyses during the drafting and screening of letters of intent. Similarly, the Proposal Review Committee has already utilized many of these tools to support their work. Better information will surely support project monitoring and evaluation and redirecting UNITAID projects as needed.
- **Communication.** UNITAID aims to make easily available the information, tools, and evidence it creates as a 'public good' aspect of its work. UNITAID aims to strategically disseminate insights and information to other key stakeholders towards a more coordinated approach to shaping markets for public health.

Work on the medicines landscapes will continue over the next several months and is expected to be finalized before the next UNITAID Board meeting. The long term goal is to present and approach each disease from a perspective that articulates the interconnectedness of the preventive, diagnostic, and medicines markets towards an integrated approach to improving public health.

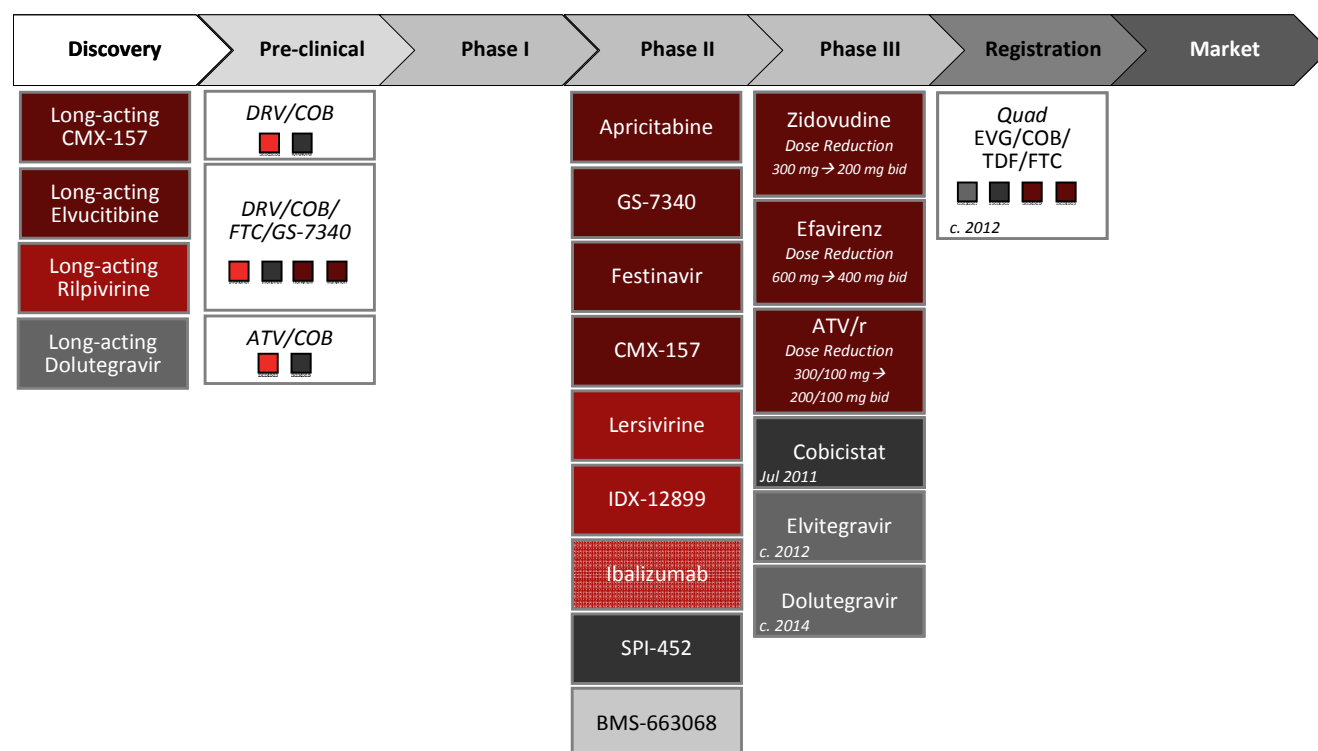
Annex 1. HIV tables and figures

Table A1-1. Projected API requirements for Core ARV Products – 2011 & 2015

API	Estimated 2011 needs (MT)	Estimated 2015 needs (MT)	Exceeds capacity Yes/No (Year)	Likely solution(s)
TDF	243	662	Y (2012)	Potential targeted support
AZT	482	715	N	--
3TC	637	1055	N	--
EFV	445	789	Y (2013)	Market adjustment
NVP	603	898	Y (2013)	Market adjustment

Source: Clinton Health Access Initiative forecasts.

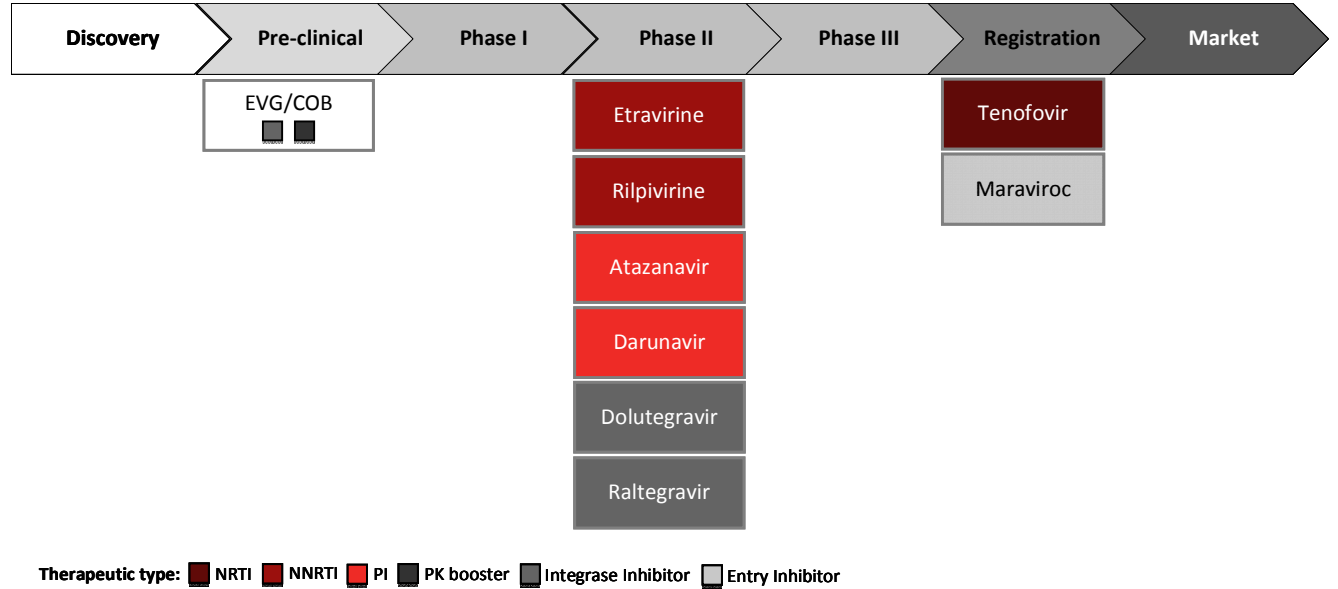
Figure A1-1. Adult antiretroviral pipeline



Therapeutic type: ■ NRTI ■ NNRTI ■ PI ■ PK booster ■ Integrase Inhibitor ■ Attachment Inhibitor

Source: Adapted from 2011 i-Base/TAG Pipeline Report (available at <http://i-base.info/home/2011-pipeline-report-2nd-edition-september-2011>) and clinicaltrials.gov.

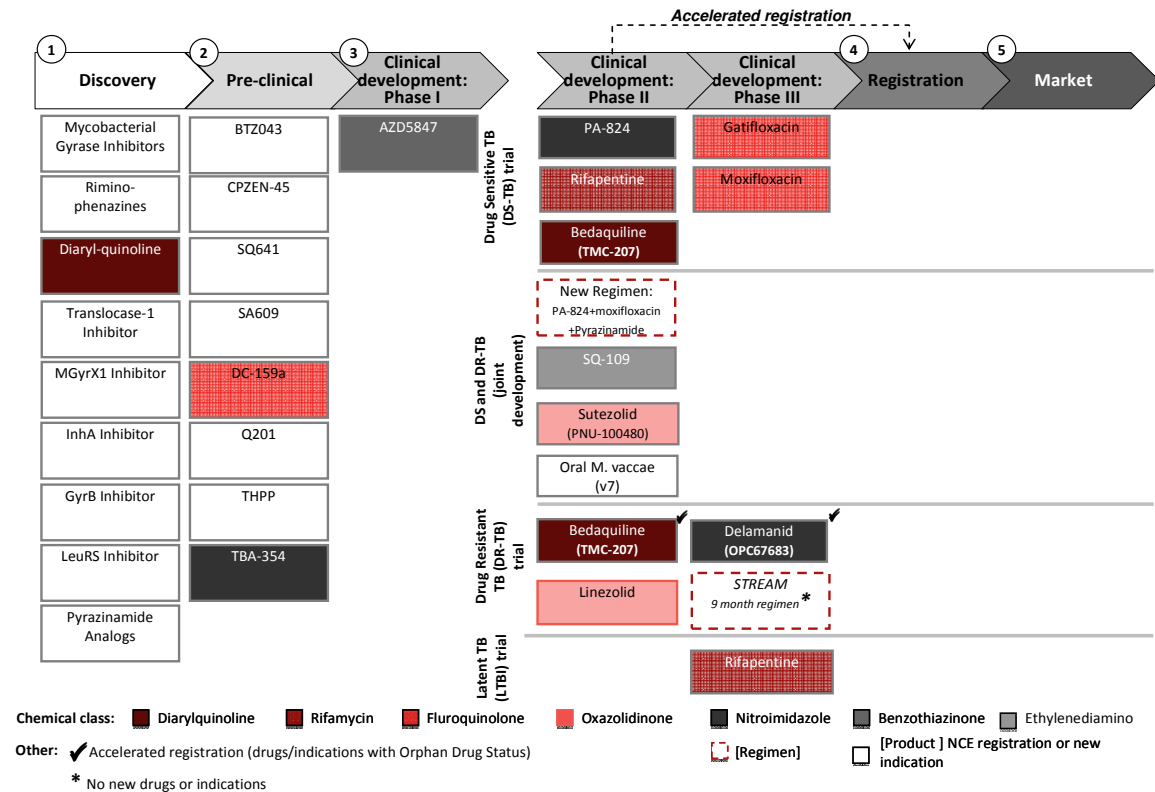
Figure A1-2. Paediatric antiretroviral pipeline



Source: Adapted from 2011 i-Base/TAG Pipeline Report (available at <http://i-base.info/home/2011-pipeline-report-2nd-edition-september-2011>) and clinicaltrials.gov.

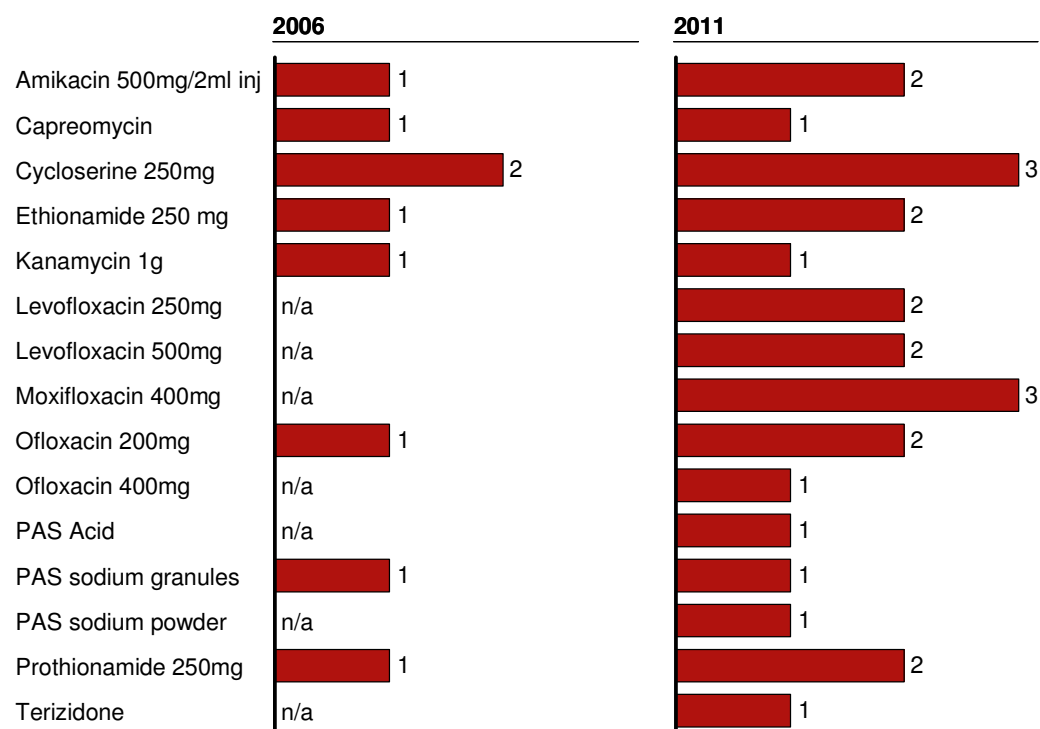
Annex 2. Tuberculosis tables and figures

Figure A2-1. Tuberculosis pipeline



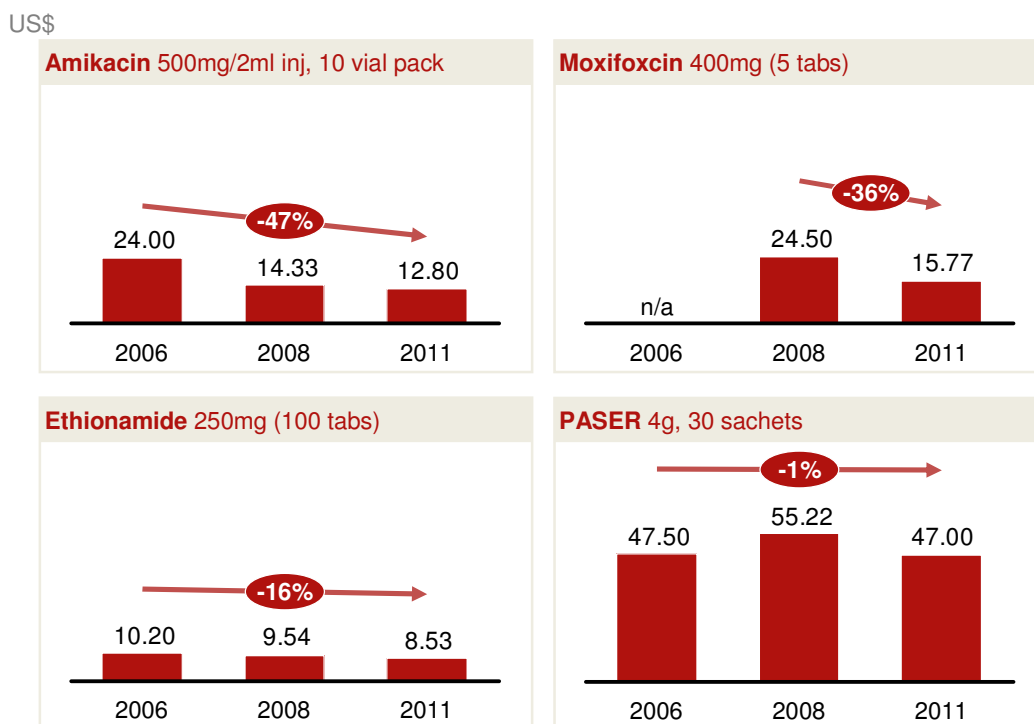
Source: Adapted from The Working Group on New TB Drugs at <http://www.newtbdrugs.org/pipeline.php>.

Figure A2-2. Number of GDF eligible manufacturers of second-line TB drugs over time

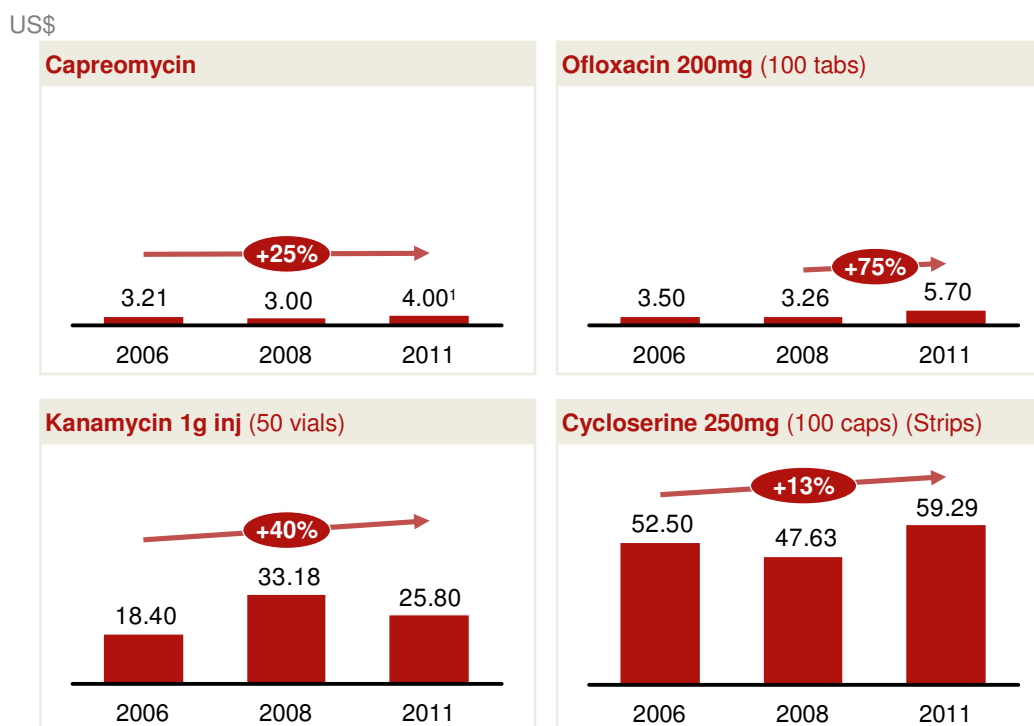


Source: GLC Approved Product list (2006) taken from the Procurement Manual for the DOTS-Plus Projects; GDF (2011), Table 11, June 2011 Interim Report, UNITAID MDR Scale-up project.

Figure A2-3. Changes in prices of defined products over time



Source: GLC Approved Product list (2006) taken from the Procurement Manual for the DOTS-Plus Projects; GDF Interim report to UNITAID (2011), Table 14.



¹ Range of \$4-8 by manufacturer

Source: GLC Approved Product list (2006) taken from the Procurement Manual for the DOTS-Plus Projects; GDF Interim report to UNITAID (2011), Table 14.

Annex 3. Malaria tables and figures

Figure A3-1. Summary of WHO recommendations for the treatment of malaria

	Treatment					
	Uncomp. falciparum		Uncomplicated others			Severe ⁵
	Pregnant women	Other	ACT	All	Mix ⁴	All
High transmission	T1: QN + Clin ¹ T2-T3: ACT ²	ACT	CQ+ PQ if resistant: AQ+ PQ or ACT ³	CQ (+ PQ for <i>P.ovale</i>)	ACT	Intravenous AS ⁶
Low transmission without epidemic				CQ (+ PQ for <i>P.ovale</i>)		AS
Epidemic period			CQ + PQ			AM ⁷ (simpler) or AS

1. Or ACTs where QN+Clin are not available.

2. If effective – alternatives are artesunate + clindamycin or quinine + clindamycin.

3. Except AS-SP for vivax.

4. Including falciparum or not.

5. Mainly falciparum, very few cases of severe vivax treated like severe falciparum.

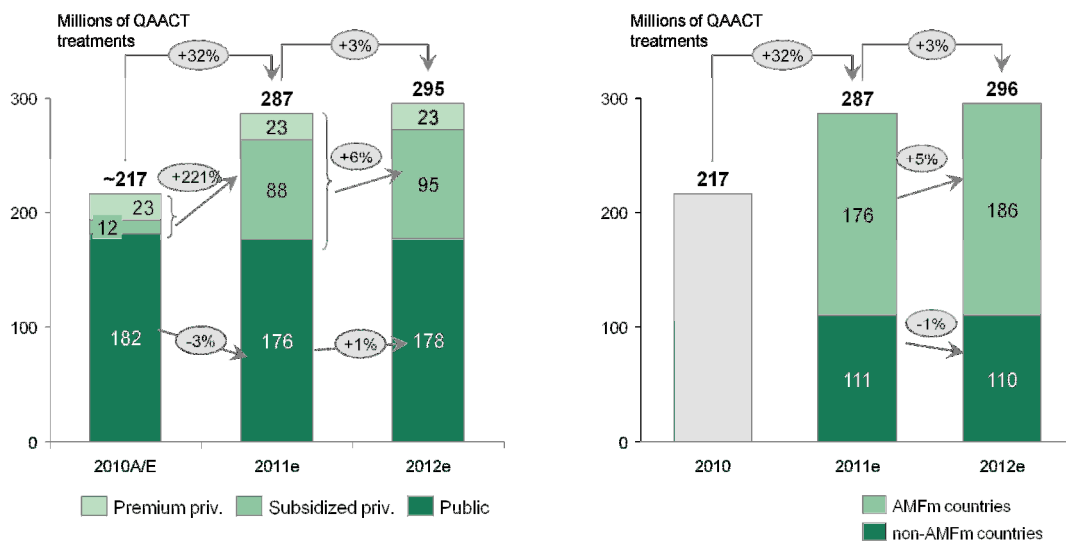
6. AM and QN can be used if no AS - For pregnant women, AS & AM are preferred to QN for second & third trimester.

7. Intramuscular Artemether

Note: QN= Quinine; Clin= Clindamycin; ACT=Artemisinin-based combination therapy; CQ= Chloroquine ; AQ = Amodiaquine; PQ = Primaquine; AS= Artesunate; AM= Artemether.

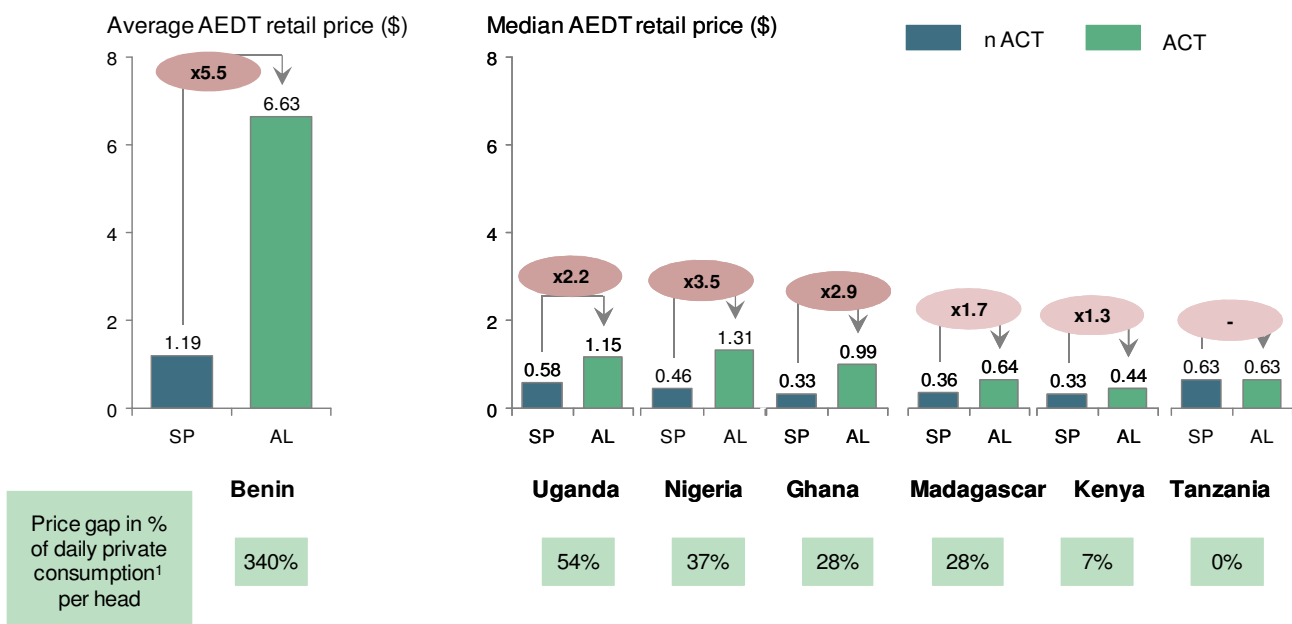
Sources: Adapted from *Malaria control today – Current WHO recommendations (WHO, 2005)*, *Guidelines for the treatment of malaria second edition (WHO, 2010)*, interviews at WHO-GMP (Case Management) and created by the Boston Consulting Group, *Malaria Markets 2011*.

Figure A3-2. Global prequalified ACT demand evolution per channel and country type



Source: UNITAID ACT Forecast, Q3 2011 by the ACT Forecast Consortium (Boston Consulting Group, Clinton Health Access Initiative, Fundacion Zaragoza Logistics Center).

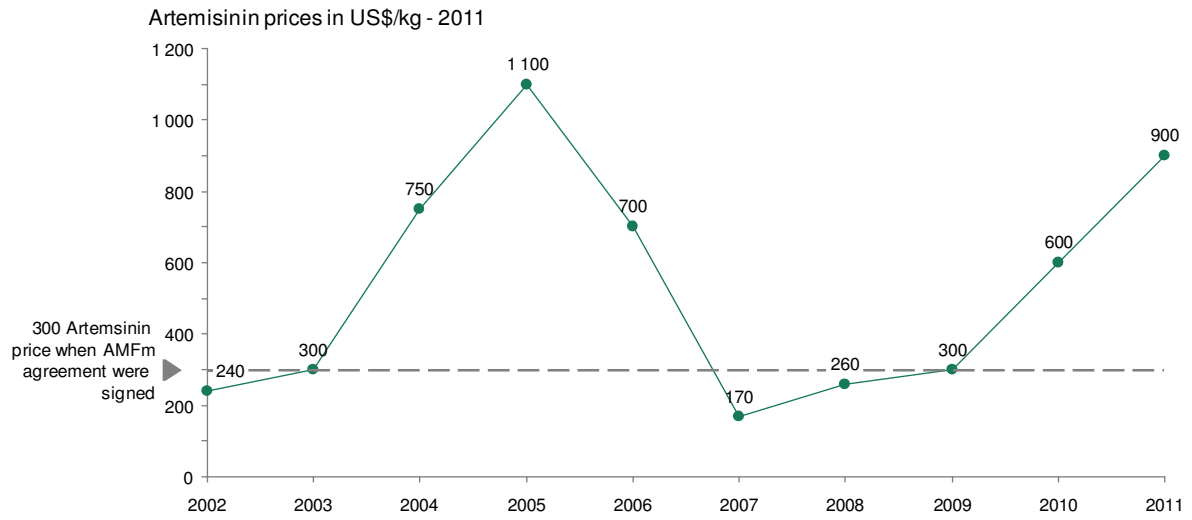
Figure A3-3. Price comparison of ACTs and non-ACTs in selected AMFm countries and one non-AMFm country (Benin) (Median AEDT retail price (US\$))



1. Private consumption expenditure is the expenditure by head on consumption goods and services, eg, housing fees and transportation
 Note: Median price not available for Benin, median price observed in AMFm countries in formal retail sites, defined as registered pharmacies
 Source: The private commercial sector distribution chain for antimalarial drugs in Benin (ACT Watch, November 2009), Retail prices of ACTs co-paid by the AMFm and other antimalarial medicines (HAJ, June 2011); Private consumption expenditure divided by population derived from IMF, International Financial Statistics - EIU Country Data - 2009

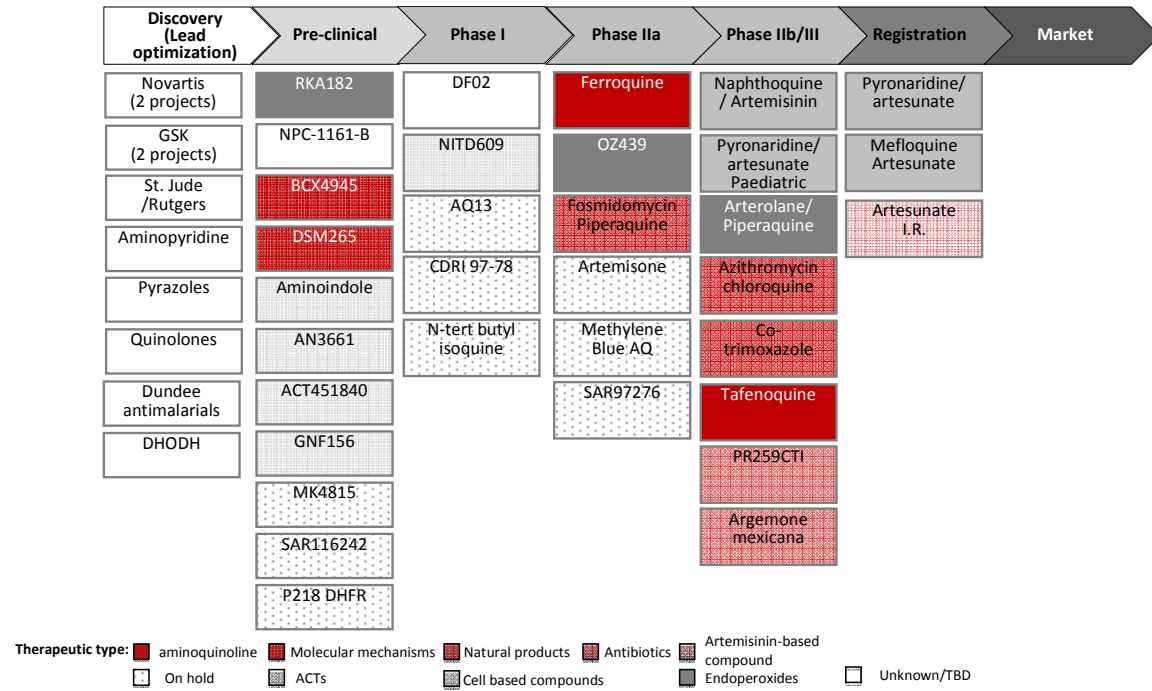
Source: UNITAID Malaria Medicines Market Landscape, 2011 by Boston Consulting Group

Figure A3-4. Artemisinin price evolution – from 2002 to 2010



Source: ARTEMISININ CONFERENCE – HANOI, NOVEMBER 2011

Figure A3-5. Current pipeline for malaria medicines



Source: Adapted from Medicines for Malaria Venture pipeline, 3Q 2011.