

How can we achieve universal access to low-cost treatment for HIV?

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Abstract

Mass production of low-cost antiretrovirals (ARVs) has already allowed over 17 million individuals to access treatment for HIV infection, mainly in low-income countries. It is possible to manufacture combination ARVs for \$110 per person-year, using tenofovir (TDF), lamivudine (3TC) and efavirenz (EFV). New combinations of ARVs costing as little as \$60 per person-year will be available in the near future. Pre-exposure prophylaxis using TDF in combination with either 3TC or emtricitabine (FTC) could also be provided for less than \$90 per person-year.

Voluntary licensing allows people in the poorest countries to access new ARVs at prices close to manufacturing costs. Patents on several key ARVs will expire by 2018 and should allow worldwide access to high-quality, low-cost triple combination therapy, such as TDF/3TC/EFV. Several protease inhibitors will also become available as generics by 2018. However, ongoing patent restrictions will lead to sustained high prices for the most recently developed ARVs in most middle- and high-income countries. These include the nucleotide tenofovir alafenamide, the integrase strand inhibitor dolutegravir and several single combination tablet regimens.

We suggest that as patents for ARVs expire, health authorities first need to rapidly import and introduce generic versions of drugs such as abacavir, 3TC, EFV and TDF. Once these low prices have been established for these generics, cost-effectiveness of patented ARVs needs to be re-evaluated. It may no longer be justified to pay high prices for these drugs. A strategy of low-cost generic ARVs for most people, with higher-cost patented alternatives used as switch options, could allow for an increased number of people to receive ARVs in the context of fixed health budgets.

Keywords: antiretrovirals, nucleoside analogues, protease inhibitors, non-nucleosides, integrase strand inhibitors, health economics

Introduction

Of the 37 million people infected with HIV worldwide, an estimated 17 million are receiving antiretrovirals (ARVs) [1]. However, this still leaves another 20 million in need of access to treatment. In 2014, UNAIDS set the '90-90-90' target, aimed at diagnosing 90% of all HIV-positive people, providing therapy for 90% of those diagnosed and achieving an undetectable HIV RNA for 90% of those receiving treatment by the year 2020 [2]. A recent analysis of HIV treatment cascades shows that many countries have still not reached these targets. For example, the percentage of people living with HIV who were diagnosed and on ARVs was only 48% in Brazil, 35% in the USA, 18% in China and 14% in Russia [3].

The demand for ARVs will continue to rise as more people become infected with HIV and death rates fall – there were 2 million new infections in 2014 alone [2]. As a result, it is likely that at least 37 million people will need treatment by 2020 in order to include newly infected people in the 90-90-90 targets – this is over double the number currently taking ARVs worldwide.

In parallel, there is a need for cheap sources of drugs for pre-exposure prophylaxis (PrEP), using either tenofovir (TDF)/emtricitabine (FTC) or TDF/lamivudine (3TC) in people at risk of acquiring HIV infection. Health departments in both the United Kingdom and Australia have declined to fund PrEP because of its high cost. This is despite its proven benefits in lowering the risk of HIV acquisition [4,5].

Worldwide sales of ARVs generate substantial revenues for pharmaceutical companies. In 2015 alone, sales of the top 10 drugs totalled \$15.3 billion, according to a recent analysis [6]. In low-income countries, which mainly use generic drugs, sales of ARVs totalled \$1.7 billion in 2014 [7]. Most of these drugs are cheap to manufacture but sold in middle- and high-income

countries at high prices. For example, the combination of TDF/FTC/efavirenz (EFV) (Atripla), which is the most widely used first-line ARV treatment worldwide, has a list price of \$34,428 per person-year in the USA [8], \$8,314 in the United Kingdom [9] and \$110 in low-income countries [10]. This pattern of price differentials is consistently repeated across all classes of ARVs [8–11], as shown in Table 1.

Low-income countries can normally access mass-produced, cheap ARVs manufactured by generic companies through voluntary licensing arrangements with the originator pharmaceutical companies [10,12]. Small reductions in the unit cost of ARVs in countries with large epidemics can allow a larger number of people to be treated within a fixed health budget. Currently, a year of treatment with TDF/3TC/EFV is available in most low-income countries for approximately \$110–180 per person-year [13]. There are predictions that the unit cost of treatment could fall even lower by using newer ARVs that require lower daily doses. For example, the target price for tenofovir alafenamide (TAF)/3TC/dolutegravir (DTG) has been set at \$60 per person-year [14,15]. However, these new combinations are not yet available and will only be accessible at these low prices in the countries with voluntary licensing agreements.

Middle-income countries that are not included in voluntary licensing agreements have to pay much higher prices for ARVs. For example, according to a recent analysis of the World Health Organization (WHO) database, the price of the protease inhibitor (PI) darunavir (DRV) is \$755 per person-year in Uganda (which is included in the voluntary licence), but \$6,539 in Tunisia and \$6,010 in Jamaica, which are excluded from a voluntary licensing agreement [13]. At present, there are several countries in South America, South-east Asia and Eastern Europe with large HIV epidemics that are not included in voluntary licensing agreements.

International donor funding for HIV/AIDS is expected to remain at the same level over the next 5 years, despite countries signing up to a United Nations declaration to end AIDS by 2030 [1].

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Table 1. Current prices for antiretrovirals in the USA, UK and low-income countries [8–11]

Antiretroviral	Patent expiry	Price per person-year (US\$)*		
		USA	UK	Global lowest
Nucleos(t)ide analogues				
Abacavir	Generic/2016 (Europe)	\$7,236	\$2,778	\$123
Lamivudine	Generic	\$3,408	\$483	\$18
Tenofovir	2017–8	\$14,464	\$3,182	\$39
Zidovudine/3TC	Generic	\$10,536	\$1,107	\$46
Abacavir/3TC	2016	\$18,600	\$4,664	\$161
Tenofovir DF/3TC	2017–8	not sold	not sold	\$47
Tenofovir DF/FTC	2021	\$21,120	\$5,553	\$67
Tenofovir DF/FTC/EFV	2021	\$34,428	\$8,314	\$110
Non-nucleosides				
Nevirapine	Generic	\$7,776	\$1,825	\$28
Efavirenz	Generic/2017 (USA)	\$12,120	\$1,606	\$38
Rilpivirine	2021	\$12,900	\$3,120	\$40
Etravirine	2021	\$15,696	\$4,695	\$438
Protease inhibitors				
Atazanavir	2017–9	\$19,872	\$4,726	\$219
Lopinavir/r	2016	\$13,272	\$4,446	\$243
Darunavir/r	2017–19	\$19,584	\$4,648	\$658
Integrase strand inhibitors				
Dolutegravir	2027	\$20,484	\$7,768	\$600*
Raltegravir	2025	\$18,540	\$7,347	\$973
Elvitegravir	2027	\$37,116	\$8,314	No data

* Using a conversion rate of 1.3 US dollars to 1 UK pound.

Funding is required for a range of HIV services, which include primary prevention, HIV testing, PrEP and patient retention in care [16]. Minimising the burden of ARV costs could therefore allow more people to be diagnosed, treated and monitored.

In this review, we have first assessed the ARV prices in low- and high-income countries. We then suggest a two-stage mechanism to drastically cut prices worldwide, including in high- and middle-income countries. This could be achieved by the end of 2018 – initially by the rapid introduction of low-cost generic combinations as drug patents expire, and by a subsequent re-negotiation of branded ARV prices.

Stage 1: widespread and worldwide introduction of generic ARVs

Many ARVs are now becoming available worldwide as low-cost generics. Patents have already expired for EFV, nevirapine (NVP), abacavir (ABC), zidovudine (ZDV) and 3TC, while the basic patents on TDF, atazanavir (ATV) and lopinavir/ritonavir (LPV/r) will expire by 2018 [10,12]. Patent expiry dates are shown in Table 1 for individual ARVs and combination tablets. When drugs are on patent a system of value-based pricing in middle- and high-income countries allows originator pharmaceutical companies to make profits from their research and development. However, once patents expire, the price of most ARVs should fall significantly providing there is robust competition between generic suppliers.

Generic suppliers have been approved by the US Food and Drug Administration (FDA) to provide ARVs to the President's Emergency Plan for AIDS Relief (PEPFAR) programme. In parallel, pre-qualification of suppliers by the WHO is a prerequisite for these generic ARVs to be used in the Global Fund treatment access

programmes [10,12]. Until now, most generic ARVs have been used in low-income countries where voluntary licensing rules permit supplying these drugs. However, they can now be exported to middle- and high-income countries where drug patents have expired. Importantly, there is no lower limit to the prices that could be achieved if the main buyers from middle- or high-income countries could organise competitive tenders with multiple generic suppliers. This is one of the main reasons why ARV prices have fallen significantly in low-income countries over the past 5 years.

Generic nucleoside reverse transcriptase inhibitor (NRTI) backbones with ABC/3TC and ZDV/3TC should become available in most countries by the end of 2016, with generic TDF/3TC by early 2018 [10,12]. The price of these ARVs could be below \$200 per person-year provided there are high-volume orders [7,10,12]. Slightly higher prices may be required to provide generic suppliers with an acceptable profit margin and fund regulatory approvals and company operations in these new countries. It will therefore be difficult for these companies to justify prices such as \$7,236 for generic ABC in the USA [8], when the same product is sold for 98% less, e.g. \$123 per person-year, in low-income countries [10]. In terms of the combination of TDF/FTC there is a patent restriction that could prevent it from being available as a generic until 2021 [10].

Generic versions of the non-nucleoside EFV and NVP are already available in most countries. Generic EFV will be available in the USA in 2017. These drugs are very cheap to manufacture with FDA pre-approved versions of EFV already available for \$20 per person-year, while generic NVP costs \$24 per person-year [10]. It should then be possible for generic manufacturing companies in India to export a single-tablet regimen containing TDF, 3TC and efavirenz for use in any country for less than \$200 per person-year. This combination is already widely used in low-income countries and there should be no patent restrictions on its use.

Generic PIs will become available within the next 3 years. The basic patent on ATV expires in early 2017. It is unclear whether a secondary patent on the chemical structure can be upheld; it may be challenged. The patent on DRV has expired in several countries and generics are already being manufactured; however, in some high-income countries patents extend to 2017. Generic lopinavir/ritonavir should be available in 2017 [12].

As patents expire, middle- and high-income countries will also be accessing generic ARVs at very low prices. Provided that there is robust competition between generic suppliers, high-quality generic ARVs should become available in a wide range of countries at prices close to those seen in low-income countries.

Cost-effectiveness of new ARVs versus low-cost generics

After the widespread introduction of generic ARVs in 2017–2018, many middle- and high-income countries will face a difficult choice. These generic combinations will initially consist of a generic dual NRTI backbone (TDF/3TC, ABC/3TC or ZDV/3TC) plus either a

Table 2. Summary Week 144 results from the SINGLE trial: first-line dolutegravir versus efavirenz [19]

Treatment arms:	ABC/3TC/DTG	TDF/FTC/EFV 600 mg
	(n=414)	(n=419)
Sample size	414	419
HIV RNA <50 copies/mL (NC=F)	72%	63%
Virological non-responders	10%	7%
Discontinuation of treatment	18%	30%
Drug resistance	0%	1.4%

NC=F: non-completer equals failure; 3TC: lamivudine; ABC: abacavir; DTG dolutegravir; EFV: efavirenz; FTC: emtricitabine; TDF: tenofovir disoproxil fumarate.

Table 3. Summary Week 96 results from the ENCORE-1 trial [22]

Treatment arms:	TDF/FTC/EFV 400 mg	TDF/FTC/EFV 600 mg
	(n=312)	(n=309)
HIV RNA <50 copies/mL	86.3%	86.7%
Virological failure	n=10	n=13
Drug resistance	n=2	n=3
EFV-related adverse events	37.7%	47.9%
Discontinuation for EFV-related adverse events	8.3%	15.5%

EFV: efavirenz; FTC: emtricitabine; TDF: tenofovir disoproxil fumarate.

non-nucleoside (EFV or NVP) or a boosted PI (ATV, lopinavir or DRV). However, low-cost integrase inhibitors such as DTG will not be available in middle- and high-income countries. Tenofovir disoproxil fumarate will be generic, but the new alternative, TAF, will remain on patent for another 10 years. Several co-formulated single tablets will be available as patented versions, but some generic combinations may require people to take 2–3 pills per day.

As shown in Table 1, the costs of most generic ARVs should be very low. The alternative patented ARVs, such as DTG, elvitegravir (EVG) or TAF may offer benefits in tolerability, but at a much higher price than the generics that will soon be available.

Dolutegravir versus generic efavirenz

The WHO guidelines recommend first-line treatment for HIV with TDF, 3TC (or FTC) and either the non-nucleoside EFV or the integrase strand inhibitor DTG [17]. Other treatment guidelines tend to recommend first-line use of integrase inhibitors rather than EFV [8,18].

In low-income countries, integrase inhibitors should become available in the future at a low price through voluntary licensing. However, in middle- and high-income countries, patents on integrase strand inhibitors such as DTG will remain in place for at least another 10 years, which could keep prices high [10].

The most recent International Antiviral Society–USA HIV treatment guidelines [18] state: ‘Although relative efficacy in viral suppression is lower with an efavirenz-based regimen than with integrase-based regimens, the differences are modest and driven by tolerability rather than potency. Where resource constraints limit the ability of a health system to provide widespread treatment to all HIV-infected persons, a strategy of using generic formulations of recommended regimens first with use of more expensive drugs for those who demonstrate intolerance may be reasonable.’

In the SINGLE trial, the largest head-to-head study comparing DTG and EFV [19] (Table 2), the percentage of individuals with

HIV RNA <50 copies/mL after 144 weeks of randomised treatment was 72% for ABC/3TC/DTG and 63% for TDF/FTC/EFV. However, the virological failure rate at week 144 was actually slightly higher for DTG (10%) than for EFV (7%). There were more discontinuations for adverse events or other reasons in the EFV arm (30%) than the DTG arm (18%). There was a small, but not statistically significant, difference in the risk of treatment-emergent resistance between arms (1.4% for EFV, 0% for DTG). The difference in response rates between ABC/3TC/DTG and TDF/FTC/EFV was established within the first 24 weeks of the study and then remained constant over the next 2 years of randomised treatment [19].

In the SINGLE study, 28% of individuals randomised to ABC/3TC/DTG had stopped randomised treatment after 3 years, showing that the durability of treatment depends on factors other than just the type of treatment. Other interventions such as adherence counselling, regular viral load monitoring and engagement in care may help to improve response rates, on any ARV treatment.

There are two other concerns regarding DTG that may limit its value: first, its safety profile has not been fully characterised in pregnancy.

Second, there is very little clinical experience of this first-line treatment for people with tuberculosis in the DTG registration trials programme [15], although clinical trials are in progress.

So what is the value of a new drug such as DTG, which is better tolerated than a standard dose of EFV, and may have a higher genetic barrier, but does not improve virological suppression rates? In a recent US analysis, DTG has failed to show cost-effectiveness compared to EFV, even at branded prices [21]. The current list price of DTG is \$20,484 in the USA [8], \$7,768 in the UK [9] and \$600 in South Africa [20], versus less than \$100 per year for generic EFV [10].

One option, as proposed by the IAS–USA treatment guidelines panel [18], in the context of limited health budgets, would be to start patients on low-cost generic drugs and to consider a switch to more expensive integrase inhibitors only in the case of adverse events. Health authorities will need to re-evaluate the cost-effectiveness models for DTG versus EFV, using revised generic drug prices. This may then show that DTG is only cost-effective at a price far lower than the present one. Therefore, it may be more cost-effective to start patients on cheaper generics and to switch only a minority of them to integrase inhibitors if none of the generic treatments can be tolerated.

Another alternative to the use of high-priced DTG could be a lower dose of generic EFV – 400 mg once daily. As shown in Table 3, the ENCORE-1 trial showed non-inferior efficacy of EFV at the 400-mg dose compared to the standard dose (600 mg), when both given in combination with TDF/FTC [22]. Results at 96 weeks also showed no difference in the risk of treatment-emergent resistance between the arms and a lower number of EFV-related adverse events for the EFV 400-mg dose. The ENCORE 1 trial investigators concluded that 400 mg EFV should be recommended as part of routine care (although caution was noted with rifampicin co-administration). The efficacy results in ENCORE-1 were consistent across different races and CYP2B6 polymorphisms, which are known to affect EFV concentrations.

Table 4. Week 96 results from Phase 3 randomised trials of first-line tenofovir alafenamide (TAF) versus tenofovir disoproxil fumarate (TDF) [23]

Treatment arms:	TAF/FTC/EVG/c	TDF/FTC/EVG/c
	(n=866)	(n=867)
HIV RNA <50 copies/mL	87%	85%
Virological failure	5%	5%
Drug resistance	1.2%	0.9%
Grade 3 or 4 clinical adverse events	12%	12%
Grade 3 or 4 laboratory adverse events	28%	25%

c: cobicistat; EVG: elvitegravir; FTC: emtricitabine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Tenofovir disoproxil fumarate (TDF) versus alafenamide (TAF)

Results from Phase 3 trials comparing two forms of tenofovir are shown in Table 4. Overall, there was no difference in efficacy between TAF and TDF across the four studies in terms of the percentage of patients with HIV RNA <50 copies/mL at week 96, the number of virological failures, or the risk of treatment-emergent drug resistance. There was also no significant difference in the risk of clinical adverse events between TAF and TDF. Patients receiving TAF were more likely to show increases in LDL cholesterol and total cholesterol plasma levels, as tenofovir tends to be associated with more favourable lipid levels. By contrast there was a significant difference in some toxicity biomarkers such as eGFR and bone mineral density in favour of TAF at the time of the week 48 analysis [23].

In the pivotal Phase 3 trials, the differences in lipid, bone and renal markers between TAF and TDF were established within 24 weeks of starting treatment. These differences remained constant at week 96 with no further divergence between treatment arms [23]. It is not clear whether these differences in lipid, renal or bone markers will translate into clinically significant outcomes in terms of the risk for adverse events with long-term use (for example myocardial infarction, proximal renal tubulopathy, Fanconi syndrome or bone fractures). In addition, there are two other disadvantages in using TAF. First, there is very little clinical experience with the drug in pregnancy. TAF leads to a high concentration of intracellular tenofovir diphosphate and it is not known whether this might have adverse consequences during fetal development. Second, its administration is currently contraindicated during rifampicin-based treatment of tuberculosis, owing to a strong predicted drug interaction that is expected to lower TAF drug levels [15].

The current price of TDF/FTC is \$21,120 per person-year in the USA [8] and \$5,553 in the UK [9], versus a minimum price for the generic of \$67 [10]. It is unlikely that the generic TDF/FTC will become available at a price as low as \$67 in the USA and UK, but reductions from list prices of over 90% have been achieved in other therapeutic areas after patent expiry.

If generic TDF becomes available at a price at least 90% lower than current levels, what would be the additional value of using TAF at a significantly higher price? A recent economic analysis, based on prices in the USA, suggested that the toxicity profile of tenofovir alafenamide may justify a price \$1,000 per person-year higher than for TDF [24]. However, the authors also concluded that, once generic co-formulations of TDF plus 3TC become available, the appropriate premium for TAF will probably need to be adjusted downwards, using generic TDF costs as the benchmark. Similarly, the German Institute for Clinical Care Quality has

concluded that there is no economic benefit to the use of TAF versus TDF [25].

Another alternative, for people with long-term HIV-1 RNA suppression, would be to stop TDF and maintain viral suppression on combinations of 3TC with a boosted PI. This treatment strategy has shown non-inferior efficacy to triple combination treatment across five randomised clinical trials [15,26–31]. A combination of 3TC with a generic PI could become very cheap in many countries after patents expire in 2017 [10].

Single-tablet regimens versus generic combinations

There are patents on the combined use of several ARVs in single tablets that could lead to sustained high prices for the next 10 years [10,12]. It might be possible to produce some generic co-formulations as single tablets in early 2018 (for example TDF/3TC/EFV or ABC/3TC/EFV). However, other generic ARVs may need to be given in the form of two or three pills per day (for example TDF/3TC with a boosted PI). It is not clear whether using a regimen of two or three pills per day will affect long-term treatment efficacy in comparison to using a single tablet containing the same ARVs. Single tablets containing three ARVs might be larger and more difficult to swallow than two or three individual ARVs taken singly.

Conclusions

In order to achieve the UNAIDS 90–90–90 targets for ARV treatment coverage in the context of restricted health budgets, difficult decisions will need to be made. In low-income countries, fixed-dose combinations including integrase inhibitors should be available for under \$100 per person-year if generic manufacturing can be scaled up. However, for most middle- and high-income countries, prices of patented ARVs are likely to remain high. This could restrict access to more recent drugs in regions such as South America, South Asia and Eastern Europe where the HIV epidemic is growing rapidly.

The most important priority remains to start people on ARVs. The combination of TDF/3TC/EFV, recommended by the WHO for the past 4 years, has already been widely used. In countries where voluntary licences are not permitted, low-cost generics should be introduced rapidly when patents expire at prices close to the cost of production – i.e. in the range of \$100–200 per person-year. The cost-effectiveness of newer, patented treatments should then be re-evaluated against the new prices for mass produced generics. This strategy could lead to significant falls in HIV drug costs worldwide.

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Competing interests

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