Highly active antiretroviral treatment as prevention of HIV transmission: review of scientific evidence and update

Reuben Granich[a], Siobhan Crowley[a], Marco Vitoria[a], Caoimhe Smyth[a], James G. Kahn[b], Rod Bennett[c], Ying-Ru Lo[a], Yves Souteyrand[a] and Brian Williams[d]

[a]Antiretroviral Treatment and HIV Care Unit, Department of HIV/AIDS, World Health Organization, Geneva, Switzerland, [b]University of California at San Francisco, San Francisco, California, USA, [c]Independent Consultant, UK and [d]South African Centre for Epidemiological Modelling and Analysis, Stellenbosch, Western Cape, South Africa

Correspondence to Reuben Granich, MD, MPH, Antiretroviral Treatment and HIV Care Unit, Department of HIV/AIDS, World Health Organization, Avenue Appia 20, CH-1211, Geneva 27, Switzerland
Tel: +41 22 791 1459; fax: +41 22 791 4834; e-mail: granichr@who.int

Current Opinion in HIV and AIDS 2010, 5:298–304

Purpose of review

An estimated 33 million people are living with HIV and universal access remains a dream for millions of people. By the end of year 2008, four million people were on treatment; however, over five million needed treatment, and in 2007, there were 2.7 million new infections. Without significant improvement in prevention, we are unlikely to meet universal access targets including the growing demand for highly active antiretroviral treatment (HAART). This review examines HAART as a potential tool for preventing HIV transmission.

Recent findings

We discuss recent scientific evidence regarding the treatment and prevention gap, importance viral load and HIV transmission, HAART and HIV transmission, when to start, HIV counseling and testing, modeling results and next steps.

Summary

HAART has considerable treatment and prevention benefits and it needs to be considered as a key element of combination prevention. To explore HAART as an effective prevention strategy, we recommend further evaluation of human rights and ethical considerations, clarification of research priorities and exploration of feasibility and acceptability issues.

Keywords

highly active antiretroviral treatment, HIV, modeling, prevention, universal access

Curr Opin HIV AIDS 5:298–304

1746-630X

Introduction

After over 27 years, it is important to pause and consider the devastating extent of the HIV pandemic [1]. Over 25 million people have died and an estimated 33 million people are living with HIV [2•]. In 2008, about 68% of people living with HIV were in sub-Saharan Africa with around 35% in eight countries alone [2•]. HIV is the strongest risk factor for tuberculosis (TB) and an estimated 1.4 million people living with HIV developed TB causing 500 000 (23%) of total HIV-related deaths [3•]. In 2005 and 2009, the G8 met in Scotland and Italy and committed to achieving universal access to HIV prevention, care and treatment by 2010 [2•]. However, universal access remains a dream for millions of people and faces serious technical, economic and political challenges on a number of fronts [2•].

There has been an unprecedented investment in confronting the HIV pandemic – UNAIDS estimates US$13.8 billion in 2008 [4]. One of the major challenges facing us is how to not only sustain but also expand our response to the HIV epidemic in the face of the worst economic crisis since the 1930s. The significance and implications of the economic predicament are at times beyond comprehension. Over US$14.5 trillion, or 33%, of the value of the world's companies has been wiped out and US taxpayers alone will spend some US$9.7 trillion in bailout packages and plans [5]. The economic disaster is being felt worldwide and has already impacted investment in international and national public health.

Treatment and prevention gap

The imperative of providing life-saving antiretroviral therapy (ART) is now undisputed, and there is a pressing need for both increased investment and more efficient use of funding. By the end of year 2008, four million people were on highly active antiretroviral treatment (HAART) [2•]. Despite this remarkable achievement, over five million needed treatment and in 2007 there were 2.7 million new infections [2•]. Around 23 million

people were waiting, mostly unknowingly, to become treatment-eligible, sicken or die. The estimated coverage of ART reached 42% in low- and middle-income countries using the lower 200 CD4 cell count eligibility criteria [2]. If we do not dramatically reduce HIV incidence, it is unlikely that we will be able to meet universal access targets including the growing demand for HAART.

The human rights gap

The HIV epidemic highlights the serious lack of equity and human rights in our global public health response. The millions of people living with or at risk for HIV without access to HIV prevention, treatment and care can be interpreted a serious breach of the fundamental right to healthcare [6]. Coercion and other mandatory approaches to addressing the HIV epidemic have often had perverse negative outcomes. Engaging the community as a meaningful partner in the design and implementation of HIV programs is critical, particularly when the potential for stigma and human rights violations exist [7]. The existing stark economic disparities may exacerbate human rights issues and could further widen the increasingly divergent approaches to HIV prevention, care and treatment that are seen between rich and poor countries [8,9].

If it is broken then we should fix it...

Stopping the HIV epidemic remains elusive in most settings, and there is a need to re-examine our current approaches to stopping HIV. Combination prevention includes evidence-based interventions to address behavioral change, HAART, other biomedical strategies, and structural, social justice and human rights interventions [10,11]. Of 27 randomized controlled trials of different biomedical interventions, including vaccines, microbicides and herpes suppression trials, 22 failed to show efficacy [12–14]. Positive trials include those for male circumcision and the sexually transmitted infection intervention trial in Mwanza, Tanzania, over a decade ago, of limited generalizability [14]. Users of the microbicide gel Pro 2000 had a nonstatistically significant 30% reduction in HIV incidence [15•]. Pre-exposure prophylaxis (PrEP) is being assessed in 10 ongoing or planned international randomized controlled trials with results expected in 2010. Although the concept of PrEP is promising, it will undoubtedly be difficult to give drugs to HIV-uninfected persons when many people are dying from lack of access to HAART and may also face operational challenges around the need to repeat HIV testing to ensure that only those without HIV receive mono or dual therapy. A vaccine may provide an important future intervention [16•]; however, the overall situation has prompted many people to consider the potential prevention role of HAART [17,18••].

Scientific evidence for highly active antiretroviral treatment as prevention of HIV transmission

There is increasingly strong scientific evidence for HAART as prevention of HIV transmission. HIV transmission only occurs from people with HIV, the greatest risk factor for HIV transmission is the viral load and lowering the viral load is essential to interrupting transmission [1,19]. Viral load predicts the risk of sexual transmission of HIV-1, which is rare among persons with levels of less than 1500 copies of HIV-1 RNA per milliliter [19,20]. HAART dramatically lowers viral load and numerous observational studies have demonstrated its potential for prevention of HIV transmission [21,22]. HAART with couples counseling in Uganda reduced transmission by 98% [22]. A 2009 meta-analysis [23] including 11 cohorts (5021 heterosexual couples) found zero risk of sexual transmission while on HAART for HIV-1 ribonucleic acid below 400 copies (upper confidence limit of 1.27 per 100 years). A recent randomized controlled study [24••] of genital herpes simplex virus (HSV) treatment among long-term, HIV-serodiscordant heterosexual couples in Africa found a 92% reduction in transmission if the HIV-positive partner was on HAART. The proportion of couples who had unprotected sex actually decreased when the HIV-positive partner started treatment, allaying fears about behavioral change [24••].

Prevention of maternal-to-child transmission (PMTCT) offers further proof of concept that HAART interrupts HIV transmission. In the USA, perinatal AIDS cases have been virtually eliminated most likely due to the implementation of guidelines for the universal counseling, voluntary HIV testing and HAART for pregnant women and newborn infants [25]. In 2008, the majority of the 430 000 new pediatric HIV infections were in sub-Saharan Africa, where there is recent evidence that HAART can be used to decrease transmission to 1% [26•].

Studies also suggest a potential for the community-level impact of HAART on HIV transmission. In British Columbia, a decrease in community plasma HIV RNA concentrations and HIV incidence among injecting drug users is associated with HAART use [27••] In San Francisco between 2004 and 2008, the number of HIV diagnoses fell by 45%, the average viral load among the HIV-positive population by 40% and the actual HIV incidence fell by one-third between 2006 and 2008 [28••]. In Taiwan, a 53% reduction in new HIV cases was associated with free access to HAART [29••].

When to start?

Although there are over four million people on ART, it is not known with certainty how early to start HAART. In

sub-Saharan Africa, people start HAART very late at a median CD4 cell count of around 100 and, despite progress with improving earlier access, mortality remains markedly higher when compared with other contexts [30••,31]. Starting late sharply increases the risk of death even for patients on HAART and is associated with the time spent below 200 $CD4^+$ cells/μl [32••,33••]. Even after testing positive and entering care, one South African study [34••] found that patients with higher CD4 cell counts are being monitored too infrequently for the timely start of treatment and 25% of people die waiting for HAART. Although mortality rates at the higher CD4 cell count levels are lower, they are not zero, and may represent a significant impact on morbidity and mortality. In Zimbabwe, HIV mortality within 24 months postpartum in the absence of HAART was 54 times higher for those with CD4 cell counts less than 200 cells/ml, 5.4 times higher for counts 400–600, and the hazard remained elevated at 6.2 for counts greater than 600 [35••]. North American cohort data showed a 94% increase in mortality for those who started treatment below CD4 cell count level of 500 when compared with those who started earlier [36••]. Europe and North America cohorts including over 40 000 patients showed that starting treatment earlier reduced the risk of acquired immunodeficiency syndrome or death, with those starting before reaching 450 having the most benefit [30••]. Other cohort studies [37,39,40••,41] also suggest that starting earlier is better and the evidence increasingly points to the damaging effects of HIV even at higher CD4 cell count levels and the negative effects of letting CD4 cell counts drop too low. HAART has a significant role to play in preventing TB morbidity, transmission and mortality. In a randomized clinical trial [42••] of 642 patients coinfected with HIV and TB in South Africa, starting HAART earlier during TB therapy reduced mortality rates by 56%. To prevent TB, we may have to intervene with HAART earlier before people living with HIV spend too long in the $CD4^+$ 'death zone' (<500 CD4 cells) for TB [32••,33••]. Recognizing this, WHO recently revised its guidelines to recommend ART for all with less than 350 CD4 cells [43••].

Trial data also point in the direction of an earlier start. The CIPRA HT 001 randomized clinical trial in Haiti was stopped by the Data Safety Monitoring Board because there were significantly fewer deaths and cases of TB in patients who started HAART earlier between 200 and 350 [44••]. Survival curves show a 47% reduced progression or death in patients receiving immediate as opposed to deferred HAART in ACTG A 1564 [45•]. The SMART trial and more recent work have suggested that starting earlier was superior and found that HIV may be associated with serious non-AIDS-defining events including cardiovascular, renal, and liver disease and non-AIDS malignancies [37,38,46•]. The growing evidence suggests that HIV infection is likely a chronic inflammatory disease process, and provides additional rationale for an earlier start of HAART.

People living with HIV will eventually need HAART and the question is how long to wait until a person is immunocompromised enough to be eligible for treatment. Data from 30 international studies and 16 cohorts of untreated adults found relatively low CD4 cell count levels after HIV infection and a fairly rapid progression to CD4 cell count thresholds such as 500, 350 and 200 [47••]. The time to eligibility was variable and, in some settings, only a few years after HIV infection [47••]. From this perspective and assuming access to HAART, decisions whether to start at 200, 350 or 500 represent a few years earlier in the course of a much longer life span. Guidelines written for wealthier countries recommend starting people earlier before severe immunocompromised and use factors such as CD4 cell count decline, viral replication and discordant couple status as potential eligibility criteria even at higher CD4 cell counts [48]. The recently revised WHO guidelines also advise an earlier start [43••]. Our challenge is to narrow the current treatment gulf that is largely based on available resources.

HIV counseling and testing

Regardless of when people should start HAART, universal access to prevention, care and treatment will require that millions of people with HIV learn their status. Despite considerable efforts to expand access to HIV testing, an estimated 80% of people living with HIV in sub-Saharan Africa do not know their status and 90% do not know their partners' status [2,49]. In Kenya, a leader in improving access for HIV counseling and testing, 57% of people eligible for HAART by Kenyan CD4 cell count criteria have no idea that they have HIV [50••]. However, 92% of those who knew their status and were eligible were on HAART [50••]. HIV counseling and testing itself – particularly when it includes couples counseling – is a remarkably effective prevention intervention [22,51–53]. Community-based efforts, including home-based couples counseling and testing, have considerable promise. In a district in Western Kenya, a private sector company with local nongovernmental organizations, Centers for Disease Control Kenya and the Ministry of Health were able to test 41 040 or 80% of the men and women between 15 and 49 years during a 7-day campaign [54].

Modeling results

Models help us to better understand what we think we know and perhaps most importantly what we need to find out. Our model focused on a generalized HIV epidemic

setting largely driven by heterosexual sex and used data from South Africa, Uganda, Malawi and elsewhere [18••]. It builds on and extends, earlier analyses suggesting that rapid scale-up of conventional HAART approaches could significantly reduce mortality [55] and have a substantial impact on HIV incidence [56,17]. The modeled universal voluntary HIV testing and immediate HAART strategy with combined prevention interventions resulted in a 95% reduction in HIV incidence in 10 years – a reduction from 15 000–20 000 per million population to 1000 per million. The prevalence becomes less than 1% by 2050 [18••]. HAART for all less than 350, as per current WHO recommendations, could save nearly 2.41 million lives, whereas the universal voluntary HIV testing combined prevention approach nearly triples that number to 7.35 million but we are left with a persistent epidemic [18••]. A rough costing for the strategies is considerably less than what UNAIDS projected for universal access to prevention, care and treatment [18••]. Current work includes an in-depth analysis of the economic impact of ART including human rights and campaign program elements and further modeling on the impact of ART on TB, which suggests a potential 60% reduction in incidence (unpublished data).

Modeling 'test and treat' for Washington, District of Columbia, concluded that the strategy could potentially decrease the number of new HIV infections there by as much as 26% over 10 years, and work in San Francisco suggests that incident infections could be reduced by 91% [57••,58••]. Other mathematical modeling studies [57••,58••,59•–61•,62,63•] have reviewed assumptions and examined 'test and treat' in other contexts, but a full discussion is beyond the scope of this article. Models are perhaps most useful when used to examine the potential impact of public health interventions and discuss programmatic targets for maximal impact. Models are sensitive to key assumptions, and when using more pessimistic parameters or a different context, the results are predictably less optimistic [59•–61•,62]. One modeling group using hypothetical assumptions raised the spectre of widespread resistance [62] but actual data from programs providing HAART and population-based threshold studies [64–67,68••] suggest that these claims may not reflect the actual situation. Resistance is of course a serious concern and WHO is working with stakeholders to monitor the situation through the WHO/HIVResNet HIVDR Laboratory Network, which currently includes over 30 laboratories covering the WHO's African, South-East Asia, Western Pacific and the Caribbean Regions [69,70]. Although modeling is important, research studies and field trials will need to examine the key thresholds for program performance raised in the supporting information of the recent *Lancet* paper [18••] and in subsequent articles by the modeling community [57••,58••,59•–61•,62,63•].

Next steps

While expanding HAART to meet universal access targets, there is a need for further scientific evaluation and discussion to define the requirements for public health decision-making on how to best use HAART for prevention and control of HIV/AIDS [17,18••,71••,72]. In November 2009, WHO held two HAART for prevention stakeholders meetings to explore human rights and ethical considerations, clarify research priorities and review feasibility and acceptability issues (the presentations, list of participants and outcomes of the meeting are available at http://www.who.int/hiv/events/artprevention/). WHO and its collaborators are engaged in further modeling on the impact of HAART on TB, the relative importance of drug resistance and other assumptions, the effect of combination PrEP and 'test and treat', effects on PMTCT and an in-depth economic analysis of the various strategies. There are a number of planned field trials and analyses, including ongoing and planned work in Washington, District of Columbia; and the Bronx in New York City [73,74]; Vancouver, British Columbia [75••]; San Francisco, California [28••]; Botswana [76]; and Kwa-Zulu Natal, South Africa [77]. Scientific and community opinion leaders have called for expansion of access to treatment during further research on HAART as prevention [17,71••,77]. Funding opportunities are increasing and more data on this important topic should be available in the near future [17,71••,77].

Conclusion

HIV is an infectious disease, and with the right interventions, it can be controlled and possibly even eliminated. Without a considerable effort to achieve universal access, millions of people will die before accessing HAART. HAART has considerable benefit both as treatment and in prevention and it is likely that it will be increasingly considered as a key element of combination prevention.

Acknowledgements

The opinions and statements in this article are those of the authors and do not represent the official policy, endorsement or views of the WHO.

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 351).

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50 Mohammed I. HIV prevalence and unmet need for HIV testing, care and •• treatment in Kenya: results of a Nationally Representative Survey. CROI 2009. http://www.retroconference.org/2009/Abstracts/36616.htm.
Important early look at Kenya HIV counseling and testing, CD4 and ART coverage among other things. Should produce a number of significant papers and policy decisions. Among HIV-infected married/cohabitating persons, 43.8% had an uninfected partner. Among all HIV-infected persons, 81.3% did not know their current HIV status; 54.4% had never been tested and 26.9% reported being uninfected based on their last test. Among those aware of their status, 74.9% were taking cotrimoxazole and 92.1% were on ART. In Kenya, a minority of people know their HIV status, but when it is known, people do access ART.

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Modeling looking at potential impact of test and treat in District of Columbia, which shows that compared with background screen and ART at 350 cell/μl or less (current standard, bold), annual testing with immediate ART increases HIV^+ life expectancy by 2.8 years and decreases secondary cases by 26% over 10 years.

58 Charlebois E. Effect of expanded ART strategies on the MSM HIV epidemic in •• San Francisco [abstract #996]. 17th Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, USA; 2010. http://www.retroconference.org/2010/Abstracts/39042.htm. [Accessed 13 March 2010]
Modeling looking at potential impact of ART treatment for all adults currently in care at CD4 cell count below 500 cells/μl, ART for all adults in care regardless of CD4 cell count, ART for all adults in care and community-wide annual HIV testing, comparing these strategies to the current practice of ART for CD4 cell count below 350 cells/μl in San Francisco, which showed a percentage reduction in incident infections with the three strategies of 49, 71, and 91% over the first 10 years for strategies, respectively. The number of new infections averted by the three strategies is estimated at 3559, 5153 and 6560 at 10 years.

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60 Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by • 'test and treat' in hyperendemic settings. AIDS 2010; 24:729–735.
Model uses less optimistic adherence assumptions and shows that a test-and-treat intervention that does not reach full implementation or coverage could, perversely, increase long-term ART costs. Interventions that prevent new infections through ART scale-up may hold substantial promise.

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