Global Access of HIV patients to HAART therapy-
What after Doha?

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ATHENS 2012
ABBREVIATIONS

3TC: Lamivudine
AIDS: Acquired Immunodeficiency Syndrome
ART: Antiretroviral Therapy
ARV: Antiretroviral drug
ATV: Atazanavir
AZT: Zidovudine
DRV: Darunavir
EFV: Efavirenz
ETV: Etravirine
HAART: Highly Active Antiretroviral Therapy
HBV: Hepatitis B Virus
HIV: Human Immunodeficiency Virus
IP: Intellectual Property
MENA: Middle East and North Africa
MSF: Médecins Sans Frontières
NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI: Nucleoside Reverse Transcriptase Inhibitor
NGO: Non-Governmental Organization
PEPFAR: US President’s Emergency Plan for AIDS Relief
PI: Protease Inhibitor
RAL: Raltegravir
S&D: Special and Different treatment
TB: Tuberculosis
TDF: Tenofovir
TPP: Trans-Pacific Partnership
TRIPS: Trade Related Aspects of Intellectual Property Rights
UNAIDS: United Nations Joint Programme on HIV/AIDS
UNICEF: United Nations Children’s Fund
WHO: World Health Organization
WTO: World Trade Organization
ABSTRACT

The past decade has seen remarkable progress in increasing access to antiretroviral therapy, especially in resource-limited settings. Early concerns about the cost of treatment were overcome thanks to the efforts of a global coalition of health providers, activists, academics, and people living with HIV/AIDS, who argued that every effort must be made to ensure access to essential care when millions of lives depended on it. Government and civil society reacted to the increases in drug prices, precipitated a series of events, culminating in the 2001 World Trade Organization’s Doha Declaration on the Agreement on Trade-Related Aspects of Intellectual Property Rights and Public Health. The Declaration affirmed that patent rules should be interpreted and implemented to protect public health and to promote access to medicines for all. Since Doha, more than 60 low- and middle-income countries have procured generic versions of patented medicines on a large scale.

Despite these changes, however, a “treatment time bomb” awaits. First, increasing numbers of people need access to newer antiretrovirals, but treatment costs are rising since new ARVs are likely to be more widely patented in developing countries. Second, policy space to produce or import generic versions of patented medicines is shrinking in some developing countries. Third, funding for medicines is falling far short of needs.

The challenge for the next decade is to further increase access to treatment and support sustained care for those on treatment, while at the same time ensuring that the package of care is continuously improved such that all patients can benefit from the latest improvements in drug development, clinical science and public health.

Key words: Antiretroviral therapy, cost of treatment, Doha Declaration, patent rules, access to medicines, Intellectual Property Rights, generic versions.
ΠΕΡΙΛΗΨΗ

Την τελευταία δεκαετία υπήρξε μία αξιοσημείωτη πρόοδος στην αύξηση της πρόσβασης στη θεραπεία του AIDS με αντιρετροϊκά φάρμακα ιδιαίτερα σε χώρες με περιορισμένους πόρους. Οι ανησυχίες για το κόστος της θεραπείας ξεπεράστηκαν χάρη στις προσπάθειες ενός παγκόσμιου συνασπισμού, που αποτελούνταν από άτομα που παρέχουν υπηρεσίες υγείας, ακτιβιστές, πανεπιστημιακούς, και ανθρώπους που ζουν με HIV/AIDS, ο οποίος υποστήριζε ότι πρέπει να καταβληθεί κάθε προσπάθεια για να εξασφαλιστεί η πρόσβαση στη θεραπεία. Η αντίδραση λοιπόν στις αυξήσεις των τιμών των φαρμάκων έγινε με μια σειρά από εκδηλώσεις, με αποκορύφωμα τη Διακήρυξη της Ντόχα το 2001 του Παγκόσμιου Οργανισμού Εμπορίου σχετικά με τη συμφωνία για τις εμπορικές πτυχές των δικαιωμάτων πνευματικής ιδιοκτησίας και τη δημόσια υγεία. Στη διακήρυξη αυτή επιβεβαιώθηκε ότι οι κανόνες διπλωμάτων ευρεσιτεχνίας πρέπει να ερμηνεύονται και να εφαρμόζονται για την προστασία της δημόσιας υγείας και την προώθηση της πρόσβασης σε φάρμακα για όλους. Από τη στεγανή εκείνη, περισσότερες από 60 χώρες χαμηλού και μεσαίου εισοδήματος έχουν αγοράσει σε μεγάλη κλίμακα γενόσημα φάρμακα με διπλώματα ευρεσιτεχνίας. Παρά τις αλλαγές αυτές, όμως, πολλές προκλήσεις παραμένουν. Πρώτον, έχουμε αύξηση του αριθμού των ανθρώπων που χρειάζονται πρόσβαση σε νεότερα αντιρετροϊκά φάρμακα. Όμως το κόστος θεραπείας με αυτά αυξάνεται καθώς τα νέα αντιρετροϊκά φάρμακα είναι πιθανόν να καταχωρίζονται με διπλώματα ευρεσιτεχνίας στις αναπτυσσόμενες χώρες. Δεύτερον, η πολιτική να παράγουν ή να εισαγάγουν γενόσημα φάρμακα με διπλώματα ευρεσιτεχνίας μειώνεται σε ορισμένες αναπτυσσόμενες χώρες. Τρίτον, οι χρηματοδοτήσεις για τα φάρμακα του AIDS υπολείπονται κατά πολύ των αναγκών. Η πρόκληση για την επόμενη δεκαετία είναι να αυξηθεί περαιτέρω η πρόσβαση στη θεραπεία και η υποστήριξη των ατόμων αυτών, ενώ ταυτόχρονα να εξασφαλιστεί ότι το πακέτο φροντίδας θα βελτιώνεται συνεχώς έτσι ώστε όλοι οι ασθενείς να μπορούν να επωφεληθούν από τα τελευταία επιτεύγματα όσον αφορά την ανάπτυξη φαρμάκων, την κλινική επιτήμημα και τη δημόσια υγεία.

Λέξεις Κλειδιά:
Θεραπεία του AIDS, αντιρετροϊκά φάρμακα, κόστος θεραπείας, πρόσβαση στη θεραπεία, Διακήρυξη της Ντόχα, δικαιώματα πνευματικής ιδιοκτησίας, διπλώματα ευρεσιτεχνίας.
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Introduction

Since its first appearance in 1981, the HIV epidemic remains a major global public health challenge, with dramatic consequences for entire communities. Most people who die from AIDS-related illnesses are young adults- among the most economically productive members of society. Across the world, an estimated 17.5 million children have lost at least one parent to HIV. Treatment, hospitalization and loss of income, as well as providing care for family members living with HIV and for orphans, results in a high economic burden for households [1, 2]. This is the reason that a global movement is trying to combat the HIV epidemics.

Globally, the number of people living with HIV is constantly growing, reaching an estimated 34 million at the end of 2010, including 3.4 million children under 15 years old [3]. At the same time, the annual number of people newly infected with HIV is declining. More specifically, an estimated 2.7 million people were newly infected with HIV, in 2010, 15% less than the 3.1 million people newly infected in 2001 and more than one fifth (21%) fewer than the estimated 3.4 million in 1997, the year when the number of people newly infected with HIV peaked [3]. The same progress we have also at the annual number of people dying from AIDS-related causes worldwide. From a peak of 2.2 million in 2005 it is steadily decreasing to an estimated 1.8 million in 2010.

This huge progress is a consequence from many scientific, political and economical changes that took place the recent years. An important role to this progress played the invention of the Highly Active Antiretroviral Therapy (HAART), which led the HIV to its gradual evolution from a fatal disease to a chronic condition. A total of 2.5 million deaths have been averted in low- and middle-income countries since 1995 due to antiretroviral therapy being introduced [4]. Moreover, we had a huge increase of the availability of antiretroviral therapy as well as care and support, to people living with HIV, especially in sub-Saharan Africa. Actually in 2010 alone, 700.000 AIDS related deaths were averted due to the rapid scale-up of access to treatment [4]. But these statistics differ very much from country to country. For example, Sub-Saharan Africa remains the region most affected by HIV where, in 2010, 68% of all HIV-infected people resided there. However, AIDS-related deaths have steadily decreased, as free antiretroviral therapy has become more widely available in the region. On the other side, in Eastern Europe and Central Asia, there was a 250% increase in the number of people living with HIV from 2001 to 2010 and, unlike most regions, AIDS-related deaths continue to rise [4]. The main reason for this situation is the unequal access in HIV treatment and, even though it has been an exciting progress, several commercial interests put barriers to the universal access to high-cost therapies.

This study summarizes the progress that has been made over the global access to the HAART during the last years, especially to the low- and middle-income countries and all the actions that have been taken in this direction. Finally, the new global targets that have been established by WHO and how they can be achievable are discussed.
1. What is HAART and why is important

Highly Active Antiretroviral Therapy (HAART) is the name given to aggressive treatment regimens used to suppress HIV viral replication and the progression of HIV disease [5]. There are three main types-classes of antiretroviral drugs; each of them attacks HIV in a different way, or on a different stage of the HIV-life cycle. The first class of anti-HIV drugs are the Nucleoside Reverse Transcriptase Inhibitors (NRTIs) which block the step where the HIV genetic material is used to create DNA from RNA in order to make copies of itself. The second class contains the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) which block the same step but in a different way. The third class is the Protease Inhibitors (PIs) which stop HIV replication by preventing the enzyme protease from cutting the virus into the shorter pieces that it needs to make copies of itself. So, incomplete, defective copies are formed which can’t infect cells. There are also newer classes of antiretroviral drugs, such as the Entry Inhibitors and the Integrase Inhibitor [5].

The usual HAART regimen combines three or more different drugs such as two NRTIs and a PI, two NRTIs and a NNRTI or other such combinations. Three drugs are used in order to reduce the likelihood of the virus developing resistance.

According to the WHO’s antiretroviral therapy guidelines, all patients with HIV infection and a CD4 count at or below 350 cells/mm³, should be started on ARV. Adolescents, adults as well as pregnant women, are all included, regardless of whether they have clinical symptoms or not. Those with severe or advanced clinical disease or co infected with HIV and TB or HBV should start ART irrespective of their CD4 cell count [6]. Guidelines from wealthy countries however, recommend even earlier initiation of ARVs, at a CD4 cell count of 500 cells/mm³ or above [7, 8].

These HAART regimens have proven to reduce the amount of active virus and in some cases can lower the number of active virus until it is undetectable by current blood testing techniques [5]. Actually, it has been proven that ART has achieved to both reduce mortality and morbidity rates among HIV-infected people, and to improve their quality of life [9]. It also prevents the transmission of the virus from HIV-infected mothers to their children by two-thirds during the perinatal period and while breastfeeding [10]. ART also has a significant impact on reducing HIV and TB transmission [11], which remains the number one killer of people living with HIV/AIDS [12]. Recent evidence suggests that it may also have an impact on reducing malaria incidence [13].

Despite these advantages, there were many obstacles to provide these medicines to all over the world. More specifically, there were many concerns that treatment was too expensive, too complex, and that drug resistance would be promoted by inadequate programmes. In particular, it was argued that ART was not cost-effective and that prevention interventions should be prioritized [14]. Despite these concerns, treatment programmes began to deliver ART at scale, and in less than a decade, more than five million people were successfully started on treatment. This remarkable progress was supported by a global coalition of doctors, patients, civil society actors, governments, and non-governmental organizations, who refused to accept that millions of people could be consigned to an early death from a disease that in developed countries had been transformed into a chronic, manageable condition [15]. So, let’s take a look at some of the work that is being done in an effort to bring down the cost of HIV medications.
2. The beginning of ARV medicines

When antiretroviral medicines became available in the industrialized countries, they remained far out of reach of most developing countries that also have the biggest problem. At this time only one in a thousand people living with HIV in Africa had access to HIV treatment [16]. This was because antiretroviral drugs were available only from the originated companies that controlled the patents of these medicines and came with a paralysing price tag of US$ 10,000 to US$ 15,000 per patient per year [8].

The situation seems to change when in 1999, at the United Nations in Geneva, a group of NGOs and AIDS activists held a conference on compulsory licensing for HIV medicines. Since then, each member of WTO should follow the TRIPS agreement. The TRIPS Agreement sets minimum standards in the international rules governing patents, including on medicines. Countries that are members of the WTO agree to certain common standards in the way they enact and implement their patent laws. These standards include, amongst others, that patents be given for a minimum of 20 years; that patents may be given both for products and processes; and that pharmaceutical test data be protected against ‘unfair commercial use’. Developing country members of the WTO generally had until the beginning of 2000 to implement TRIPS. Some countries were given a longer transition period – those like India that did not grant patents on pharmaceutical products were given until 2005, and least-developed countries were initially given until 2006 [17]. A compulsory license is a way to remedy problems caused by a patent, whereby a government body (such as a ministry, court or a statutory tribunal) grants a license to an entity other than the patent holder, allowing them to produce the patented product in exchange for “adequate remuneration” [8]. This was only the start of a global mobilization.

Under increasing public pressure to support rather than hinder efforts to combat the epidemic, the patentholding pharmaceutical industry began to respond. Actually, in May 2000, five pharmaceutical companies offered price discounts on HIV-related medicines and diagnostics in developing countries. However, even with the discounts, the prices offered through this initiative paled in comparison with the prices offered by generic producers. At the XIII International AIDS Conference in July 2000 in Durban, South Africa, activists, community leaders, scientists and health care providers joined forces to demand access to treatment and an end to the enormous health inequities between the global North and global South [3].

Widespread access to affordable antiretrovirals became feasible after the announcement by an Indian generics manufacturer, Cipla, in early 2001 that triple therapy could be manufactured for less than a dollar a day [18]. The lowest publicly announced originator price for the same combination of drugs offered by Cipla was about $1000 at the time, but countries negotiated case-by-case with originator companies for price discounts, with a wide variation in prices by country [18, 19]. Whereas, Cipla publicly offered its price to all countries. This established a dynamic of global market competition that in 10 years has brought down the price of standard triple therapy from US$ 10,000 per patient/year to almost US$ 50 per patient/year [15]. India quickly was becoming the “pharmacy of the developing world”. Today, over 80% of ART used in low- and middle-income countries is purchased from Indian generics companies [20].

Although these facilities, under some circumstances, life-saving medicines were considered in the same vein as mere consumer goods and the devastating impact of high prices is mostly ignored. The balance between the private interests of the patent holder and the larger interests of society was severely skewed. But the response came quickly, one year after, in 2001, at the annual ministerial meeting of the WTO in Doha.
3. The landmark for global access to affordable medicines

The 14\textsuperscript{th} November 2001 was an important day in the history of the world trade, which had also a huge impact to the access to the affordable medicines. That was the date that the 4\textsuperscript{th} Ministerial Conference of the World Trade Organization (WTO) was held at the capital of Qatar, Doha [21]. At that conference, trade ministers of the members of the WTO agreed to undertake a new round of multilateral trade negotiations [22].

As far as the public health is concerned, these declarations dealt with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and allow governments to be flexible of TRIPS in a way that supports public health - by promoting both access to existing medicines and the creation of new medicines. Specifically, it is emphasized that “the TRIPS Agreement does not and should not prevent member governments from acting to protect public health” [21 p. 1]. It affirms governments’ right to use the agreement’s flexibilities in order to avoid any reticence the governments may feel [21].

Furthermore, the Declaration specifically reaffirms member countries’ rights to determine the grounds on which compulsory licenses may be issued, to determine what constitutes a national emergency or circumstance of extreme urgency, and to determine their own regime for the exhaustion of intellectual property rights [21, 23]. Another noteworthy development issue deals with a review of provisions of giving special and differential (S&D) treatment to developing countries [24].

The final significant achievement of Doha was to extend the deadline by which the least-developed countries had to grant and enforce pharmaceutical patents, from 2006 to 2016 [21, 24]. This was essential in making lower cost generic versions of patented medicines available on a large scale.

Eventually, the Declaration had important impacts to many countries. For example, Thailand and Brazil issued compulsory licenses and implemented universal access to antiretroviral therapy [25, 26]. At the same time over 60 developing countries had procured lower-cost medicines on a large scale using TRIPS flexibilities [8, 27]. Twenty-six out of 32 least developed country WTO members authorized importation of generic ARVs with reference to the Doha Declaration, which allowed them to delay granting or enforcing medicines patents until at least 2016 [27]. Companies also responded to patent challenges by agreeing to voluntary licenses to their patent, under the threat of non-voluntary measures, such as compulsory licenses and patent oppositions [28].
4. The peak of mobilization- International Funds

Over the next years, financial facilities followed in order to have all countries achieve the WHO’s challenging goals over combating HIV-epidemics. It started in 2002 with The Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), a result of extensive efforts by many advocates to create a new approach to financing the international response to HIV and other global health concerns.

The Global Fund is an international financing institution that invests the world’s money to save lives. It is almost completely funded by contributions from the largest developed nations’ governments/tax payers and currently more than 96% of its yearly contributions are received from government organizations. Its largest private contributor by far is the Bill & Melinda Gates Foundation, which committed US$ 100 million, spread over a few years [29, 30].

To date, it has committed US$ 22.6 billion in 150 countries to support large-scale prevention, treatment and care programs against the three diseases, AIDS, tuberculosis, malaria [29]. Specifically, by the end of 2011, programs supported by The Global Fund, reported 3.3 million people on ART [26].

Continually, in 2003, the United States Government announced the United States President’s Emergency Plan for AIDS Relief (PEPFAR). PEPFAR was a commitment of US$ 15 billion over five years (2003–2008) from United States President George W. Bush to fight the global HIV/AIDS pandemic [31]. It was the largest single funding commitment for a disease in history and it was reauthorized in 2008 for up to US$ 48 billion to combat AIDS, TB and malaria for 2009–2013 [31, 32]. The program initially aimed to provide antiretroviral treatment to 2 million HIV-infected people in resource-limited settings, to prevent 7 million new infections, and to support care for 10 million people (the "2–7–10 goals") by 2010. PEPFAR establishes bilateral programs in host countries and also works closely with multilateral partners, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and the United Nations programme on AIDS (UNAIDS) [33]. It has been called the largest health initiative ever initiated by one country to address a disease.

The impact of PEPFAR was also huge. It is worth mentioning that PEPFAR increased the number of Africans receiving ART from 50,000 at the start of the initiative in 2004 to at least 1.2 million in early 2008 [34]. Moreover, according to a 2009 study published in Annals of Internal Medicine, the programme had averted about 1.1 million deaths in Africa and reduced the death rate due to AIDS in the countries involved by 10% [35].

Additional innovations in global health funding followed. By 2006, Brazil, Chile, France, Norway and the United Kingdom had agreed to create UNITAID, an international drug purchase facility financed through a modest levy on airline tickets and now is supported by 29 countries, the Bill & Melinda Foundation, NGOs’ and communities [8]. UNITAID now finances and supports strategic interventions in the drug and diagnostics markets in 94 countries [36].

The results of all these global movements- political declarations and global funds- were significant. A lot of countries were allowed to begin purchasing HIV medicines in large scales. By 2010, such purchases were predominantly generic drugs [37]. For example, by 2008, 95% (by volume) of the global donor-funded ARV market was comprised of generics, primarily from India. The generic proportion of PEPFAR-purchased ARVs grew from 15% to 89% from 2005 to 2008, with estimated savings to PEPFAR totaling US$ 323 million over the four-year period [38].
5. Progress in access to HAART and nowadays

Thanks to these declarations and global efforts, now we have huge progress in the percentage of HIV patients who have access to HAART.

It is estimated that at least 6.6 million people in low- and middle-income countries are receiving HIV treatment. This is an increase of more than 1.35 million over the previous year. In low- and middle-income countries 47% of the 14.2 million eligible people living with HIV were on antiretroviral therapy at the end of 2010, compared to 39% at the end of 2009. In addition, at least 745,000 people were receiving antiretroviral therapy in high-income countries at the end of 2010, including about 430,000 in Europe, 300,000 in North America and the Caribbean, and 16,700 in Asia, Oceania and the Middle East. This means that at the end of 2010, almost 7.4 million people worldwide, including high-income countries, were accessing antiretroviral therapy. In total, 1.7 million people initiated treatment in 2010; of these, 1.4 million were alive and on treatment at the end of 2010 [3, 10].

But we should also mention the variability of the progress among regions and even subregions [10]. As we can see in figure 2, the most significant increases in antiretroviral therapy coverage have occurred in sub-Saharan Africa, with a 30% increase between 2009 and 2010 alone.

Figure 2. Access to antiretroviral treatment, by region, 2002-2010

![Figure 2. Access to antiretroviral treatment, by region, 2002-2010](Source: UNAIDS Data tables 2011, p.3 [10].)

A characteristic example is the difference in coverage between the countries with similar financial backgrounds (annex 1). Whereas 56% of the people eligible for antiretroviral therapy in East and Southern Africa were receiving it, coverage in West and Central Africa stood at 30% [10]. In Middle East and North Africa there is the lowest coverage, only 10% where Oman has the best estimated coverage in the region, with 45% of adults and children living with HIV receiving treatment by the end of 2010. But also, the number of people needing treatment has increased there from 57,000 in 2001 to 210,000 in 2010, both due to a higher HIV prevalence in the region and a change in the treatment protocols by WHO. However, it is worth noting that four countries in the region make up 85% of the
number of the people eligible for antiretroviral therapy: Iran (26,000), Pakistan (22,000), Somalia (25,000), and Sudan (93,000) [39].

It is also remarkable that ten low- and middle-income countries (Botswana, Cambodia, Chile, Croatia, Cuba, Guyana, Namibia, Nicaragua, Rwanda and Slovakia) had achieved universal access to antiretroviral therapy (defined as providing antiretroviral therapy to at least 80% of patients in need) by the end of 2010. Seven other countries (Argentina, Brazil, Dominican Republic, Mexico, Swaziland, Uruguay and Zambia) had coverage levels between 70% and 79% [10]. Totally, in low- and middle-income countries, treatment has averted 2.5 million AIDS deaths since 1995, the majority in the past few years [4].

Mothers and children

In this section, progress is already considerable. New child infections were rising until 2002 when they reached their peak of 560,000. By 2010 they had fallen to an estimated 390,000. It is estimated that more than 350,000 new infections among children have been averted since 1995 due to the provision of antiretroviral prophylaxis to HIV-positive pregnant women [10]. In the past two years alone, rapid increase of coverage of HIV treatment and prevention services for pregnant women resulted in a doubling of cumulative HIV infections averted [4].

In 2010, 48% of the estimated 1.5 million pregnant women living with HIV in low- and middle-income countries received effective regimens to reduce the risk of HIV transmission to their infants and for their own health [10]. In annex 2 we can recognize the variability of the coverage of pregnant women among some regions. Coverage was highest in Europe and Central Asia (79%), and lowest in the Middle East and North Africa (4%) [39].

As we can see in figure 3 the most significant progress was in sub-Saharan Africa, where there was the majority of child infections averted (85%), with the other regions following [10].

Figure 3. Number of women receiving antiretroviral treatment to prevent HIV infections among children, by region, 2004-2010

Source: UNAIDS Data tables 2011, p. 7 [10].
According to WHO, all infants born to mothers living with HIV should receive antiretroviral prophylaxis even when their mother also receive antiretroviral therapy. This includes not just the short postpartum prophylaxis for 4–6 weeks recommended for all HIV-exposed infants, regardless of the regimen used for preventing mother-to-child transmission or of breastfeeding, but also extended antiretroviral therapy or other antiretroviral medicine for the mother or infant during breastfeeding [40]. Although the coverage of antiretroviral prophylaxis among infants was still less than the coverage among mothers in 2010, the reported coverage among infants increased between 2009 and 2010 from 32% to 42% of the estimated 1.49 million infants born to mothers living with HIV. Despite this increase, the gap between infants’ and mothers’ uptake of antiretroviral medicine is still substantial, suggesting problems with providing the postpartum prophylaxis to the infant. In 2010, the coverage of antiretroviral prophylaxis was higher in Eastern Europe and Central Asia (75%) and it remained lowest and relatively stagnant in Western and Central Africa (14%), as we can see in figure 4 [3].

**Figure 4.** Percentage of infants born to pregnant women living with HIV who received prophylaxis for preventing mother-to-child transmission, 2005, 2009 and 2010

![Figure 4](image)


Also, the number of children younger than 15 years of age receiving antiretroviral therapy in low- and middle-income countries increased by 29% between 2009 and 2010. About 456,000 children younger than 15 years were receiving antiretroviral therapy at the end of 2010, up from 354,600 in December 2009 [3].

However, coverage of antiretroviral therapy among children and adolescents continues to be considerably lower than adults in low and middle-income countries. Children represented 7% of the people receiving antiretroviral therapy and 14% of the people who needed it. Out of the two million children estimated to be in need of antiretroviral therapy in 2010, only 23% had access to treatment, compared with 51% of adults (annex 3). Only in Europe and Central Asia is the coverage among children higher than among adults [3]. Again, there is considerable variation across regions. Actually, as we can see in figure 5, coverage of pediatric antiretroviral therapy increased substantially only in Europe and Central Asia, from 56% to 65% in 2009–2010. In the same period, coverage in sub-Saharan Africa hardly changed, and stood at a low 21% in 2010, in a region that accounts for about 91% of global pediatric treatment need. An estimated 388,000 of the 1.8 million children needing antiretroviral therapy
in that region were receiving it at the end of 2010. Coverage was unchanged in East, South and South-East Asia at 39% in 2010, and in North Africa and the Middle East at 5% but decreased in Latin America and the Caribbean, from 45% to 39%, in 2009–2010 (fig. 5). Again, Botswana and Thailand achieved respectively to have the highest level of coverage of antiretroviral therapy for children (85% and 69%) among low- and middle-income countries. At the same time, Chad and Sudan had the lowest rates (5% and 2% accordingly) [10].

**Figure 5.** Percentage of children living with HIV receiving antiretroviral therapy in low- and middle-income countries, 2005, 2009 and 2010


**HIV-related Deaths and Diseases**

The annual number of people dying from AIDS-related causes worldwide is steadily decreasing from a peak of 2.2 million in 2005 to an estimated 1.8 million in 2010 (Fig. 6). AIDS-related mortality began to decline in 2005–2006 when the availability of antiretroviral therapy, as well as care and support, to people living with HIV, increased, especially in sub-Saharan Africa, where an estimated 460,000 (30%) fewer people died from AIDS-related causes in 2010 than in 2004 [3].

The trends in AIDS-related deaths also differ. For example, in Eastern Europe and Central Asia, the number of people dying from AIDS-related causes increased from 7800 in 2001 to 90,000 in 2010. In the same period, AIDS mortality increased by 60% in the Middle East and North Africa and more than doubled in East Asia. In North America and in Western and Central Europe, the number of people dying from AIDS-related causes began to decline soon after antiretroviral therapy was introduced in 1996 [3].
Especially, tuberculosis is the leading HIV-associated opportunistic infection in low- and middle-income countries, and it is a leading cause of death among people living with HIV globally. In 2010, out of 8.8 million incident TB cases worldwide, 1.1 million were among people living with HIV, with an estimated 350,000 deaths, which makes TB responsible for one in four AIDS deaths. Sub-Saharan Africa continues to account for the global majority of the people living with HIV and TB, with an estimated 82% in 2010 [3].

Although antiretroviral therapy is shown to reduce incidence of tuberculosis at the individual and population level, and mortality, the percentage of co-infected patients that are receiving treatment is low in the most countries [41]. In 2010, only 20% of the total estimated number of people with TB and HIV were receiving antiretroviral therapy [3].
6. The black holes in HIV-treatment

Although we observed an exceptional progress at the section of HIV treatment the last years, there are also a lot of deficiencies and inequalities that must be captured in order to be able to say that all people have access to HAART. Apart from the variability in access to HAART from region to region and the variability among children and adults, as it is mentioned above, there are also other barriers that make the situation more difficult.

It is true that the main reason of this progress was the significant reduction of prices of antiretroviral drugs. As we can see in annexes 4a and 4b, the prices of all combinations, both for first-line and second-line regimens, have decreased from 2008 to 2010. Actually, in 2010 the weighted median price of antiretroviral drugs in low-income countries was 60% lower than in 2006, ranged from US$ 52 to US$ 242 per person per year [3]. The Doha Declaration which allowed the growing use of generic medicine was mainly responsible for this rapid decline in median prices. Specifically, in countries where the drugs are not under patent or where patents owners permit generic competition, the one-pill once-a-day generic triple combination containing tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) is now available for $173 per person per year [12]. But, in some lower-middle-income countries, patents prevent access to generic products, meaning that countries have to rely on the discounted price offered by originator companies -US$ 1.033- nearly six times the cost of the alternative equivalent generic version [12]. So, patents remain a barrier to improve treatment.

To make matters worse, recently, a number of drug companies confirmed to refuse to extend standardized price discounts to middle-income countries, something which was previously routine practice. This move ignores the fact that the majority of people in middle-income countries, like India, Brazil or Thailand, should pay higher prices for medicines. Moreover, these countries are losing the support global health mechanisms like Global Fund [42].

Another major barrier to scaling-up the access to HIV treatment is the price of newer medicines (fig 7). The second-line regimen with zidovudine and atazanavir (AZT/3CT/ATV) recommended by WHO is today priced at US$ 442 [12]. Although price has come down, this is still three times more than the TDF-based first-line regimen recommended by WHO (annex 4b). The price of a possible third-line regimen is close to 20 times more than the most affordable WHO recommended first-line regimen, and over six times more than the most affordable second-line regimen [12]. So, the relative higher cost of second-line regimens remains an important objective as antiretroviral therapy programmes mature and the number of people who need second-life regimens is continually growing.

Figure 7. Price comparisons of first-line, second-line and possible third-line medicines

Source: Antiretroviral price reductions- 14th Edition 2011, p.5 [12].
The extensive reduction of the cost of HIV treatment over the past decade was caused by the competition among multiple generic pharmaceutical manufacturers in countries where medicines were not patented. Prices were falling as the number of generic competitors was increasing – securing generic competition was therefore essential to bringing the cost of drugs down to affordable levels (annex 5).

However, at the same time, U.S. and European Union who both have pharmaceutical industries, push developing countries to accept harsh provisions in free trade agreements; these include the negotiation between countries in the European Free Trade Area and India, as well as US trade negotiations with several Asia Pacific countries in the Trans-Pacific Partnership Agreements (TPP). These agreements demand aggressive intellectual property provisions that undermine the Doha Declaration and the safeguarding of public health [43, 44].

Another important problem has to do with the global donations. The current economic crisis and the dwindling international resources have reduced the financial resources made available for the AIDS response. More specifically, the Global Fund stated in May 2011 that it was short by US$ 1.3 billion for 2011 through 2013, seeking at least US$ 13 billion to cover minimum estimated needs but only holding pledges of US$ 11.7 billion [45].

The organization was also adversely affected by revelations of US$ 25 million missing from community programmes in four nations in Africa, which caused Sweden and Germany to suspend their donations until the completion of the audit in 2011 [45]. Continually, in 2011, the organization's internal investigation identified 13 countries, most in Africa, where several million dollars' worth of antimalarial drugs where stolen and presumably sold on the black market. The organization suspected malaria drug valued at US$ 2.5 million were stolen from Togo, Tanzania, Sierra Leone, Swaziland, and Cambodia from 2009 to 2011, with some cases earlier. Investigations continued to determine the amount of theft in other countries [46]. Finally, in November 2011, the Global Fund's board cancelled all new grants for 2012.

The same lack of funding was recognized at PEPFAR. While the Bush administration had promised to increase funding for PEPFAR, January 2010's Obama administration budget proposes to 'flatline' its funding. Though Obama had pledged $1.05 billion per year for the Global Fund to Fight AIDS, TB, and Malaria for 2010 and 2011, the actual % contributed were 75% and 60% respectively. Overall funding has decreased by 22.5% between fiscal years 2008 and 2011 [47, 48].
In 2011 WHO established the new strategic goals in the way to combat HIV-epidemics. According to this, the visions for 2015 are to achieve “Zero new infections, Zero AIDS-related deaths and Zero discrimination among people with AIDS” [49]. Specifically, this means that new infections of AIDS in young people (15-24 years) must be reduced by 50% and the new HIV infections in children must be reduced by 90%. Moreover, HIV-related deaths must be reduced by 25% and the tuberculosis-related mortality must be reduced by 50% [49]. These targets will be achieved by following four strategic directions.

The first direction deals with the effort to optimize the HIV prevention, diagnosis, treatment and care. The most important is to revolutionize the HIV prevention by generating political commitment to address how and why people are getting infected, mobilizing communities to effectively demand transformative social and legal change and by directing resources to epidemic hot spots through the right interventions. In the process to catalyze the next face of treatment, care and support, it must be ensured that people living with HIV can access effective treatment when they need it and the national and community systems must be strengthened to deliver treatment, care and support. In addition, there must be a scaling up access to care, support and social protection by people living with and are affected by HIV. A promising solution is a new campaign called Treatment 2.0 [50]. This model, using a combination of efforts, it could reduce treatment costs, make treatment regimens simpler and smarter, reduce the burden on health systems and improve the quality of life for people living with HIV and their families. It is suggested that, compared with current treatment approaches, Treatment 2.0 could avert an additional 10 million deaths by 2025 [51].

The second strategic direction addresses the links between HIV programmes and other health programmes [49]. For example, countries should implement mechanisms for intensified collaboration and joint planning between HIV and tuberculosis programmes or HIV services should be integrated within a package of core interventions for maternal, newborn and child health. Moreover, a comprehensive package of harm-reduction services should be integrated into drug prevention, treatment, rehabilitation, detoxification and control programmes, whether they be delivered by the health sector or other sectors.

Another direction is dealing with the effort to strengthen the building blocks of health systems, in order to have strong and sustainable ones [49]. Under this direction, more countries should be encouraged to initiate public sector production of generics through new and strengthened South–South cooperation and public-private partnerships. The bulk purchasing of HIV medicines by the Global Fund, UNITAID, the United States President’s Emergency Plan for AIDS Relief and others should continue to support treatment scale-up. Additionally, for universal access to become a reality, international and domestic funding must be scaled up and available. HIV funds must be used more efficiently. Closing the inefficiency gap and making better use of existing funding is fundamental to producing better overall results in HIV treatment and care.

But international funding is not the best of solutions. Middle-income countries must assume greater responsibility for domestic funding of their responses, address internal inequity and engage in South–South partnerships grounded in principles of human rights and aid effectiveness. Emerging economies are wielding more clout in global negotiations on trade, development, human rights, intellectual property rights and other issues. This will have profound implications for many organizations responsible for HIV response. The historical role of the BRICS countries (Brazil, Russian Federation, India, China and South Africa) in relation to the World Trade Organization Agreement on
Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) and essential medicines is a potential advantage for the HIV response [51, 52].

The last but not the least in any way direction addresses the vulnerability and the structural barriers to access HIV services [49]. This means that countries must be supported in protecting human rights in the context of HIV and to create protective social and legal environments that enable access to HIV programmes. Gender equality must be promoted and harmful gender norms must be removed. Especially, it must be ensured that national HIV strategies address the needs and rights of women in the context of HIV.
Ten years after the Doha Declaration the forefront of HIV treatment has changed a lot. A growing international movement fought against the high cost of treatment and in just a few years succeeded in reducing the price of ART to a fraction of its original price. This caused a significant effect at the percentage of HIV-patients that have access to HAART, which in many cases multiplied. This was a great step to limit the HIV-epidemics all over the world.

However, this review draws also attention to the multiple challenges that must be tackled before universal access to HIV prevention, treatment, care and support becomes a global reality. We can easily realize that the treatment gap remains also a global challenge for public health, while there is a huge variability among different countries or even among patients in the same country. Some examples of these deficiencies are the very small percentages of access to treatment of certain groups, such as children. More specifically, as we mentioned above, in low- and middle-income countries only 47% of the people who are eligible are getting antiretroviral therapy, and while the percentage among adults has reached to 51%, among children remains only at 23%. This seems that the playing field is still tilted in favor of rich countries and bullying tactics employed by wealthy countries threaten to tilt the field even further. In other words, this progress is fragile and unevenly distributed and much more effort must be done in order to achieve the ambitious global visions of WHO for HIV response.

So many questions appear after this review which must be resolved if we want to continue the same or better progress. First of all, we have to solve the problem of prices. As we have already mentioned, prices for the first-line medicines have significantly been reduced. But what have we done for the second-line medicines or even for the possible third-line? If we also take into consideration that patients who need second-line regiments is constantly increasing, it is easily understandable that this is a huge barrier towards the suitable therapy. Secondly, we should think about the countries which now profit from non-patenting products. These countries, including India, Brazil, Thailand, will be required to start issuing product patents by 2016. Once this deadline passes, the world's poorest countries will have to keep up with the policies of wealthy nations, which is simply unsustainable. So, what will happen with these countries? Will they have to pay for the original medicines? And finally, what will be done for the patients who are under a therapeutic programme and their international fund is over? Will they stop their therapeutic programme? If this prospect comes true, a lot of HIV-projects in low- and middle-income countries will return to the beginning, resulting in an increase in new infections, due both to downturns in effective prevention programming and a stagnation or decline in treatment access.

In conclusion, the challenges towards universal access are considerable, but so are the technical resources, political support and commitment of all partners involved in the global HIV response. Additional focused investment and building on current achievements and applying the lessons learned from implementing programmes can enable the efficiency, quality and coverage of interventions to be increased and ultimately make universal access to large-scale, high-quality HIV prevention, treatment, care and support a reality.
REFERENCES


ANNEXES
Annex 1

Number of adults and children (combined) receiving and eligible for antiretroviral therapy, and estimated percentage coverage in low- and middle-income countries by region, December 2009 to December 2010.

<table>
<thead>
<tr>
<th>Geographical region</th>
<th>December 2010</th>
<th>December 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of people receiving antiretroviral therapy</td>
<td>Estimated number of people eligible for antiretroviral therapy [range]</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>5,064,000</td>
<td>[9,700,000-11,000,000]</td>
</tr>
<tr>
<td>Eastern and southern Africa</td>
<td>4,221,000</td>
<td>[7,100,000-8,000,000]</td>
</tr>
<tr>
<td>Western and central Africa</td>
<td>842,000</td>
<td>[2,600,000-3,300,000]</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>521,000</td>
<td>[710,000-920,000]</td>
</tr>
<tr>
<td>Latin America</td>
<td>461,000</td>
<td>[620,000-810,000]</td>
</tr>
<tr>
<td>Caribbean</td>
<td>60,300</td>
<td>[91,000-110,000]</td>
</tr>
<tr>
<td>East, South and Southeast Asia</td>
<td>922,000</td>
<td>[2,100,000-2,500,000]</td>
</tr>
<tr>
<td>Europe and Central Asia</td>
<td>129,000</td>
<td>[500,000-650,000]</td>
</tr>
<tr>
<td>North Africa and the Middle East</td>
<td>14,900</td>
<td>[120,000-190,000]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6,650,000</strong></td>
<td><strong>14,200,000</strong></td>
</tr>
</tbody>
</table>

Annex 2

Estimated number of women living with HIV receiving the most effective antiretroviral regimens for preventing mother-to-child transmission and coverages with most effective regimens and with single dose nevirapine, low- and middle-income countries, by geographical region, 2010

Annex 3

Number of children 0–14 years old receiving and estimated to need antiretroviral therapy and percentage coverage among children and adults in low- and middle-income countries, by region, December 2010.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>387 500</td>
<td>1 840 000 [1 600 000-2 100 000]</td>
<td>21% [19-24%]</td>
<td>55% [52-58%]</td>
</tr>
<tr>
<td>Eastern and southern Africa</td>
<td>337 200</td>
<td>1 290 000 [1 100 000-1 400 000]</td>
<td>26% [23-29%]</td>
<td>62% [59-65%]</td>
</tr>
<tr>
<td>Western and central Africa</td>
<td>50 200</td>
<td>550 000 [480 000-630 000]</td>
<td>9% [8-11%]</td>
<td>35% [33-38%]</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>16 300</td>
<td>41 400 [34 000-50 000]</td>
<td>39% [32-48%]</td>
<td>64% [58-74%]</td>
</tr>
<tr>
<td>Latin America</td>
<td>13 600</td>
<td>36 600 [25 000-38 000]</td>
<td>44% [36-55%]</td>
<td>65% [58-75%]</td>
</tr>
<tr>
<td>Caribbean</td>
<td>2 700</td>
<td>10 800 [8 700-13 000]</td>
<td>25% [21-31%]</td>
<td>64% [57-70%]</td>
</tr>
<tr>
<td>East, South and South-East Asia</td>
<td>43 800</td>
<td>113 000 [84 000-140 000]</td>
<td>39% [30-52%]</td>
<td>39% [32-43%]</td>
</tr>
<tr>
<td>Europe and Central Asia</td>
<td>7 500</td>
<td>11 400 [10 000-12 000]</td>
<td>65% [55-71%]</td>
<td>22% [19-25%]</td>
</tr>
<tr>
<td>North Africa and the Middle East</td>
<td>840</td>
<td>18 500 [12 000-25 000]</td>
<td>5% [3-7%]</td>
<td>10% [8-14%]</td>
</tr>
<tr>
<td>All low- and middle-income countries</td>
<td>456 000</td>
<td>2 020 000 [1 800 000-2 300 000]</td>
<td>23% [20-25%]</td>
<td>51% [48-54%]</td>
</tr>
</tbody>
</table>

Annex 4a

Median annual cost (in US dollars) of first-line antiretroviral drug regimens for adults in low-income countries, 2008–2010


Annex 4b

Median annual cost (in US dollars) of second-line antiretroviral drug regimens for adults in low-income countries, 2008–2010

Annex 5

Price of generic and number of quality-assured generics

Month/Year

Source: Antiretroviral price reductions- 14th Edition 2011, p. 7 [12].