The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic

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> "The upshot of this widespread failure to recognize that AIDS is an exceptional crisis and threat is that the response to the pandemic is not made commensurate to the challenges—and so the epidemic escalates even while it erodes our capacities to check it."
>
> *Dr Peter Piot, UNAIDS Executive Director*[1]

Continuing expansion of the HIV/AIDS pandemic has been recognised as an exceptional challenge to global health, international development, and world security. UNAIDS estimates that there were more than 38 million people living with HIV at the end of 2005, with just over 4 million new infections that year.[2] While most new cases continue to emerge from developing nations, even in developed countries HIV incidence remains unacceptably high.[3] The high incidence is not likely to change in the foreseeable future because: (1) HIV-prevention strategies are only partly effective and remain severely underused;[4–10] (2) a preventive vaccine remains elusive;[11] and (3) current treatment strategies cannot eradicate HIV infection.[12–15] Nowadays, the exceptional threat to humanity that the HIV pandemic represents, and the similarly exceptional interventions that will be needed to stem the relentless global growth of AIDS deaths and new HIV infections, is widely recognised.[1,16,17]

Highly active antiretroviral therapy (HAART), first introduced in 1996,[18–20] substantially reduced AIDS-related hospital admissions and death rates in both developed and developing nations.[21–23] Despite these encouraging results, the early optimism generated by HAART was tempered by regimen complexities, adverse effects, toxicities, and cost.[24,25] In the past decade, HAART regimens have become markedly simpler, better tolerated, less toxic, and more effective.[26–28] As a result, expansion of HAART programmes in developing nations has become a welcome reality.[29] Although concerns have been expressed with regard to the potential negative effects of suboptimal adherence leading to HIV-drug resistance in settings where scale-up of HAART is taking place, recent data suggest that good adherence can be attained in resource-limited settings and in marginalised populations in developed nations.[30,31]

The important role that the provision of HAART has in the overall strategy to control the advance of the HIV/AIDS pandemic is now generally agreed. However, a great deal of attention has been focused on the potential negative effect of HAART on the overall expansion of the pandemic if enhanced access to the treatment was to promote an increase in risky behaviours. By contrast, the potential direct contribution of HAART to reducing the spread of HIV has received only limited attention. We examine here the potential role of HAART in HIV prevention and the resulting effect this would have on the cost-effectiveness of the treatment. We also discuss a theoretical HAART-driven strategy to control the continued expansion of the HIV/AIDS pandemic.

HAART and HIV prevention

HIV causes AIDS.[32] The transmission of HIV from infected to uninfected people through exposure to an infected person's bodily fluids (mainly semen, vaginal secretions, breast milk, and blood) is established.[33–35] More recently, HAART has been shown to reduce HIV-1-RNA plasma concentrations predictably to undetectable concentrations in most treated patients.[36] International guidelines have uniformly recognised that sustained complete suppression of HIV-1-RNA is needed to achieve a steady increase in CD4-positive T-lymphocyte (CD4) cell count as well as a beneficial clinical response, and to avoid the emergence of drug resistant HIV mutants.[37,38] Furthermore, the use of HAART leads to a marked reduction in HIV-1 RNA concentrations in both the female genital tract and in semen.[39,40]

Evidence of the effect of HAART on the prevention of HIV transmission can be derived from experience in the mother-to-child-transmission setting. Here, even before the HAART era, the key role of maternal plasma HIV-1-RNA concentrations in HIV transmission had been clearly established.[41] Subsequently, clinical trials have shown that reducing the mother's plasma HIV-1-RNA concentration with HAART dramatically reduces mother-to-child transmission of HIV.[42,43] Since the widespread availability of HAART, mother-to-child transmission of HIV has become exceedingly rare in developed nations.[44]

Consistent results have emerged from several studies of HIV sero-discordant heterosexual couples. In a study from Uganda, Quinn and colleagues[45] showed that viral load is the main predictor of the risk of heterosexual transmission of HIV-1, and that transmission is rare in those with plasma HIV-1-RNA concentrations of less than 1500 copies per mL. In this study there were no cases of HIV transmission for couples in which the index case had plasma HIV-1-RNA of less than 400 copies per mL. Similarly, in a study from Thailand, Tovanabutra and co-workers[46] showed a dose-response effect between viral load and risk of HIV transmission within sero-discordant heterosexual couples. No cases of HIV transmission were seen when the index case's plasma HIV-1-RNA was less than 1100 copies per mL in the same study.

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Additional studies to assess the effect of HAART on HIV incidence in sero-discordant couples have also been shown reduced HIV transmission. Before the HAART era, use of zidovudine alone was associated with a 50% reduction in HIV transmission in a study of Italian sero-discordant couples.[47] In the HAART era, a study of Spanish sero-discordant couples showed that no HIV sero-conversions took place in the sexual partners of HAART treated patients, use of HAART being independently associated with an 86% reduction in HIV transmission in multivariate analyses.[48] As a result, Hosseinipour and colleagues[49] have asked whether HAART can be used to curb the spread of HIV. However, a possible role for HAART in reducing HIV transmission was substantially tempered by several mathematical modelling studies, which consistently suggested that any possible benefit derived from the use of HAART in this setting could be readily offset if expanded use of HAART results in increased HIV-risk behaviour.[50–52]

These concerns have been alleviated by an ecological study from Taiwan, which provided compelling evidence about the effect of HAART on HIV transmission.[53] The study showed a 53% reduction in new positive HIV tests after the introduction of free access to HAART. This reduction took place without any change in rates of syphilis, used as a marker of sexual risk behaviour during the study. In British Columbia, Canada, new HIV infections fell between 1995 and 1998 after the introduction of HAART by about 50%, and have remained unchanged to the present despite a noticeable increase in syphilis rates (Rekart M, British Columbia Centre for Disease Control, personal communication).

Further ecological evidence of an effect of HAART on HIV transmission can be derived from a detailed review of the UNAIDS statistics.[2] As shown in the table, in 2005, about 38 600 000 people were estimated to be living with HIV or AIDS worldwide, with more than 4 000 000 new HIV infections and 2 800 000 AIDS-related deaths in that year. HIV-prevalent cases are the source of new HIV infections, so investigation of the ratio between new and prevalent cases on a regional basis is of interest. The table shows numbers of people living with HIV, numbers of new HIV infections, and the ratio of new HIV infections per 100 people living with HIV in 2005 by region.[2] The ratios show clear regional differences, which correlate inversely with regional availability of HAART (figure).[54] Use of HAART is fairly widespread in western and central Europe and North America, intermediate in Oceania and Latin America, and limited in the rest of the world.

Ecological evidence has some limitations that should be recognised. The accuracy of the HIV prevalence and incidence data are not known, and our calculations could be affected by this. Also, the number of transmitted cases might not be exactly proportional to prevalence of HIV infection in a given area, because a limited number of individuals with very high viral load could contribute a disproportionate number of transmission events. Finally, HAART might be only one of several factors that contribute to reduced transmission in areas where such treatment is accessible. We must stress that we do not see HAART as a replacement for strengthening of the prevention effort, but rather as an essential part of it.

	People living with HIV/AIDS	New HIV infections	Ratio of new infections per 100 people living with HIV/AIDS
East Europe and central Asia	1 500 000 (1 000 000–2 300 000)	220 000 (150 000–650 000)	14·7
North Africa and middle east	440 000 (250 000–720 000)	64 000 (38 000–210 000)	14·5
East Asia	680 000 (420 000–1 100 000)	97 000 (55 000–290 000)	14·3
Caribbean	330 000 (240 000–420 000)	37 000 (26 000–54 000)	11·2
Sub-Saharan Africa	24 500 000 (21 600 000–27 400 000)	2 700 000 (2 300 000–3 100 000)	11·0
South and southeast Asia	7 600 000 (5 100 000–11 700 000)	830 000 (530 000–2 300 000)	10·9
Oceania	78 000 (48 000–170 000)	7 200 (3 500–55 000)	9·2
Latin America	1 600 000 (1 200 000–2 400 000)	140 000 (100 000–420 000)	8·8
North America	1 300 000 (770 000–2 100 000)	43 000 (34 000–65 000)	3·3
Western and central Europe	720 000 (550 000–950 000)	22 000 (18 000–33 000)	3·1
Total	38 600 000 (33 400 000–46 000 000)	4 100 000 (3 400 000–6 200 000)	

Based on May, 2006, UNAIDS Report of the global AIDS epidemic.[2] Data are number (range) unless otherwise indicated.

Table: **Estimated HIV/AIDS prevalence, HIV incidence, and ratio of new HIV infections per 100 people living with HIV/AIDS in 2005 by region**

Cost effectiveness of HAART revisited

Traditionally, HAART has been deemed to be cost effective on the basis of patient-centred outcomes;[55] however, this fails to consider the effect of HAART on HIV transmission. Regional incidence to prevalence ratios can be used to estimate the number of new HIV infections that have failed to materialise in 2005 in any given region. For example, to raise the index in North America to the level seen in developing countries, where access to HAART is limited, would take nearly 100 000 additional HIV infections in North America. The precise proportion of these missing new infections that are directly attributable to the use of HAART is not clear; however, on the basis of the data from Taiwan and British Columbia, a 50% or so yearly reduction in new HIV cases can reasonably be attributed to the introduction of HAART. This proportion would represent about 43 000 new cases in North America in 2005, which in turn translates to an averted HAART cost of US$10·3 billion, based on an estimated lifetime treatment cost, in 2001, of US$241 000 per person treated.[55]

HAART use is estimated to have averted 400 new infections in British Columbia in 2005. This would represent a total cost, in 2001, of US$96·4 million of averted lifetime treatment expenditure, in addition to the direct health benefit of HAART to the HIV-infected individuals. This is particularly striking if we consider that 3963 individuals received HAART in British Columbia in that same year for a total HAART cost (using patented drugs) of US$49 million. On the basis of these data, HAART, which was already deemed cost effective on a patient-centred basis, has generated an additional substantial cost saving once its effect on HIV transmission is considered.

A potential HAART-driven HIV-control strategy

The patient-centred approach to HIV management is based on the use of HAART to modify the natural history of the disease with the expectation that HIV infection will be transformed into a manageable chronic condition. This approach is supported by many clinical trials and population-based studies showing that health outcomes, such as death or progression to AIDS, can be delayed as long as individuals are highly adherent to therapy and start treatment with CD4-cell counts of greater than 200 per µL. No additional patient-specific benefit has been documented when treatment was initiated at earlier stages of the disease.[25] As a result, a large global effort is currently underway to expand access to HAART for individuals with AIDS-related symptoms or CD4-cell counts of less than 200 per µL.[29] The "3 by 5" plan proposed to expand the use of HAART regimens to an additional 3 million HIV positive individuals by 2005. Despite substantial progress, the "3 by 5" plan has failed to meet its target.[56,57] In fact, the number of new HIV infections in 2005 was more than double the number of individuals who started HAART in the same year.

Current estimates are that between 30% and 40% of HIV-infected individuals globally are in need of HAART.[58] In view of the well-characterised and relentless decline of CD4-cell count in untreated HIV-infected individuals, most currently infected individuals will become eligible for HAART within a decade. Most of the 38 million HIV positive individuals already infected worldwide will become eligible for HAART therapy by the year 2015. The continued expansion of the global HIV/AIDS caseload threatens to make the current HAART strategy unsustainable.

In view of the potential effect of HAART on HIV transmission, what would be the implications of an alternative prevention-centred strategy for the use of HAART? This approach would be based on the notion that new HIV infections are overwhelmingly contributed to by index HIV-infected individuals who are not on HAART. A prevention-centred approach would therefore argue that treating 100% of HIV-infected individuals at once could greatly reduce HIV transmission. While this would be costly in the short term, it could prove highly cost effective. The short-term cost of treatment of all HIV-infected individuals would be more than offset by the number of new infections that it would prevent. In fact, as the cohort of today's HIV-infected individuals on HAART matures, after about 20–40 years this cohort will no longer be interacting substantially with the populations at risk, therefore drastically reducing the likelihood of new infections. Although treating 100% of HIV-infected individuals worldwide might not be feasible or even ethically acceptable at this time, given the state of the pandemic, consideration of this possibility is worthwhile.

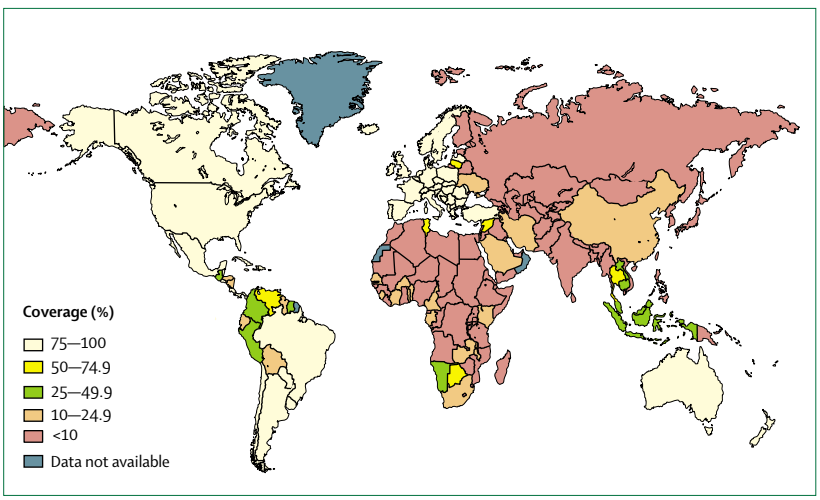

Figure: **Estimated percentage of people receiving antiretroviral therapy of those in need as of June 2005**
Reproduced from reference 54.

We have, therefore, developed a hypothetical population-based model to illustrate the potential effect of a prevention-centred approach on the worldwide HIV pandemic (unpublished). The model estimates the rate of decline in HIV prevalence in low-income and middle-income countries. We have assumed that all HIV-infected people would be given therapy in the first year and that, after the first year, there would be no new HIV infections. We also assume the cost of HAART therapy, with use of generic medications, would remain at the present cost of US$365 per person per year. However, the model incorporates a moderate increase in the yearly cost of therapy at 3% per year for future inflation. We also assume that the death rate will fall initially with the use of HAART, but increase to baseline levels in a stepwise fashion as the population receiving treatment needs more complicated therapeutic regimens. This optimistic population-based model shows that, in 45 years, HIV prevalence could be reduced by more than 70 times from more than 7 cases per 1000 people to less than 0·1 case per 1000. The number of HIV-infected people could be reduced from 38 million to less than 1 million. The cost of therapy would be about US $7 billion per year, with costs declining from $15 to $1 billion. Such a programme would be expected to cost $338 billion over

45 years. The prospect of treating nearly 40 million HIV-infected individuals worldwide seems daunting today but, in view of the limited effect of current efforts on global prevention of new infections, this approach merits consideration if it can offer a means to control the relentless growth of the pandemic.

The logistical and infrastructural challenges that lie ahead for this kind of approach are substantial. Many of the same structural obstacles that have faced HAART scale-up programmes, such as poor health infrastructure, a scarcity of trained health-care workers, and rural-based populations, would be multiplied many fold. One additional important concern is the potential for increased transmission of drug-resistant strains of HIV with expansion of HAART use. However, drug-resistant HIV might be less transmissible.[59] A study from Montreal[60] showed that increased population rates of suppression of plasma HIV RNA as a result of HAART were associated with reduced rates of resistance in the community. Further reassurance is provided by examination of the early history of antiretroviral therapy in developed nations. Between the introduction of zidovudine in 1986 and HAART in 1996, treatment of HIV infection relied exclusively on the use of single and dual nucleoside analogues. Nucleoside resistance in this context was an almost universal occurrence in treated individuals within a year of starting therapy. Despite this resistance, an epidemic of primary-nucleoside-resistant HIV did not materialise, and in fact the rates of primary resistance to nucleosides continue to be modest.[61–65] Zidovudine and lamivudine remain highly effective and in widespread use in developed nations. As has previously been proposed, we conclude that fear of emergence of drug resistance should not prevent expansion of HAART programmes, even in developing countries.[66] However, any effort directed toward the expansion of HAART programmes should include careful monitoring of resistance.

Previous concerns about the cost and acceptability of HAART regimens have been alleviated in recent years. The availability of generic stavudine, lamuvidine, and nevirapine in a fixed dose combination tablet at US$1 a day set a precedent by making the expansion of HAART programmes feasible in developing countries. This specific treatment would not be appropriate for the implementation of a global universal treatment programme, because of the potential for nevirapine and stavudine toxicity. However, an alternative one pill once daily HAART regimen with a fixed-dose combination of tenofovir, emtricitabine, and sustiva is now available. This represents a simple, safe, and well-tolerated regimen that would be viable at all stages of the disease; with a single-dose scheme, without food restrictions, with no refrigeration needs, and limited need for laboratory monitoring. This opens the door to consideration of the effect of different levels of expansion of HAART coverage on HIV transmission.

Conclusions

The present approach to the management of HIV/AIDS is clearly not sustainable, and the status quo no longer acceptable if we hope to control the continued growth of the HIV global pandemic. A prevention-centred approach to the use of HAART, as discussed here, would be challenging and would need careful consideration of associated emerging ethical issues. However, expanded free access to HAART on a global scale provides a potential means to curb the growth of the HIV pandemic. As such, expansion of HAART programmes could have a major role in the much needed strengthening of the prevention effort. This hypothetical but testable approach deserves to be urgently and thoroughly evaluated in highly controlled environments. The global expansion of HAART programmes now underway provides a unique opportunity to further characterise the effect of HAART on HIV incidence in various settings. Monitoring of HIV incidence should be an integral part of HAART expansion programmes.

Conflict of interest statement

J Montaner has received grants from, served as an ad-hoc adviser to, and spoken at events sponsored by Abbott, Boehringer Ingelheim, Bristol-Meyers Squibb, Gilead Sciences, GlaxoSmithKline, Hoffmann-La Roche, Janssen-Ortho, Merck Frosst, Pfizer, Tibotec, Trimeris. R Hogg is supported by a Michael Smith Foundation for Health Research Senior Scholar award. In the past 5 years, he has also held grant funding from the Canadian Institutes of Health Research and National Institutes of Health. He has also received funding for research and continuing medical education programmes from Abbott, Boehringer Ingelheim, and GlaxoSmithKline. M Tyndall has served on advisory boards for Abbott, Boehringer Ingelheim, GlaxoSmithKline, Bristol-Meyers Squibb, and has received research support from Merck Frosst Canada. A R Levy is supported by a Michael Smith Foundation for Health Research Senior Scholar award and a Canadian Institutes of Health Research New investigator award. He is a shareholder in Oxford Outcomes, a consultancy specialising in contract research for clients in the life sciences industry, including public sector organisations and pharmaceutical and other private companies. P R Harrigan has served as a consultant, received research funding or medical education or both from Abbott, Boehringer Ingelheim, GlaxoSmithKline, Merck, Roche, Pfizer, and Virco. E Wood and T Kerr declare that they have no conflict of interest.

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