Antiviral Therapy 2014; **19 Suppl 3**:5–14 (doi: 10.3851/IMP2896)

Review

The discovery and development of antiretroviral agents

*Joep MA Lange[1#], Jintanat Ananworanich[2,3,4]**

[1]Department of Global Health, Academic Medical Center, University of Amsterdam, Amsterdam Institute for Global Health and Development, Amsterdam, the Netherlands
[2]The Thai Red Cross AIDS Research Center, Bangkok, Thailand
[3]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA
[4]Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA

*Corresponding author e-mail: jananworanich@hivresearch.org
#Deceased 2014

Since the discovery of HIV as the causative agent of AIDS in 1983/1984, remarkable progress has been made in finding antiretroviral drugs (ARVs) that are effective against it. A major breakthrough occurred in 1996 when it was found that triple drug therapy (HAART) could durably suppress viral replication to minimal levels. It was then widely felt, however, that HAART was too expensive and complex for low- and middle-income countries, and so, with the exception of a few of these countries, such as Brazil, a massive scale-up did not begin until the WHO launched its '3 by 5' initiative and sizeable funding mechanisms, such as the Global Fund to Fight AIDS, TB and Malaria and the US President's Emergency Plan for AIDS Relief (PEPFAR), came into existence. A pivotal enabler of the scale-up was a steady lowering of drug prices through entry of generic antiretrovirals, competition between generic manufacturers and the making of volume commitments. The WHO Prequalification of Medicines Programme and the Expedited Review Provision of the US Food and Drug Administration have been important for the assurance of quality standards. Antiretroviral drug development by research-based pharmaceutical companies continues, with several important innovative products, such as long-acting agents, in the pipeline.

Introduction

In 1981, the first reports appeared about a new deadly syndrome in men who had sex with men (MSM) and injection drug users (IDUs) in cities on the East and West Coasts of the United States. Major clinical manifestations were *Pneumocystis carinii* pneumonia (PCP; now *Pneumocystis jirovecii*) and Kaposi's sarcoma [1–4]. The underlying pathology was a severe immunodeficiency [3,4].

Even though one of these reports included IDUs [4], the first name given to this new syndrome was gay-related immunodeficiency syndrome (GRID) because the majority of 'cases' were MSM [5]. The fact that the syndrome was subsequently found to also develop in people who had haemophilia, in recipients of blood transfusions and in Haitians, made it likely that it had an infectious origin.

In 1983, researchers at the Institut Pasteur isolated a retrovirus from a lymph node from a man with signs including swollen lymph nodes and symptoms that often preceded what was by now called acquired immune deficiency syndrome (AIDS), and called it lymphadenopathy-associated virus (LAV) [6]. In 1984, a group at the US National Institutes of Health (NIH) isolated a similar virus from patients with AIDS, 'pre-AIDS' and 'at risk for AIDS', and called it human T-lymphotropic virus type III (HTLV-III) [7,8]; in that same year a group from the University of California San Francisco isolated a similar virus from AIDS patients in San Francisco and called it AIDS-associated retrovirus [9]. To eliminate the multiplicity of names, in 1986 a subcommittee of the International Committee on Taxonomy of Viruses recommended that the retrovirus isolates identified as causative agent for AIDS be renamed with a virus group name: human immunodeficiency virus (HIV) [10]. This name has been adopted universally.

In 1986, a virus related to HIV, which was subsequently renamed HIV-1, but more similar to simian T-lymphotropic virus type III of African green monkeys (STLV-III$_{AGM}$), was isolated from individuals in West Africa [11]. This virus was subsequently called HIV-2.

In this article we will only discuss HIV-2 in the context of susceptibility to antiretroviral (ARV) agents and lack of market incentives to develop HIV-2-specific drugs.

The isolation and propagation of the virus enabled the development of antibody and antigen tests, which made it possible to perform epidemiological studies. These made it clear that AIDS was the tip of the iceberg and that there were many asymptomatic carriers of HIV-1 [12]. Unfortunately over time it became evident that almost all of those progressed to symptomatic infection and death [13].

It also became apparent that AIDS and HIV-1 were not restricted to high-income countries, but were also highly prevalent in resource-poor settings, in particular in sub-Saharan Africa [14], the cradle of human immunodeficiency viruses [15].

In the initial years of the AIDS epidemic, except for symptomatic treatment and treatment of a few opportunistic infections, such as PCP [16], cryptococcal meningitis [17], toxoplasmosis [18], and oropharyngeal and oesophageal *Candida albicans* infections [3,4,19], little could be done for the patients. If they recovered from a treatable affliction, another opportunistic disease manifestation would follow, often an untreatable one, and death would follow.

The rush to develop antiretroviral agents

When AIDS first appeared, there were hardly any effective antiviral agents on the market, the most prominent being acyclovir, an acyclic nucleoside analogue active against herpes simplex virus infections [20,21]. Nucleoside and nucleotide analogues are chain terminators of DNA synthesis, and some of these compounds were found to be potent inhibitors of HIV-1 replication; 3′-azido-3′-deoxythymidine (AZT), later called zidovudine (ZDV) appeared to be the most promising of these nucleoside analogue reverse transcriptase inhibitors (NRTIs) [22,23]. The drug was first synthesized in 1964 in an academic institution as a potential anti-cancer agent under a grant from the US National Institutes of Health (NIH), but development was shelved after it proved biologically inert in mice [24,25]. It then rapidly went into clinical development for HIV-1. After just one small exploratory study [26] and a double-blind placebo-controlled trial in 282 patients with AIDS and 'AIDS-related complex', ZDV was rapidly approved by the regulatory authorities and came on the market in early 1987. The latter study had been terminated prematurely because of an impressive survival benefit in those receiving active drug [27,28].

The short time between discovery of a disease agent and the approval of a drug active against it was unprecedented. This rapid pace of development, to a significant extent, resulted from extremely strong patient activism, which was also extraordinary. AIDS appeared in the MSM community in the US when it was already relatively well-organized because of the struggle for gay emancipation. When this terrible scourge appeared on stage, killing scores of MSM, the movement effectively changed course and put enormous pressure on pharmaceutical companies, research agencies, such as the NIH, the US regulatory authority and the Food and Drug Administration (FDA), to develop and make available drugs expeditiously to prevent more deaths. Of course there was also a market incentive for pharmaceutical companies, since this appeared to be a disease that was prevalent in high-income countries.

Hopes were high for ZDV, but unfortunately, despite impressive initial results, beneficial effects were of limited duration. It soon became evident that with continued treatment, viral resistance developed [29]. In the following years, additional NRTIs, such as didanosine (2′,3′-dideoxyinosine [ddI]) [30] and zalcitabine (2′,3′-dideoxycytidine [ddC]) [31], appeared on the market; however, the lessons of tuberculosis (TB) drug development were ignored and the drugs were not used in combination, but as sequential monotherapy.

Despite early negative results in one dual NRTI combination study (ACTG152) evaluating ZDV–ddC [32], further studies comparing dual nucleoside combination therapy to monotherapy showed better outcomes for combination therapy used in ARV-naive patients [33–37]. The ACTG152 study compared continuation of ZDV monotherapy with the addition of ddC to ZDV in patients who no longer appeared to benefit from ZDV alone, while latter studies compared monotherapy versus dual therapy by starting two ARVs at the same time in ARV-naive patients.

Although the effects of dual-NRTI combination therapy were much better than those of monotherapy, they were still of limited duration. Only in 1996, when triple ARV drug therapy, highly active antiretroviral therapy (HAART), was introduced did the effects of treatment become durable. With HAART, viral replication could be suppressed to minimal levels and a high genetic barrier against development of drug resistance was created [38,39].

The possibility and success of triple drug therapy was partially due to the appearance of new drug classes, such as protease inhibitors (PIs) [38] and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [39], but even more so to the emergence of molecular amplification techniques, such as PCR, which enabled researchers to quantify the virus and to gain insight in viral dynamics [40]. Because of the extremely rapid emergence of viral resistance against NNRTIs in monotherapy studies [41], several companies discarded development of drugs belonging to this class in the

early 1990s. If we had been able to measure viral load in those early days and gain insight in viral replication dynamics, we could have had triple combination therapy, consisting of 2 NRTIs + 1 NNRTI around 1992, which would have saved many lives.

The development of NNRTIs has not only been important in allowing for an alternative to PI-based HAART, but also for making it possible to scale-up ARV therapy in resource-poor settings. This is because NNRTIs are considerably cheaper to produce than PIs, allow for single-tablet regimens and, unlike ritonavir-boosted PIs in those days, were heat-stable.

By now, more than 25 ARV drugs, excluding fixed-dose combinations (FDCs), belonging to 6 different classes, have been approved by the FDA; some of those, like delavirdine and ddC were later withdrawn by the companies involved because they became obsolete (Table 1).

Table 1. Antiretrovirals approved by the US FDA 1987–2014

Antiretroviral (abbreviation)	Drug class	Year of US FDA approval
Zidovudine (ZDV)	NRTI, nucleoside	1987
Didanosine (ddI)	NRTI, nucleoside	1991
Zalcitabine (ddC)	NRTI, nucleoside	1992
Stavudine (d4T)	NRTI, nucleoside	1994
Lamivudine (3TC)	NRTI, nucleoside	1995
Abacavir (ABC)	NRTI, nucleoside	1998
Tenofovir disoproxil fumarate (TDF)	NRTI, nucleotide	2001
Emtricitabine (FTC)	NRTI, nucleoside	2003
Saquinavir (SQV)	PI	1995
Ritonavir (RTV or r)	PI	1996
Indinavir (IDV)	PI	1996
Nelfinavir (NFV)	PI	1997
Amprenavir (APV)	PI	1999
Fosamprenavir (fos-APV)	PI	2003
Lopinavir (LVP)	PI	2000
Tipranavir (TPV)	PI	2005
Darunavir (DRV)	PI	2006
Nevirapine (NVP)	NNRTI	1996
Delavirdine (DLV)	NNRTI	1997
Efavirenz (EFV)	NNRTI	1998
Etravirine (ETV)	NNRTI	2008
Rilpivirine (RPV)	NNRTI	2011
Enfuvirtide (T20)	Fusion inhibitor	2003
Maraviroc (MVC)	CCR5-blocker	2007
Raltegravir (RAL)	Integrase inhibitor	2007
Elvitegravir (EVT)	Integrase inhibitor	2012
Dolutegravir (DTG)	Integrase inhibitor	2013

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; US FDA, United States Food and Drug Administration.

Bringing antiretrovirals to resource-poor settings

HAART was introduced to high-income countries and some middle-income countries, such as Brazil [42–44], in 1996; however, this did not lead to an immediate concrete initiative to broaden access to these life-saving drugs in low-income countries, particularly sub-Saharan Africa, despite the fact that the disease burden was greatest here.

Indeed, very little happened in sub-Saharan Africa for years to come until May 2000 and, on the eve of the *XIIIth International AIDS Conference* in Durban, South Africa, an announcement was made about an agreement between UNAIDS and five large pharmaceutical companies to start providing ARVs at greatly reduced prices to poor countries through the Accelerating Access Initiative (AAI) [45]. The timing of this agreement had at least something to do with the fact that this was the first time that the *International AIDS Conference* was held in sub-Saharan Africa: how could the pharmaceutical companies and the UN agencies go there without having something concrete to offer?

The AAI was a start that allowed for demonstration projects [46,47]; however, because very little external funding for treatment was available at the time, it did not result in significant national scale-up programmes. Botswana was the exception, but even in this middle-income country most of the funding was provided by external donors: the Merck Foundation and the Bill & Melinda Gates Foundation [48]. However, the world rapidly moved beyond the AAI. In 2001, the Report of the Commission on Macroeconomics and Health appeared, which stressed the importance of health for economic development and made a special plea to tackle the 'big three' infectious diseases, and can be considered to be a prelude to the creation of the Global Fund to Fight AIDS, TB and Malaria (GFATM) [49]. In the same year the UN General Assembly Session on HIV/AIDS (UNGASS) was held – the first time a General Assembly session was devoted to a single disease. The Declaration of Commitment coming out of UNGASS firmly put HIV treatment on the agenda [50]. In 2003, the WHO launched the '3 by 5' initiative, which set a target of 3 million people on ARV treatment by 2005 [51]. The launch of '3 by 5' more or less coincided with or was followed shortly thereafter by the launch of sizable funding mechanisms: the World Bank's Multicountry AIDS Program (MAP) [52], the GFATM [53] and the US President's Emergency Plan for AIDS Relief (PEPFAR) [54]. At the end of 2002, approximately 300,000 people in low- and middle-income countries were receiving ARV treatment, whereas at the end of 2012 this number was 9.7 million. The rise in sub-Saharan Africa has been spectacular: from 50,000 people living with HIV (PLHIV) on ARVs in 2002 to 7.5 million a decade later [55].

The place of generic drugs

This dramatic scale-up of ARV treatment would not have been possible without the entry of generic ARVs and competition among generic manufacturers. Countries like Brazil, which was already producing generic ARVs, also used the threat of domestic generic production of new drugs if the price of originator company products would not be reduced to acceptable levels [42,43]. Both Thailand and Brazil have used compulsory licenses to the same end [56]. Negotiated drug prices in Brazil were lowest for patented ARVs for which there was generic competition [44].

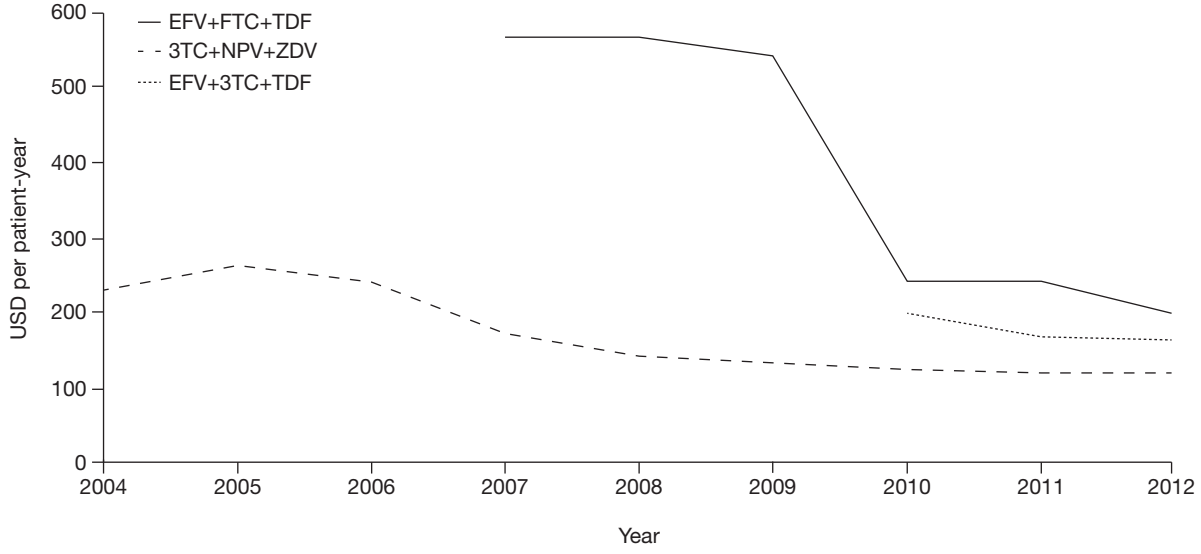
After initial resistance by originator companies to generic competition, more and more of them, but not all, decided not to uphold patents in the poorest and hardest hit countries in sub-Saharan Africa. Companies may give licenses to generic manufacturers to produce 'their' ARVs for these countries, for which the originators will receive royalties. Some of them even have joined the Medicines Patent Pool (MPP), which was created in 2010, through the WHO-based financing mechanism UNITAID, in order to cause further reductions in the price of key HIV medicines for those living in low- and middle-income countries and to encourage the development of 'better adapted' HIV medicines, including paediatric treatment. It does this through voluntary licenses from patent holders and sublicenses to generic manufacturers [57].

The Clinton Health Access Initiative (CHAI), which began in 2002 as the Clinton HIV/AIDS Initiative, has played a crucial role in further price reductions of generic ARVs, in which the making of volume commitments has been important [58]. Figure 1 shows how median prices of WHO-recommended first-line regimens in low- and middle-income countries have decreased over time [59].

A critical component of the ARV scale-up has been the assurance of quality standards, through the WHO Prequalification of Medicines Programme [60] and the Expedited Review Provision of the FDA [61], for the generic drugs being used in GFATM and PEPFAR-funded programmes, respectively.

Prices have now gone down so much that concern has been voiced that generic drug manufacturers consider current prices unsustainable, unless tender procedures are amended, regulatory procedures simplified, forecasting of need is improved and ARV treatment guidelines simplified [62]. For paediatric formulations specifically, which are much needed by some, the overall demand is relatively low and the opportunity costs of having to manufacture different dosages may be too high, if one realizes that the same production facilities may be used for more profitable products. The relative lack of paediatric ARV formulations is a clear example of market failure, which can only be addressed by providing sufficient incentives and pooled procurement, such as UNITAID tries to do [63].

Figure 1. Median prices of WHO-recommended first-line regimens in low- and middle-income countries 2004–2012[a]



[a]USD per patient-year. The strategic use of antiretrovirals to help end the HIV epidemic (reproduced with permission from the WHO [134]). EFV, efavirenz; FTC, emtricitabine; NPV, nevirapine; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine; 3TC, lamivudine.

Ongoing antiretroviral drug development

There is still considerable investment in the discovery and development of new ARV products, although the pace of development appears to have slowed down somewhat. Efficacy and safety profiles of ARVs have become better over time and FDCs, including single-tablet daily regimens, have taken the lead – it has thus become more difficult to improve upon existing products.

When HAART became available in 1996 there were three ARV drug classes: NRTIs, NNRTIs and PIs. This meant that the chance to achieve durable complete viral suppression for those with extensive NRTI drug resistance, stemming from the NRTI mono- and dual therapy days, was limited. This changed between 2003 and 2007 when we saw the appearance of drugs belonging to three new drug classes: the fusion inhibitor enfuvirtide (T20) [64,65], the CCR5 inhibitor maraviroc [66,67] and the integrase inhibitor raltegravir [68,69]. Now achieving an undetectable plasma virus load in patients with extensive prior drug resistance was no longer the exception [64–69].

Following that 'second revolution' in ARV therapy, development of ARVs aimed at new targets has not been very successful. Both inhibitors of viral maturation and viral attachment to the CD4-receptor thus far suffer from the fact that a significant proportion of viral isolates are less susceptible to these agents [70,71]. The attachment inhibitor prodrug BMS-663068, however, was recently found to show similar efficacy as atazanavir/ritonavir in ARV-experienced patients with virus that was sensitive to it [71].

That does not mean that no new ARVs have made it to the market, but they belong exclusively to existing drug classes: the NNRTIs etravirine [72,73] and rilpivirine (RPV) [74,75] and the integrase inhibitors elvitegravir (EVG) [76,77] and dolutegravir [78,79].

In addition, cobicistat, a drug that is not an ARV, but a new pharmacological booster that may be used as an alternative to ritonavir [80], has made it to the market. The single-tablet regimen QUAD contains tenofovir disoproxil fumarate (TDF) + emtricitabine + elvitegravir + cobicistat [77,80,81].

Tenofovir alafenamide fumarate is a TDF prodrug in clinical development, which appears to have less renal- and bone toxicity than TDF [82]. Other drugs in clinical development are the NNRTI MK-1439 [83] and the aforementioned BMS-663068 [72].

Quite a few of the initial wave of ARVs have gone or are going off patent soon [84], which opens the door for generic versions. Paradoxically this may stimulate new drug development or at least 'better' versions of existing agents, including new FDCs, in order to substitute or prolong patents ('evergreening'). In a worst-case scenario these new drugs have a negligible improvement when compared with the old ones.

Some ARVs in development, such as the NNRTI 'RPV long-acting' and the integrase inhibitor GSK1265744 (GSK744), may be given as long-acting injectable nanoformulations [85,86]. This may revolutionize both prevention and treatment of HIV infection. A recent study showed that an oral combination of RPV + GSK744 as maintenance therapy after 24 weeks of triple-drug lead-in therapy was well-tolerated and showed good antiviral activity through 24 weeks [87]. A study in macaques showed that monthly injections of 'GSK744 long-acting', that reproduced the human dose, gave full protection against repeated vaginal SHIV exposures [88]. Likewise, long-acting formulations for local vaginal delivery of ARVs are also in development [89]. Thus, before too long, women may have a choice between oral, subcutaneous and local ARV-based prevention methods.

It is always risky to predict the future, but as long as there is a sizable market for ARVs in high-income countries, pharmaceutical companies will remain interested in developing innovative products, such as the long-acting agents, for HIV-1 infection. With life expectancy of HIV-1-infected individuals who start ARV therapy in a timely manner approaching that of non-HIV infected individuals [90–93], the market will be there for a long time.

Similar to paediatric HIV-1 infection, HIV-2 has been a stepchild of ARV drug development. This virus is not susceptible to NNRTIs [94] and the activity of some PIs against it is also far from optimal [95]. Although most *in vitro* studies have shown that similar concentrations of NRTIs are needed to block both HIV-1 and HIV-2 replication, data suggest that some NRTIs may not be as effective against HIV-2 [96–98]. Given the limited size of the HIV-2 epidemic, there has been no market incentive to develop HIV-2-specific ARVs. Fortunately, integrase inhibitors appear to have activity against HIV-2 [99–101]. Given that HIV-2 uses a broad range of co-receptors, this is unlikely for maraviroc [102]. HIV-2 is intrinsically resistant to T20 [103,104].

In many resource-poor settings second-line options are limited and have a price that is considerably higher than first-line regimens. Dose optimization studies may point the way to combinations that remain effective even if they contain lower than standard doses of particular drugs, thus allowing for cost savings [105].

Conclusions

The ARV scale-up represents an unprecedented success story in global health. When the WHO's '3 by 5' was launched, it was difficult to believe that 10 years later almost 10 million people in low- and middle-income

countries, of whom 7.5 million live in sub-Saharan Africa, would have initiated treatment with these life-saving drugs [55].

Yet, challenges remain. There are great disparities in access to treatment across countries, regions and populations [55,106]. Even in high-income countries, a significant proportion of patients present late for care and treatment [107–110] and many people in low-income countries present extremely late [55]. Weak health-care systems lead to frequent stock-outs of ARVs [111,112], thus exposing patients to the danger of development of ARV drug resistance, especially if the drugs used in the combination do not have similar half-lives. From this perspective it is questionable to recommend replacing emtricitabine by lamivudine in an FDC with TDF and efavirenz, which is being promoted for cost considerations [113]. The exponential growth of funding for global health, including HIV, appears to be over [114], which implicates that more has to be done for less money. By contrast, the finding that ARV treatment is a highly effective means to prevent onward transmission of HIV-1 (Treatment as Prevention [TASP]) [115–117] has proven to be a major stimulus to broaden the WHO treatment guidelines to include people with higher $CD4^+$ lymphocyte counts [118]. However, the primary objective of treating people with HIV infection is keeping them healthy and alive, and the prevention effect is a secondary benefit. Benefits for individual health and prevention of onward transmission are greatest if treatment is started early [90–93,117,119]. Early treatment has the additional benefit of making it much easier to task-shift, which is essential in environments with critical health-care worker shortages [120].

Treatment and prevention benefits of ARVs are contingent on good adherence and everything possible should be done to promote adherence and also to minimize the still significant treatment discontinuation and loss to follow-up [121,122].

Further expansion of ARV therapy will lead to an initial increase in costs, but in the end it will be cost-saving [123,124]. It is unlikely that donors are willing to take such a long-term view and make the upfront extra money available. Countries themselves are now bearing more than half of the treatment costs, but quite a few are still highly or almost exclusively dependent on donor money [125]. It is clear that further efficiency gains, innovation and dose optimization [105] are essential. We should also think about creating more innovative financing mechanisms [126], including the use of funnelling HIV money through health insurance [127].

We should not ignore the fact that non-communicable diseases are of increasing importance in resource-poor settings [128,129], and that we need to move from 'AIDS exceptionalism' to 'health exceptionalism' and use HIV programmes to increase access to care and treatment of other diseases as well [130].

Lastly, now that we are about to have highly effective oral therapy for HCV infections [131], the cause of an enormous disease burden in some developing countries such as Egypt [132], it is clear that tiered pricing will be necessary to increase access to these drugs. However, although HIV infection is a chronic affliction that requires lifelong treatment, HCV is curable with short-term treatment [133]. In this case, tiered pricing may lead to massive 'medical tourism' from high- to middle-income countries, stimulated by health insurance companies. HIV changed the world by mobilizing massive streams of donor money. HCV may change the world by forging convergence of drug prices in high- and middle-income countries or the outsourcing of medical care from high- to middle-income countries.

Disclosure statement

JMAL in the past 5 years has consulted for Bristol–Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals and Roche. He has also received honoraria for presentations from Gilead Sciences and Merck. His institute (AIGHD) has received support for an annual HIV workshop in Africa (INTEREST) from Abbott/AbbVie, Gilead Sciences, Janssen Pharmaceuticals, Merck, Mylan and ViiV. JA declares no competing interests.

References

1. Centers for Disease Control. *Pneumocystis* pneumonia – Los Angeles. *MMWR Morb Mortal Wkly Rep* 1981; **30:**250–252.
2. Centers for Disease Control. Kaposi's sarcoma and *Pneumocystis* pneumonia among homosexual men – New York City and California. *MMWR Morb Mortal Wkly Rep* 1981; **30:**409–410.
3. Gottlieb MS, Schroff R, Schanker HM, *et al*. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med* 1981; **305:**1425–1431.
4. Masur H, Michelis MA, Greene JB, *et al*. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med* 1981; **305:**1431–1438.
5. Altman LK. New homosexual disorder worries health officials. New York Times. (Updated 11 May 1982. Accessed 21 July 2014.) Available from http://www.nytimes.com/1982/05/11/science/new-homosexual-disorder-worries-health-officials.html
6. Barré-Sinoussi F, Chermann JC, Rey F, *et al*. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 1983; **220:**868–871.
7. Popovic M, Sarngadharan MG, Read E, Gallo RC. Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. *Science* 1984; **224:**497–500.
8. Gallo RC, Salahuddin SZ, Popovic M, *et al*. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* 1984; **224:**500–503.

9. Levy JA, Hoffman AD, Kramer SM, Landis JA, Shimabukuro JM, Oshiro LS. Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS. *Science* 1984; **225:**840–842.
10. Coffin J, Haase A, Levy A, *et al*. Human immunodeficiency viruses. *Science* 1986; **232:**697.
11. Kanki PJ, Barin F, M'Boup S, *et al*. New human T-lymphotropic retrovirus related to simian T-lymphotropic virus type III (STLV-III_{AGM}). *Science* 1986; **232:**238–243.
12. Goedert JJ, Biggar RJ, Weiss SH, *et al*. Three-year incidence of AIDS in five cohorts of HTLV-III-infected risk group members. *Science* 1986; **231:**992–995.
13. Moss AR, Bachetti P, Osmond D, *et al*. Seropositivity for HIV and development of AIDS or AIDS-related condition: three year follow-up of the San Francisco General Hospital Cohort. *BMJ* 1988; **296:**745–750.
14. Serwadda D, Mugerwa RD, Sewankambo NK, *et al*. Slim disease: a new disease in Uganda and its association with HTLV-III infection. *Lancet* 1985; **2:**849–852.
15. Worobey M, Han G-Z. The origins and diversification of HIV. In Volberding PA, Greene WC, Lange JMA, Gallant JE, Sewankambo N (Editors). *Sande's HIV/AIDS Medicine: Global Care*. Philadelphia: Elsevier Saunders 2012; pp. 15–24.
16. Kovacs JA, Hiemenz JW, Macher AM, *et al*. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med* 1984; **100:**663–671.
17. Chuck SL, Sande MA. Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome. *N Engl J Med* 1989; **321:**794–799.
18. Luft BJ, Remington JS. Toxoplasmic encephalitis in AIDS. *Clin Infect Dis* 1992; **15:**211–222.
19. Holmstrup P, Samaranayake LP. Acute and AIDS-related oral candidiasis. In: Samanarayake LP, MacFarlane TW (Editors). *Oral candidiasis*. London: Wright 1990; pp. 133–155.
20. Elion GB. The purine path to chemotherapy. *Science* 1989; **244:**41–47.
21. Whitley RJ, Gnann JW, Jr. Acyclovir: a decade later. *N Engl J Med* 1992; **327:**782–789.
22. Mitsuya H, Weinhold KJ, Furman PA, *et al*. 3′-Azido-3′-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*. *Proc Natl Acad Sci U S A* 1985; **82:**7096–7100.
23. Mitsuya H, Broder S. Inhibition of the *in vitro* infectivity and cytopathic effect of HTLV-III/LAV by 2′, 3′-dideoxynucleosides. *Proc Natl Acad Sci U S A* 1986; **83:**1911–1915.
24. Horwitz JP, Chua J, Noel MJ. The monomesylates of 1-(2-deoxy-β-D-lyxofuranosyl) thymines. *J Org Chem* 1964; **29:**2076–2078.
25. Broder S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS epidemic. *Antiviral Res* 2010; **85:**1–18.
26. Yarchoan R, Klecker RW, Weinhold KJ, *et al*. Administration of 3′-azido-3′deoxythymidine, an inhibitor of HTLV-III/LAV replication, to patients with AIDS or AIDS-related complex. *Lancet* 1986; **1:**575–580.
27. Fischl MA, Richman DD, Grieco MH, *et al*. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. *N Engl J Med* 1987; **317:**185–191.
28. Richman DD, Fischl MA, Grieco MH, *et al*. The toxicity azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. *N Engl J Med* 1987; **317:**192–197.
29. Larder BA, Darby G, Richman DD. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science* 1989; **243:**1731–1734.
30. Dolin R. Didanosine. In Dolin R, Masur H, Saag MS (Editors). *AIDS Therapy*. New York: Churchill Livingstone 2003; pp. 39–56.
31. Bartlett JA. Zalcitabine. In Dolin R, Masur H, Saag MS (Editors). *AIDS Therapy*. New York: Churchill Livingstone 2003; pp. 57–65.
32. Fischl MA, Olson RM, Follansbee SE, *et al*. Zalcitabine compared with zidovudine in patients in patients with advanced HIV infection who received previous zidovudine therapy. *Ann Intern Med* 1993; **118:**762–769.
33. Schooley RT, Ramirez-Ronda C, Lange JM, *et al*. Virologic and immunologic benefits of initial combination therapy with zidovudine and zalcitabine or didanosine compared with zidovudine monotherapy. *J Infect Dis* 1996; **173:**1354–1366.
34. Hammer SM, Katzenstein DA, Hughes MD, *et al*. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200–500 per cubic millimeter. *N Engl J Med* 1996; **335:**1081–1090.
35. Delta Coordinating Committee. Delta: a randomized double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabline with zidovudine alone in HIV-infected individuals. *Lancet* 1996; **348:**283–291.
36. Katlama C, Ingrand D, Loveday C, *et al*. Safety and efficacy of lamivudine-zidovudine combination therapy in antiretroviral-naive patients: a randomized controlled comparison with zidovudine monotherapy. *JAMA* 1996; **276:**118–125.
37. Staszewski S, Loveday C, Picazo JJ, *et al*. Safety and efficacy of lamivudine-zidovudine combination therapy in antiretroviral-experienced patients: a randomized controlled comparison with zidovudine monotherapy. *JAMA* 1996; **276:**111–117.
38. Hammer SM, Squires KE, Hughes MD, *et al*. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* 1997; **337:**725–733.
39. Montaner JSG, Reiss P, Cooper D, *et al*. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS trial. *JAMA* 1998; **279:**930–937.
40. Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics *in vivo*: virion clearance rate, infected cell life-span, and viral generation time. *Science* 1996; **271:**1582–1586.
41. de Jong MD, Loewenthal M, Boucher CA, *et al*. Alternating nevirapine and zidovudine treatment of human immunodeficiency virus type 1-infected persons does not prolong nevirapine activity. *J Infect Dis* 1994; **169:**1346–1350.
42. Levi GC, Vitoria M. Fighting against AIDS: the Brazilian experience. *AIDS* 2002; **16:**2373–2383.
43. Galvão J. Access to antiretroviral therapy drugs in Brazil. *Lancet* 2002; **360:**1862–1865.
44. Nunn AS, Fonseca EM, Bastos FI, *et al*. Evolution of antiretroviral drug costs in Brazil in the context of free and universal access to AIDS treatment. *PLoS Med* 2007; **4:**e305.
45. Joint United Nations Programme on HIV/AIDS (UNAIDS). New public/private sector effort to accelerate access to HIV/AIDS care and treatment in developing countries 2000. (Accessed 21 July 2014.) Available from http://www.essentialdrugs.org/edrug/archive/200005/msg00027.php
46. Van der Borght S, Rinke de Wit T, Janssens V, Schim van der Loeff M, Rijckborst H, Lange J. HAART for HIV-infected employees of large companies in Africa. *Lancet* 2006; **368:**547–550.
47. Van der Borght S, Janssens V, Schim van der Loeff MF, *et al*. The accelerating access initiative: experience with a multinational workplace programme in Africa. *Bull World Health Organ* 2009; **87:**794–798.
48. ACHAP – Partnerships for a healthy Africa (Accessed 21 July 2014.) Available from www.achap.org
49. World Health Organization. Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. (Updated 2001. Accessed 21 July 2014.) Available from http://whqlibdoc.who.int/publications/2001/924154550X.pdf

50. UNAIDS. 2001 Declaration of commitment on HIV/AIDS. (Accessed 21 July 2014.) Available from http://www.unaids.org/en/aboutunaidsunitednationsdeclarationsandgoals/2001declarationofcommitmentonhivaids/
51. World Health Organization. Treating 3 million by 2005: making it happen. (Updated 2003. Accessed 21 July 2014.) Available from http://www.who.int/3by5/publications/documents/en/Treating3millionby2005.pdf
52. The World Bank. The Multi-Country HIV/AIDS Program for Africa (MAP). (Accessed 21 July 2014.) Available from http://web.worldbank.org/WBSITE/EXTERNAL/COUNTRIES/AFRICAEXT/EXTAFRHEANUTPOP/EXTAFRREGTOPHIVAIDS/0,,contentMDK:20415735~menuPK:1001234~pagePK:34004173~piPK:34003707~theSitePK:717148,00.html
53. The Global Fund to fight AIDS, Tuberculosis and Malaria. (Accessed 21 July 2014.) Available from www.theglobalfund.org
54. PEPFAR. About PEPFAR. (Accessed 21 July 2014.) Available from http://www.pepfar.gov/about/
55. World Health Organization/UNICEF/UNAIDS. Global update on HIV treatment 2013: results, impact and opportunities. WHO report in partnership with UNICEF and UNAIDS. (Updated June 2013. Accessed 21 July 2014.) Available from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/20130630_treatment_report_en.pdf
56. Ford N, Wilson D, Costa Chaves G, Lotrowska M, Kijtiwatchakul K. Sustaining access to antiretroviral therapy in the less-developed world: lessons from Brazil and Thailand. *AIDS* 2007; **21 Suppl 4:**S21–S29.
57. Medicines Patent Pool. (Accessed 21 July 2014.) Available from www.medicinespatentpool.org
58. Clinton Foundation. (Accessed 21 July 2014.) Available from www.clintonfoundation.org/our-work/clinton-health-access-initiative
59. World Health Organization. The strategic use of antiretrovirals to help end the HIV epidemic. (Updated July 2012. Accessed 21 July 2014.) Available from http://apps.who.int/iris/bitstream/10665/75184/1/9789241503921_eng.pdf?ua=1
60. 't Hoen EF, Hogerzeil HV, Quick JD, Sillo HB. A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme. *J Public Health Policy* 2014; **35:**137–161.
61. US Food and Drug Administration. Tentative approval of efavirenz, lamivudine and tenofovir disporoxil fumarate tables. US Department of Health and Human Services. (Updated 1 June 2014. Accessed 21 July 2014.) Available from http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm327644.htm
62. Nakakeeto ON, Elliott BV. Antiretrovirals for low income countries: an analysis of the commercial viability of a highly competitive market. *Global Health* 2013; **9:**6.
63. UNITAID. (Accessed 21 July 2014.) Available from http://www.unitaid.eu/en/who/about-unitaid
64. Lalezari JP, Henry K, O'Hearn M, *et al*. Enfuvirtide, an HIV-1 fusion inhibitor for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003; **348:**2175–2185.
65. Lazzarin A, Clotet B, Cooper D, *et al*. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003; **348:**2186–2195.
66. Gulick RM, Lalezari J, Goodrich J, *et al*. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med* 2008; **359:**1429–1441.
67. Fätkenheuer G, Nelson M, Lazzarin A. Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. *N Engl J Med* 2008; **359:**1442–1455.
68. Steigbigel RT, Cooper DA, Kumar PN, *et al*. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med* 2008; **359:**339–354.
69. Cooper DA, Steigbigel RT, Gatell JM, *et al*. Subgroup and resistance analyses of raltegravir for resistanct HIV-1 infection. *N Engl J Med* 2008; **359:**355–365.
70. Wainberg MA, Albert J. Can further clinical development of bevirimat be justified. *AIDS* 2010; **24:**773–774.
71. Lalezari J, Latiff GH, Brinson C, *et al*. Attachment inhibitor prodrug BMS-663068 in ARV-experienced subjects: week 24 analysis. *Conference on Retroviruses and Opportunistic Infections*. 3–6 March 2014, Boston, MA, USA. Abstract 86.
72. Madruga JV, Cahn P, Grinsztejn B, *et al*. Efficacy and safety of TMC125 (etravirine) in treatment-experienced patients in DUET 1: 24 week results from a randomized, double-blind, placebo-controlled trial. *Lancet* 2007; **370:**29–38.
73. Lazzarin A, Campbell T, Clotet B, *et al*. Efficacy and safety of TMC125 (etravirine) in treatment-experienced patients in DUET 2: 24 week results from a randomized, double-blind, placebo-controlled trial. *Lancet* 2007; **370:**39–48.
74. Cohen CJ, Molina JM, Cahn P, *et al*. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the Phase 3 double-blind randomized ECHO and Thrive trials. *J Acquir Immune Defic Syndr* 2012; **60:**33–42.
75. Cohen C, Wohl D, Arribas JR, *et al*. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxyl fumarate vs. efavirenz/ emtricitabine/tenofovir disoproxyl fumarate in treatment-naive HIV-1-infected adults. *AIDS* 2014; **28:**989–997.
76. Molina J-M, Lamarca A, Andrade Villanueva J, *et al*. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomized, double-blind, Phase 3, non-inferiority study. *Lancet Infect Dis* 2012; **12:**27–35.
77. Zolopa A, Sax PE, DeJesus E, *et al*. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr* 2013; **63:**96–100.
78. Cahn P, Pozniak AL, Mingrone H, *et al*. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomized, double-blind, non-inferiority SAILING study. *Lancet* 2013; **382:**700–708.
79. Raffi F, Jaeger H, Quiros-Roldan E, *et al*. Once-daily dolutegravir versus twice daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomized, double-blind, non-inferiority trial. *Lancet Infect Dis* 2013; **13:**927–935.
80. Gallant JE, Koenig E, Andrade-Villanueva J, *et al*. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/ tenofovir disoproxil fumarate in treatment-naive HIV type-1-infected patients. *J Infect Dis* 2013; **208:**32–39.
81. Rockstroh JK, DeJesus E, Henry K, *et al*. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/ tenofovir DF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr* 2013; **62:**483–486.
82. Zolopa A, Ortiz R, Sax P, *et al*. Comparative study of tenofovir alafenamide vs tenofovir disoproxil fumarate, each with elvitegravir, cobicistat, and emtricitabine, for HIV treatment. *Conference on Retroviruses and Opportunistic Infections*. 3–6 March 2013, Atlanta, GA, USA. Abstract 99LB.
83. Morales-Ramirez JO, Gatell JM, Hagins DP, *et al*. Safety and antiviral effect of MK-1439, a novel NNRTI (+FTC/TDF) in ART-naive HIV-infected patients. *Conference on Retroviruses and Opportunistic Infections*. 3–6 March 2014, Boston, MA, USA. Abstract 92LB.
84. Camacho R. Generic antiretrovirals: will they change our clinical practice? *12th European Workshop on HIV and Hepatitis: Treatment Strategies and Antiviral Drug Resistance*. 26–28 March 2014, Barcelona, Spain.

85. Van 't Klooster G, Hoeben E, Borghys H, *et al*. Pharmacokinetics and disposition of rilpivirine (TMC278) nanosuspension as a long acting injectable antiretroviral formulation. *Antimicrob Agents Chemother* 2010; **54:**2042–2050.

86. Spreen WR, Margolis DA, Pottage JC, Jr. Long-acting injectable antiretrovirals for HIV treatment and prevention. *Curr Opin HIV AIDS* 2013; **8:**565–571.

87. Margolis D, Brinson C, Eron J, *et al*. 744 and rilpivirine as two-drug oral maintenance therapy: LAI116482 (LATTE) week 48 results. *Conference on Retroviruses and Opportunistic Infections*. 3–6 March 2014, Boston, MA, USA. Abstract 91LB.

88. Radzio J, Spreen W, Yueh YL, *et al*. Monthly GSK744 long-acting injections protect macaques against repeated vaginal SHIV exposures. *Conference on Retroviruses and Opportunistic Infections*. 3–6 March 2014, Boston, MA, USA. Abstract 40LB.

89. Chen BA, Panther L, Hoesley C, *et al*. Safety and pharmacodynamics of dapivirine and maraviroc vaginal rings. *Conference on Retroviruses and Opportunistic Infections*. 3–6 March 2014, Boston, MA, USA. Abstract 41.

90. van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F. Life expectancy of recently diagnosed symptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS* 2010; **24:**1527–1535.

91. Nakagawa F, Lodwick RK, Smith CJ, *et al*. Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS* 2012; **26:**335–343.

92. Rodger AJ, Lodwick R, Schechter M, *et al*. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. *AIDS* 2013; **27:**973–979.

93. Samji H, Cescon A, Hogg RS, *et al*. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS ONE* 2013; **8:**e81355.

94. Tuaillon E, Guedin M, Lemee V, *et al*. Phenotypic susceptibility to nonnucleoside inhibitors of virion-associated reverse transcriptase from different HIV types and groups. *J Acquir Immune Defic Syndr* 2004; **37:**1543–1549.

95. Ntemgwa M, Brenner BG, Oliveira M, *et al*. Natural polymorphisms in the human immunodeficiency virus type 2 protease can accelerate time to development of resistance to protease inhibitors. *Antimicrob Agents Chemother* 2007; **51:**604–610.

96. Ntemgwa ML, d'Aquin Toni T, Brenner BG, *et al*. Antiretroviral drug resistance in human immunodeficiency virus type 2. *Antimicrob Agents Chemother* 2009; **53:**3611–3619.

97. Smith RA, Anderson DJ, Pyrak CL, *et al*. Antiretroviral drug resistance in HIV-2: three amino acid changes are sufficient for classwide nucleoside analogue resistance. *J Infect Dis* 2009; **199:**1323–1326.

98. Boyer PL, Sarafianos SG, Clark PK, *et al*. Why do HIV-1 and HIV-2 use different pathways to develop AZT resistance? *PLoS Pathog* 2006; **2:**e10.

99. Roquebert B, Damond F, Collin G, *et al*. HIV-2 integrase gene polymorphism and phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitors raltegravir and elvitegravir *in vitro*. *J Antimicrob Chemother* 2008; **62:**914–920.

100. Garrett N, Xu L, Smit E, *et al*. Raltegravir treatment response in an HIV-2 infected patient: a case report. *AIDS* 2008; **22:**1091–1092.

101. Kobayashi M, Yoshinaga T, Seki T, *et al*. *In vitro* antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. *Antimicrob Agents Chemother* 2011; **55:**813–821.

102. New York State Department of Health AIDS Institute. HIV clinical resource. (Accessed 21 July 2014.) Available from http://www.hivguidelines.org

103. Witvrouw M, Pannecouque C, Switzer WM, *et al*. Susceptibility of HIV-2, SIV and SHIV to various anti-HIV-1 compounds: implications for treatment and postexposure prophylaxis. *Antivir Ther* 2004; **9:**57–65.

104. Poveda E, Rodes B, Toro C, *et al*. Are fusion inhibitors active against all HIV variants? *AIDS Res Hum Retroviruses* 2004; **20:**347–348.

105. Puls R and the ENCORE Study Group. A daily dose of 400 mg efavirienz (EFV) is non-inferior to the standard 600 mg dose: week 48 data from the ENCORE-1 study, a randomized, double-blind, placebo-controlled, non-inferiority trial. *7th IAS Conference on HIV Pathogenesis, Treatment and Prevention*. 30 June–3 July 2013, Kuala Lumpur, Malaysia. Abstract WELBB01.

106. Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic 2013. (Updated 2013. Accessed 21 July 2014.) Available from http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/unaids_global_report_2013_en.pdf

107. Yazdanpanah Y, Lange J, Gerstoft J, Cairns G. Earlier testing for HIV – how do we prevent late presentation? *Antivir Ther* 2010; **15 Suppl 1:**17–24.

108. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis* 2011; **52:**793–800.

109. Krastinova E, Seng R, Yeni P, *et al*. ANRS PRIMO and COPANA cohorts. Is clinical practice concordant with the changes in guidelines for antiretroviral therapy initiation during primary and chronic HIV-1 infection? *PLoS ONE* 2013; **8:**e71473.

110. van Sighem A, Gras L, Kesselring A, *et al*. HIV Monitoring (SHM). Monitoring report 2013: human immunodeficiency virus (HIV) infection in the Netherlands. (Updated 2013. Accessed 21 July 2014.) Available from http://www.hiv-monitoring.nl/files/5913/8443/2799/SHM_MonitoringReport2013.pdf

111. South Africa: monitoring essential medicines consortium. Report stock outs in South Africa. (Accessed 21 July 2014.) Available from http://www.stockouts.org

112. Kranzer K, Ford N. Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review. *Trop Med Int Health* 2011; **16:**1297–1313.

113. Mulenga LB, Mwango A, Moyo C, *et al*. Efficacy of tenofovir disoproxil fumarate/emtricitabine and tenofovir disoproxil fumarate/lamivudine both in combination with efavirenz in antiretroviral-naive, HIV-1-infected Zambians. *7th IAS Conference on HIV Pathogenesis, Treatment and Prevention*. 30 June–3 July 2013, Kuala Lumpur, Malaysia. Abstract TULBPE18.

114. Institute for Health Metrics and Evaluation. Financing global health 2012: the end of the golden age? (Updated 2012. Accessed 21 July 2014.) Available from http://www.healthdata.org/sites/default/files/files/policy_report/2012/FGH/IHME_FGH2012_FullReport_HighResolution.pdf

115. Montaner JS, Hogg R, Wood E, *et al*. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet* 2006; **368:**531–536.

116. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009; **373:**48–57.

117. Cohen MS, Chen YQ, McCauley M, *et al*. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365:**493–505.

118. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. (Updated 2013. Accessed 21 July 2014.) Available from http://www.who.int/hiv/pub/guidelines/arv2013/download/en/

119. Montaner JSG, Lima VD, Harrigan PR, *et al*. Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission: the 'HIV Treatment as Prevention' experience in a Canadian setting. *PLoS ONE* 2014; **9:**e87872.

120. World Health Organization. Working together for health: The World Health Report 2006. (Updated 2006. Accessed 21 July 2014.) Available from http://www.who.int/whr/2006/whr06_en.pdf

121. Geng EH, Bwana MB, Muyindike W, *et al*. Failure to initiate antiretroviral therapy, loss to follow-up and mortality among HIV-infected patients during the pre-ART period in Uganda. *J Acquir Immune Defic Syndr* 2013; **63:**e64–e71.

122. Tweya H, Feldacker C, Estill J, *et al*. Are they really lost? 'True' status and reasons for treatment discontinuation among HIV-infected patients on antiretroviral therapy considered lost to follow-up in urban Malawi. *PLoS ONE* 2013; **8:**e75761.

123. Lima VD, Johnston K, Hogg RS, *et al*. Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic. *J Infect Dis* 2008; **198:**59–67.

124. Granich R, Kahn JG, Bennett R, *et al*. Expanding ART for treatment and prevention of HIV in South Africa: estimated cost and cost-effectiveness 2011–2050. *PLoS ONE* 2012; **7:**e30216.

125. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS report on the global AIDS epidemic. (Updated 2012. Accessed 21 July 2014.) Available from http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_with_annexes_en.pdf

126. Atun R, Knaul FM, Akachi Y, Frenk J. Innovative financing for health: what is truly innovative? *Lancet* 2012; **380:**2044–2049.

127. Schellekens OP, de Beer I, Lindner ME, van Vugt M, Schellekens P, Rinke de Wit TF. Innovation in Namibia: preserving private health insurance and HIV/AIDS treatment. *Health Aff (Millwood)* 2009; **28:**1799–1806.

128. Beaglehole R, Bonita R, Alleyne G, Horton R. NCDs: celebrating success, moving forward. *Lancet* 2011; **378:**1283–1284.

129. Hunter DJ, Reddy KS. Noncommunicable diseases. *N Engl J Med* 2013; **369:**1336–1343.

130. Chamie G, Kwarisiima D, Clark TD, *et al*. SEARCH Collaboration. Leveraging rapid community-based testing campaigns for non-communicable diseases in rural Uganda. *PLoS ONE* 2012; **7:**e43400.

131. Thomas DL. Cure of hepatitis C virus infection without interferon alfa: scientific basis and current clinical evidence. *Top Antivir Med* 2014; **21:**152–156.

132. Gravitz L. A smouldering public-health crisis. *Nature* 2011; **474:**S2–S4.

133. Lawitz E, Poordad FF, Pang PS, *et al*. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomized, Phase 2 trial. *Lancet* 2014; **383:**515–523.

134. World Health Organization. The strategic use of antiretrovirals. (Accessed 12 September 2014.) Available from http://apps.who.int/iris/bitstream/10665/75184/1/9789241503921_eng.pdf

Accepted 19 May 2014; published online 13 October 2014