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How HIV treatment could result in effective prevention

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Abstract

As the number of HIV infections continues to surpass treatment capacity, new HIV prevention strategies are imperative. Beyond individual clinical benefits, by rendering an individual less infectious, expanding access to highly active antiretroviral therapy (HAART) could also have a larger public health impact of curbing new HIV infections. Recent guidelines have moved towards initiating HAART at higher CD4 cell counts, thus increasing the number of individuals in need of treatment. A new treatment strategy is wanting that can simultaneously curb the epidemic and provide necessary treatment to those most in need. A recent debate has centered on whether an expansion of free and universal treatment, regardless of CD4 cell count, could be a means of HIV prevention. In light of the growing access to HAART in resource-limited settings and increasing evidence suggesting the clinical and prevention benefits of initiating treatment at higher CD4 cell counts, it is conceivable that, in the future, HAART will be an integral part of both individual-level clinical treatment programs as well as public health-based HIV prevention interventions.

Keywords

AIDS; antiretrovirals; highly active antiretroviral therapy; HIV; prevention; treatment

Curbing the HIV pandemic through expanded treatment

It has been close to 15 years since highly active antiretroviral therapy (HAART) was first introduced, and AIDS-related hospitalizations and death rates have been substantially reduced in both the developed and developing world as a result [1–3]. Despite findings that HAART decreased morbidity and mortality, the ‘treat early, treat hard’ approach was soon tempered by concerns over regimen complexities, treatment toxicities and the rising costs of continued therapy [4–6]. The recently proposed HIV prevention strategy of ‘universal test and treat,’ which involves frequent testing of entire populations and the prompt initiation of all HIV-infected individuals on HAART regardless of CD4 cell count, should result in decreased HIV transmission by reducing population viral load [7,8]. Today, HAART continues to be made more sustainable, effective and simpler, but the need for treatment on a global scale has grown

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with the continued rise in the number of HIV-infected individuals [9]. Timely initiation of treatment suppresses viremia, increases CD4 cell counts, reduces the risk of drug-resistant viruses, and improves general immune function in what is otherwise a progressive disease [5]. The number of individuals receiving HAART must be put within the larger context of the estimated 33 million individuals who are currently living with HIV [10]. Approximately 3 million individuals were receiving HAART by the end of 2007; an estimated 6.7 million individuals were in need of treatment and an additional 2.7 million became infected with HIV in 2007; although the number in need of treatment would be even greater based on recently updated WHO treatment guidelines recommending treatment initiation at CD4 cell counts of 350 cells/μl or below [10].

The patient-centered approach to HIV management is based on the fact that HAART can change the history of HIV into a manageable chronic medical condition. Beyond individual clinical benefits, by rendering an individual less infectious, treatment could also have the larger public health impact of curbing the growth of the epidemic [7,11,12]. This article examines the population-level impact of HAART in slowing the global HIV pandemic through assessing both the individual and public health benefits derived from the further expansion of therapy. In light of changing treatment guidelines that are moving towards initiating HAART at higher CD4 cell counts, treatment expansion is a two-step process first achieved by assuring treatment access to those individuals who currently meet criteria for HAART initiation and then by determining whether treatment criteria should be liberalized for the larger pool of HIV-infected individuals.

HAART & control of HIV viral replication

Treatment guidelines have been built around the evidence that sustained viral suppression is necessary to achieve a continued increase in CD4 T lymphocytes for an optimal clinical response, and to minimize the development of drug-resistant mutations. The transmission dynamics of HIV-1 through body fluids, including seminal, vaginal, breast milk and blood routes, have been well documented; HAART has been demonstrated to predictably decrease HIV-1 RNA levels in both plasma and genital compartments of treated individuals [13,14]. Perhaps the best evidence of the effect of HAART on HIV transmission comes from the prevention of mother-to-child HIV transmission [15], and the increased availability of HAART in the developed world has dramatically reduced this mode of HIV transmission [16].

Further data on the impact of HAART on HIV transmission have emerged from observational studies of serodiscordant couples. The Rakai study from Uganda demonstrated that plasma viral load is the main predictor of heterosexual HIV transmission, and that transmission is rare when plasma HIV RNA levels are below 1500 copies/ml [17]. No cases of HIV transmission occurred among couples in which the index partner had an HIV RNA level below 400 copies/ml. Another study among serodiscordant heterosexual couples in Thailand reported a dose–response effect between plasma viral load and HIV transmission risk [18]. No cases of HIV transmission occurred below 1100 copies/ml. In the era prior to HAART, an Italian study of serodiscordant couples documented a 50% reduction in HIV transmission attributed to the use of zidovudine monotherapy [19]. In the HAART era, a Spanish study of serodiscordant couples showed no HIV transmission in the sexual partners of HAART-experienced patients, and that HAART was associated with a substantial reduction (80%) in HIV transmission [20]. Recent data from southern Africa have suggested that HAART use is associated with a substantially lower risk of HIV transmission among heterosexual, HIV-serodiscordant couples [21]. Furthermore, it has been recently reported from American and Canadian observational cohorts that reductions in community viral load via increased treatment access could decrease HIV incidence over time, suggesting that widescale early treatment could have a preventive impact at a population level [22,23]. These observational studies among diverse patient populations

have provided further data regarding the immune restorative effects of HAART as well as the role of HAART in decreasing HIV transmission to uninfected individuals. Further prospective data are needed to better understand the relationship between HAART coverage, plasma viral load and HIV incidence. Two randomized clinical trials currently underway, namely HIV Prevention Trials Network (HPTN)052 and HPTN065, will add to our understanding of the impact of long-term HAART use on HIV transmission.

Why treatment could be public health HIV prevention

Increasing evidence suggest that the right combination of treatment and prevention could substantially reduce HIV-associated mortality and morbidity, as well as HIV incidence [24]. Varying social and cultural mores, economic disparities and varying government responses and health-care infrastructures have undoubtedly led to very different rates of HIV infection. The dramatically different course of national HIV epidemics is highlighted by cases from Thailand, Taiwan, Brazil and South Africa. In 1996, Brazil granted free universal access to antiretroviral therapy to all of its HIV-infected citizens, regardless of socioeconomic status, and rates of new HIV infections have since stabilized [25]. Additionally, early in the epidemic the government chose to manufacture generic drugs at reduced costs. Thailand implemented a nationwide prevention effort, including the widespread use of condoms, with a clear government message and later the provision of antiretroviral therapy [26]. By the end of 2004, it was estimated that over 80% of Thai people living with AIDS had access to HAART. An ecological study from Taiwan provided evidence of the dramatic impact of HAART in curbing a regional epidemic and reported a 53% reduction in individuals testing positive for HIV following the availability of free access to HAART [27]. Rates of syphilis, which were used as a marker of sexual risk-taking behavior, remained unchanged.

The different responses that governments have taken towards their respective HIV epidemics have been shaped by wider historical and social inequities. The current HIV epidemic and the government response in South Africa must be considered within the wider paradigm of colonialism, apartheid, migrancy, inequitable social and economic investment, political disenfranchisement, and the structural vulnerabilities faced by women [28–30]. South Africa's early approach was a narrowly constructed prevention-based model, which many speculate may have been at least partially responsible for the early growth of the epidemic throughout the 1990s. South Africa now faces a twofold epidemic: one epidemic that has continued for over a decade and causes over 500,000 new infections per year, while the other epidemic is managing and mitigating the ever-growing AIDS morbidity and mortality [28]. The aforementioned examples highlight that national programs should aim for the optimal mix of both prevention and treatment so that HAART becomes sustainable when rooted within a larger prevention framework.

Different subepidemics: impact of HAART depends on epidemic phase

At best, the provision of therapy remains suboptimal in the developed world. In sub-Saharan Africa, it is estimated that nearly 80% of HIV-infected adults are unaware of their status and more than 90% do not know whether their partners are HIV infected [31]. The question of further liberalizing treatment criteria for HIV prevention in these resource-limited settings must first address how to better meet the burden of HIV-infected patients who meet current criteria for treatment but are still unable to access antiretrovirals [32]. However, the need to link patients to timely care remains a dilemma in the developed world. In Canada, with universal healthcare and ready access to free antiretrovirals, it is estimated that over 50% of Canadians infected with HIV access treatment either too late or not at all [11]. In the USA, it is estimated that over 20% of HIV-infected individuals remain unaware of their infection [33]. Further proactive interventions are needed to identify individuals with HIV and then to initiate them on therapy

in a timely manner, which could have the dual impact of further decreasing HIV-associated morbidity and mortality and decreasing the spread of the virus. The NIH trial HPTN065 is currently assessing the feasibility of an enhanced testing and linkage to care plus treatment initiative at sites in the Bronx, NY, USA, and Washington DC, DC, USA [12].

The acute phase of infection, a window period of approximately 4 weeks postinfection, can be characterized with viral loads exceeding 1 million HIV copies/ml in blood and genital secretions [34], suggesting an elevated risk of transmission. Reasons why individuals with acute infection may start HAART include decreasing viral transmission, limiting viral evolution and resistance risk, establishing a lower viral set point, and preserving HIV-specific immune responses [35]. Phylogenetic analyses from the Quebec Primary HIV Infection cohort suggested a primary role for early-stage infection in transmission [36], and data among monogamous sero-discordant couples from Uganda found a 12-fold increased transmission risk during acute and early infection relative to chronic infection [37]. Current data suggest that although starting treatment during acute infection can lead to viral suppression, after termination of treatment patients who had received therapy had similar CD4 cell counts and viral loads compared with untreated patients [38,39]. Although individuals with acute HIV infection may be particularly likely to transmit HIV, owing to high viral concentrations in relevant bodily fluids and a lack of awareness of their infection, persons with chronic asymptomatic HIV infection are still capable of transmitting infection as the chronic phase lasts years, while acute infection only lasts several weeks.

Mathematical modeling suggests that the more individuals treated at an earlier phase in the natural history of HIV in a given population, the greater the preventive impact of expanded therapy in stopping further infections, ultimately providing both individual and public health benefits [40]. The rate at which an epidemic spreads is closely related to the basic reproductive number, R_0, which is the average number of individuals directly infected by an infectious case when he or she enters a totally susceptible population. The rule is that if R_0, which can be affected by either behavioral or medical interventions, can be reduced to below 1 epidemic eradication becomes a possibility. It is unlikely that an intensive screening and treatment program would eliminate the virus (i.e., an incidence of zero), as infection may continue in small pockets of the population, as some individuals may not be screened or treated, and these individuals could potentially spread the virus [41].

Recent population-level data from Malawi suggest that a substantial reduction in AIDS mortality (overall 10%) was caused by the rapid scale-up of HAART, leading to a decline in overall adult mortality [42]. A simulation model utilizing data from South Africa compared various treatment scenarios and projected HIV-associated mortality with effective HAART, and suggested that a rapid growth scenario of universal treatment by 2011 could result in 1.2 million fewer deaths by 2012 compared with a scenario that maintains the current treatment paradigm [43]. Although the precise number of HIV cases averted that are attributable to HAART remains unclear, the reduction as a result of HAART can be estimated from other studies. Early models did show that the provision of HAART could eradicate high-prevalence epidemics, even with high levels of drug resistance and risky sex [44]. A modeling study from Canada predicted that enrolling at least 75% of individuals clinically eligible for treatment would be associated with substantial reductions in new HIV infections [45]. A recent mathematical model has suggested that the immediate commencement of HAART following detection of all individuals found to be infected through regular annual screening could dramatically reduce HIV incidence to less than one case per 1000 people per year [7]. In fact, in as little as 5 years this strategy could lead to the transition from the present epidemic phase, in which most individuals with HIV are not receiving HAART, to the elimination phase, in which most individuals with HIV are on HAART.

An approach rooted beyond the current concept of individualized treatment based on clinical stage [35] should synergize prevention and treatment through medical intervention for public health outcomes. Such an approach would require the commitment of substantial resources in addition to wide buy-in by multiple groups and governments. Rather than the current treatment approach, where individuals often with advanced immunodeficiency present to care and initiate HAART, a public health approach would require individuals who feel well to be tested for HIV and be initiated on HAART. Although an individual may not necessarily gain any personal benefits from testing and consequent early treatment, they would be benefiting their sexual partners and, by proxy, a larger population [41].

Further liberalization of HAART initiation criteria

The availability of fixed-dose generic therapy, such as lamivudine, stavudine and nevirapine as a single combination for less than US$1 a day, set the stage for the further expansion of HAART across the developing world over the past decade. However, any optimism generated regarding this regimen as a global universal first-line treatment has now been tempered by the realities of stavudine- and nevirapine-associated toxicities [46]. A more promising option is a fixed-dose combination of tenofovir, emtricitabine and efavirenz, which is a simple, safe, and well-tolerated regimen [35,47].

Recent WHO guidelines recommend the initiation of HAART at CD4 counts below 350 cells/μl [48]. Although data from controlled trials are not available to support initiation of HAART at higher CD4 cell counts for both ethical and logistical reasons, analyses from large observational cohort studies from diverse settings has guided our understanding of when to initiate HAART. The CD4 cell count at the time of initiating therapy is the strongest predictor for risk of death and AIDS [49] and initiating HAART at higher CD4 cell counts has been demonstrated to decrease the risk of death, opportunistic infections and non-HIV related comorbidities [50,51]. Observational data from North American and European cohorts have suggested that patients who begin HAART at CD4 cell counts greater than 350 cells/μl have better immunological recovery and normalization of CD4 cell counts longitudinally compared with patients who delay treatment initiation [52–54].

The scale-up of HAART in resource-limited settings was initiated under the recognition that a western model of specialist physician-driven management complemented with advanced laboratory diagnostics would not be a feasible approach [55]. The mechanism to rapidly expand the global provision of HAART has been the WHO ‘3 by 5’ plan, which had the goal of expanding the use of HAART by 3 million HIV-infected individuals by 2005. The WHO strategy was rooted in earlier experience with Directly Observed Treatment Short course (DOTS) for TB, where individual country requirements were taken into account, along with the underlying principles of standardization and simplification of treatment regimens, ensuring programs were rooted in rigorous scientific evidence, in an attempt to make treatment readily accessible to all of those in need [56]. Standardized protocols and decentralized delivery allow for large-scale treatment initiation based on four guiding clinical decisions, namely when to start treatment, when to substitute treatment after toxicity, when to switch treatment after treatment failure and when to stop treatment [55,57]. A demedicalized model neither requires sophisticated laboratory capacity nor does it depend on a labor-intensive physician workforce, two factors that are in dire shortage in resource-limited settings [58,59]. However, disadvantages include the fact that clinical assessment for patient eligibility for HAART is prone to error, dangerous drug-related toxicities can be missed, and virological and immunological failure can be left undetected until clinical failure ensues [32,60]. Despite WHO treatment guidelines, current HAART guidelines often remain country-specific and can vary. For example, South Africa adopted some aspects of the recent WHO guidelines (i.e., for

pregnant women and those coinfected with TB), but rejected other aspects (i.e., treatment initiation at 350 cells/μl).

The questions of when to start, what drugs to use and when to change therapy have become more complicated over time [61]. The expansion of treatment programs in resource-limited settings does have the potential to increase the training and information of providers regarding HAART and HIV care. Regular data collection from patients starting therapy and then who are retained on each regimen can provide the evidence base for future drug procurement by treatment programs [61,62]. International organizations have played a crucial role in the expansion of performance-based funding for HAART programs globally, including the Global Fund to fight AIDS, TB and Malaria (GFATM) and the US President's Emergency Plan For AIDS Relief (PEPFAR) [63]. Treatment programs launched by Medicins Sans Frontieres have confirmed that a public health-rooted approach of generic HAART delivery is feasible and effective in resource-limited settings [64].

There is still considerable debate over what constitutes a public health-driven approach towards HAART delivery [65]. The disheartening reality is that the number of new HIV infections each year remains more than double the number of individuals initiating therapy that year [201]. As treatment guidelines increase the CD4 cell count threshold for treatment initiation [10], a larger pool of HIV-infected individuals will be in need of treatment. Owing to the continued decline in CD4 cell counts in untreated patients, the vast majority of currently HIV-infected individuals will be in need of treatment within the next decade. This means that by 2015 most of the 38 million currently HIV-infected individuals will be HAART eligible based on the revised WHO treatment guidelines. The question then is whether the current strategy for treatment will be sustainable with the continued increase in the number of new HIV cases globally, coupled with increasing donor fatigue and changing global health priorities [66]. If universal access is the ultimate goal, then the current provision of therapy must be viewed as a necessary but short-term emergency response [58]. A major concern is whether the escalating demands for HIV care and treatment in resource-limited settings with already limited healthcare personnel may negatively impact the provision of non-HIV medical care [58,67]. When scaling up HAART, countries must develop the means of negotiating a balance between sustainability of treatment programs and equitable access in light of the need to provide structured, indefinite, chronic HIV care [32].

An alternative strategy that attempts to transcend the current chasm between treatment and prevention would be to hypothetically treat all HIV-infected individuals, regardless of CD4 cell count [7]. Although this approach may appear to be expensive and raises many logistical and ethical questions, it could potentially prove to be cost effective in the long-term because the HAART-induced reduction in infectivity should reduce further transmission, resulting in fewer people needing to access HAART. Even under this scenario, however, there will be a lag period at a population level between reduced transmission and decreased need for HAART [58]. In addition, in a few decades, the current cohort of individuals on HAART would no longer be interacting with populations at risk for HIV owing to age-mixing, which would drastically reduce the likelihood of new infections. Although this approach may not be feasible at this time, it is still worth considering the implications of such a dramatic treatment scale-up scenario.

Although HAART has been demonstrated to be effective in regards to individual patient-centered clinical outcomes [68], an expanded public health perspective would include the impact of HAART on preventing future cases of HIV [69]. Cost–effectiveness studies have demonstrated that the timely provision of HAART can lead to substantial future cost savings through decreasing hospitalization rates and opportunistic infections [70–72], as well as rates of HIV transmission [73]. The economic rationale to act expeditiously is clear as paying up-

front can lead to substantial savings from the detrimental effect of the epidemic on economic growth and development [74]. Although the total costs of providing HAART would increase in the short term based on the universal test-and-treat scenario, the cost of the present strategy would continue to increase whereas the strategy of universal treatment would first plateau and then decrease after a few decades [7]. When HAART is provided free of charge, patients have a higher probability (30%) of viral suppression [75]. Often increased hospital time and health costs are the results of treating opportunistic infections, especially rampant coinfection with TB in the developing world [76]. HAART has been shown to reduce the chance of developing TB among HIV-infected patients by 80% [77], which greatly reduces the likelihood that these patients will require future intensive care as a result of HIV-related opportunism. All of these factors mean that, in the long run, test and treat will be cost effective.

High-risk behavior, drug resistance & HAART

It has often been noted that not all individuals within a given population are equally at risk of HIV infection, and thus the optimal public health benefit from preventing further infections through HAART would be to target individuals most likely to transmit the virus to others [78]. However, such a targeted approach to treatment raises the ethical concern of whether treatment should be prioritized based on the impact of curbing further infections rather than by the individual benefit derived from therapy. At times it has been argued that further access to HAART could lead to increases in high-risk behavior leading to behavioral disinhibition or risk compensation [79]. Early concerns focused on the potential spike in sexual risk behavior with increasing access to treatment, despite individual reductions in viral load [80]. However, the data to date do not suggest increases in sexual risk-taking behaviors among HAART-experienced individuals in both developed and developing world settings [81,82].

Concerns have also been expressed regarding the potential for suboptimal adherence with the increasing roll-out of HAART in resource-limited settings. However, several studies suggest that good adherence can be achieved in these settings [83,84]. Good adherence is essential for successful prolonged viral suppression, and treatment interruptions are an important predictor of acquired drug resistance [85]. The current treatment regimens appear to be ‘more forgiving’ compared with older regimens, and are able to maintain viral load suppression at lower levels of adherence [86,87]. If the timing for treatment was liberalized, patients may potentially have to adhere to therapy when they feel well. Early experience with providing HAART in resource-limited settings suggests that primary care clinics located geographically closer to patients report greater access and adherence than secondary clinics to which patients must travel [55]. Investing in community-based health workers can improve treatment outcomes, through decreasing premature switching to expensive second-line regimens and preventing the emergence of drug-resistant viruses.

Despite concerns over the development of drug resistance caused by the lack of adequate virological monitoring and potential treatment interruptions, recent mathematical modeling shows that expanding treatment access would be associated with only a minimal increase in population drug resistance [44,45]. Further clinical data suggest that transmission from individuals with drug-resistant viral strains to their serodiscordant partners is actually less than that of individuals infected with the wild-type virus [88,89]. As a historical note, between the introduction of zidovudine in 1986 and HAART in 1996, treatment was based on mono or dual nucleoside analog-based therapy, but an epidemic of primary-nucleoside resistant virus never materialized [11]. First-line agents, such as zidovudine, lamivudine, tenofovir and efavirenz, appear to have relatively low levels of resistance and remain effective [90], which may suggest that primary resistance to nucleosides continues to be minimal [91]. In order to promptly detect the emergence of a new, resistant virus, the WHO has formed the Global HIV Drug Resistance Surveillance Network to monitor the development of HIV drug resistance [92]. While

expanding HAART programs should include careful resistance monitoring, the potential for drug resistance should not serve as a barrier to the expansion of treatment programs.

Conclusion: public health impact of HAART for prevention

Researchers have long recognized the potential of HAART in preventing the transmission of HIV. Multiple trials have demonstrated that HAART, when effectively utilized, can dramatically lower the probability of mother-to-child transmission by lowering maternal plasma concentrations of HIV RNA [24]. Additional observational studies have demonstrated that HAART is also effective against occupational exposure and between HIV serodiscordant couples [20,93]. Although it remains a challenge for models to realistically simulate clinical and behavioral realities, they can be used to provide a framework to assess the population-level impact of HAART on mortality and HIV incidence [94].

It is clear that the present treatment strategy is not sustainable in light of the continued number of new infections, and that a new approach that can simultaneously provide necessary treatment to those most in need and at the same time decrease HIV incidence is needed. Despite major logistical and feasibility issues, an expansion of free and universal treatment may be the best option to address both the public health implications of continued HIV incidence and the individual clinical needs of providing treatment to HIV-infected patients [95]. Treatment transforms HIV/AIDS from a disease of advanced immunodeficiency and opportunism into a chronic disease requiring steady life-long clinical follow-up. It has been estimated that since antiretroviral therapy became available in 1989, it has lead to 2.8 million years of life being saved in the USA alone [96]. Although we may know how many individuals are initiating HAART, a much more difficult undertaking will be needed to understand chronic disease management with no clear end point except loss to follow-up or death [55].

Despite the wide utilization of treatment as prevention historically within infectious diseases, many policy makers and researchers have been reluctant to embrace a similar treatment-based strategy to curb the growing HIV epidemic [65]. The development of a HAART-driven strategy to control the pandemic does not mean HAART replaces prevention, but rather becomes an essential part of any treatment and prevention package. The Swiss National AIDS Commission recently unveiled a statement that advised HAART-experienced HIV-infected individuals who adhere to their therapy, have undetectable plasma viral loads and no sexually transmitted infections cannot transmit HIV [97]. Further studies are needed to examine the effect of therapy on HIV prevention. The randomized controlled trial HPTN052 is assessing the impact of HAART on HIV transmission among 1750 discordant couples in eight countries [202].

Despite the increasing availability of fixed-dose generic first-line regimens, second-line regimens continue to be up to ten-times the cost of first-line agents owing to a lack of adequate generic formulations [98]. A question that will also have to be considered is that with a growing number of patients failing first-line HAART and requiring second-line therapy [99], how should the need for second-line HAART be balanced with the unmet need of patients still requiring first-line HAART? The highest cost component of providing treatment for a country remains direct drug costs paid to the manufacturer. Hence, further constructive negotiations between international organizations, governments and pharmaceutical companies are crucial towards reaching the goal of expanded access to HAART [100]. Funding the future of sustainable HAART will require a shared multifaceted approach involving a combination of government revenue, private sector programs, international development assistance and contributions from other private foundations. In the future it is possible that HAART may become part of a wider strategy of HIV biomedical and behavioral prevention, but reaching this goal will require further studies to examine the efficacy of initiating HAART at higher

CD4 cell counts and the impact of HAART on HIV transmission, as well as addressing operational and feasibility issues in the face of limited resources.

Future perspective

As the number of new HIV infections continues to surpass treatment capacity, new HIV prevention strategies become imperative. The clinical approach to HIV management is based on the fact that HAART can change the natural history of HIV into a manageable chronic medical condition. Beyond individual clinical benefits, by rendering an individual less infectious, expanding treatment access could also have a larger public health impact of curbing new HIV infections. Recent global guidelines have moved towards initiating HIV-infected individuals on HAART at higher CD4 cell counts, increasing the number of individuals in need of treatment. The expansion of therapy is a two-step process first achieved by assuring treatment access to those HIV-infected individuals who currently meet treatment criteria to improve clinical status and then by determining whether treatment criteria should be liberalized for the larger pool of HIV-infected individuals to decrease HIV transmission. It is clear that the present treatment strategy is not sustainable owing to the continued number of new infections, in addition to rising costs and dwindling donor commitment. A new approach is needed that can simultaneously curb the epidemic and provide necessary treatment to those most in need. Recent debate has centered on whether an expansion of free and universal treatment regardless of CD4 cell count could be an option to address both the public health implications of continued HIV incidence with the individualized clinical needs of providing treatment to HIV-infected individuals. However, such a universal treatment approach raises many clinical and operational issues regarding feasibility and implementation. In light of growing access to HAART in resource-limited settings and increasing evidence suggesting the clinical and prevention benefits of initiating HIV-infected individuals at higher CD4 cell counts, it is conceivable that in the future HAART will be an integral part of both individual-level clinical treatment programs as well as public health-based HIV prevention interventions.

Executive summary

- Highly active antiretroviral therapy (HAART) has been demonstrated to decrease HIV-1 RNA levels in both plasma and genital compartments of treated HIV-infected individuals. Observational data from HIV serodiscordant couples has provided evidence of the role of HAART in decreasing HIV transmission.
- Increasing evidence, including observational and modeling studies, suggest that expanding HAART access at higher CD4 cell counts could greatly reduce HIV-associated mortality and morbidity as well as HIV incidence.
- Current treatment guidelines have been built around the evidence that sustained viral suppression is necessary to achieve a continued increase in CD4 T lymphocytes and for an optimal clinical response, and to minimize the development of drug-resistant mutations. The predicament of further liberalizing treatment criteria in resource-limited settings to avoid HIV transmission must first address how to better meet the unmet burden of HIV-infected individuals who meet current treatment criteria but who are still unable to access HAART.
- The questions of when to start, what drugs to use, and when to change therapy continue to evolve. The treatment pendulum is swinging towards initiating HIV-infected individuals on HAART at increasingly higher CD4 cell counts. Recent WHO guidelines recommend the initiation of HAART at CD4 counts below 350 cells/μl. Observational data have suggested that patients who begin HAART at higher CD4 cell counts have better immunological recovery and normalization of CD4 cell counts compared with patients who delay treatment initiation.

- Concerns have been expressed regarding the potential for suboptimal adherence, drug resistance and increases in sexual risk behaviors with the increasing roll-out of HAART in resource-limited settings, but studies to date suggest that good adherence, low levels of drug resistance and decreases in sexual risk behavior can be achieved in these settings.
- It has been suggested through mathematical modeling that the more individuals treated with HAART earlier on in the natural history of HIV in a given population, the greater the preventive impact of expanded therapy on stopping further infections, ultimately providing both individual and public health benefits.
- Rather than the current treatment approach where individuals with often advanced immunodeficiency present to care and initiate HAART, a public health approach would require individuals who feel well to be tested for HIV, to access treatment earlier and to be adherent to HAART for longer periods of time.

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