Meeting the immense need for HAART in resource-poor settings

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Keywords: HIV, antiretroviral therapy, developing world

According to recent estimates, 42 million people worldwide suffer from infection with HIV, the causative agent of AIDS. Less than 5% of these live in high-income countries where highly active antiretroviral therapy (HAART) is widely available. Falling prices of antiretroviral drugs and increasing donor support from affluent countries should enable a larger portion of the world’s HIV-infected population to gain access to HAART, but public health organizations are being relatively slow, maybe even hesitant, about its large-scale implementation. This relates primarily to concerns regarding feasibility and sustainability of HAART in resource-poor settings. Clinical opinion leaders start from the underlying assumption that HAART is only effective when it is administered under guidance of laboratory markers. Here, we present the view that laboratory marker guidance might increase the efficiency of HAART, but at the same time slows down access to treatment in countries that lack a clinical and laboratory infrastructure.

Internationally accepted guidelines for the treatment of HIV-infected patients recommend close monitoring of immune system function, of the patient’s viral load and of the virus’s resistance to antiretroviral drugs. The laboratory equipment needed to perform such monitoring on a regular basis is costly, complicated to operate and can hardly be envisioned for widespread application in resource-poor settings. To that one needs to add the investments that would be required for the proper use of these technologies: training of personnel, facilities to draw blood from patients, logistics to ensure transport and storage of blood samples, documentation, etc. These requirements, as defined by standard of care in high-income countries, actually represent a significant obstacle to the use of HAART in countries where clean water and electricity are scarce, and where one in four adults is HIV-infected.

The question that should first be answered is whether knowledge of the virological and immunological status is absolutely needed to give a poor HIV-infected person life-saving treatment. A pioneering project in rural Haiti has demonstrated that HAART can be supplied safely and effectively without relying on any laboratory markers, except for HIV antibody testing. HIV-infected patients are selected to initiate HAART if they have developed severe clinical symptoms of immunodeficiency. Adherence is secured following the model for tuberculosis control, directly observed therapy (DOT), which involves community health workers who visit patients on a daily basis and observe ingestion of pills. Response to HAART is monitored solely on clinical grounds, and the results appear to be excellent: signs of immunodeficiency have disappeared and side effects were rare and readily managed.

It is evident that such a DOT approach to AIDS treatment relies on external funding, an already existing base infrastructure and a successful model programme. It remains to be determined whether this approach is scalable: the opportunities to expand existing programmes to include the distribution, supply and monitoring of antiretrovirals are limited, especially since the tuberculosis epidemic itself is worsening and previously successful treatment programmes have come under pressure. It is also not clear that the best HAART administration programme is a mere modification of existing tuberculosis control programmes, although it makes sense to capitalize on the experience that already exists. Nonetheless, the Haiti experience serves as an example that HAART can, at least on a small scale, be effective in resource-poor settings without laboratory marker monitoring. This calls for close examination of the relevance of Western antiretroviral treatment guidelines to developing countries.

As a first step in this direction, the WHO has issued guidelines for the treatment of HIV-infected adults in resource-poor settings that differ markedly from guidelines developed for use in high-income countries. In their recommendations, all patients with manifest AIDS should receive HAART. For those who present with asymptomatic HIV infection, an assessment of immune system function is considered indispensable to monitor the progression of HIV infection and decide on the initiation of HAART. CD4 cell count is recommended as the preferred marker of choice, and it is suggested that treatment is best initiated when the CD4 count is <200 cells/mm³. Assessment of virological status is currently not considered an essential prerequisite for treatment initiation, nor is it essential for treatment monitoring. Success of treatment is reflected in a significant rise of CD4 cell count and disappearance of clinical symptoms when AIDS was diagnosed.

That patients with manifest AIDS should receive HAART is obvious, but how does treatment of asymptomatic individuals, e.g. based on CD4 cell counts, contribute to the well-being of HIV-infected individuals in high-income countries?
infected individuals and the society affected by AIDS? To lower the burden of AIDS in poor societies, it is important to prevent clinical symptoms of immunodeficiency rather than to cure disease. Treatment of asymptomatic individuals will lower the number of patients who present with manifest disease, reduce hospitalization rates, reduce demand for treatment of opportunistic infections and reduce transmission of HIV via its suppressive effect on viral load. Ultimately, a strategy that incorporates treatment of asymptomatic individuals will result in a stronger reduction of AIDS-related morbidity and mortality, a stronger improvement in life expectancy, a higher gain in disease-free person years and a larger economic benefit from HAART compared with a strategy that only takes care of those already ill.

If HAART should not be restricted to those who present with manifest AIDS, the simplest way to prevent AIDS is to supply treatment to all HIV-infected patients, irrespective of disease status. Of course, the costs in terms of antiretrovirals would be huge, but the requirements for laboratory procedures and associated infrastructure would be minimal: only HIV antibody testing would be required, and this can be done with a dipstick assay using saliva or urine. Moreover, the two-fold effect of HAART (prevention of disease and reduction of transmission) would be most welcome in communities with high incidence rates of HIV infection. The vast majority of the estimated 5 million infections over 2002 did occur in poor societies: 3.5 million in sub-Saharan Africa alone.

Nonetheless, where feasible, HAART should be supplied more selectively, depending on existing clinical and laboratory infrastructures. This can be motivated by considerations of treatment efficiency. For example, one could consider an infectious disease clinic in a developing country, where HIV-infected patients tend to present in advanced stages of infection. We have calculated that if two out of three patients present with <200 CD4 cells/mm³, two out of three AIDS-related disease events could be prevented within 1 year if HAART were supplied to only those patients presenting with <200 CD4 cells/mm³. Supplying HAART to all HIV-infected patients would prevent five out of seven AIDS-related disease events within 1 year. Initiating HAART when patients have >200 CD4 cells/mm³ thus has a marginal effect on the AIDS incidence in a hospital-based setting in a developing country, while requiring a substantially higher HAART administration rate. An assessment of infection status that goes one step beyond antibody testing would make informed treatment decisions possible and contribute to efficient use of limited resources. Also, restricted HAART supply is more manageable in terms of the amount of assistance that can be given to each patient, thereby reducing the risk of poor adherence.

The cost reduction in antiretrovirals with a restricted HAART supply must be balanced against the need for extra testing, which requires laboratory infrastructure and trained personnel. Several concerted efforts have been initiated to develop and deliver affordable alternatives to the current technologies used for monitoring HIV infection. Perhaps the most promising alternative to flow cytometry for CD4 cell counting is based on automated immunocapturing methods using microchips and optical image analysis. This allows for CD4 cell counting from whole blood using a portable device, and would reduce the cost of a single test to a few dollars. An even simpler alternative would be to qualitatively test for the presence of HIV p24 antigen in whole blood. HIV antigenemia was commonly used in the Western world to monitor HIV infection in the early days of antiretroviral treatment, and positive p24 serostatus appeared to be a highly specific predictor of AIDS. We compared the diagnostic value of CD4 cell count and p24 serostatus in predicting the onset of AIDS in the absence of antiretroviral therapy. In relatively early diagnosis of HIV infection, positive p24 serostatus has a diagnostic value similar to CD4 count <200 cells/mm³. In late diagnosis, positive p24 serostatus has a predictive value equal to CD4 count <350 cells/mm³, but a much lower sensitivity (J. A. Bogaards, G. J. Weverling, A. H. Zwinderman, P. M. Bossuyt & J. Goudsmit, unpublished results). If the sensitivity of p24 testing could be increased, e.g. by prior immune complex dissociation, p24 seroassays could perhaps be used instead of CD4 lymphocyte methods to discriminate between HIV-infected individuals at high and low risk of developing AIDS in resource-poor settings. HIV antigen can easily be combined with HIV antibody testing, and could in principle allow for low cost, point-of-care diagnostics.

Whether more sophisticated technology is useful and desirable is partly determined by the frequency and scope of the monitoring of HIV-infected persons, both prior to and after initiation of therapy, and by the particular treatment setting that is addressed. For example, treatment on the basis of combined CD4 count and plasma RNA criteria increases the efficiency of HAART, but only if patients are identified in the relatively early stages of HIV infection. In a setting where patients at risk for AIDS predominantly present in advanced stages of infection, treatment on the basis of CD4 count is expected to give a similar reduction of the AIDS incidence at a particular HAART administration rate as treatment on the basis of plasma RNA or combined eligibility criteria (J. A. Bogaards, G. J. Weverling, A. H. Zwinderman, P. M. Bossuyt & J. Goudsmit, unpublished results).

If we recognize that the prime goal of the global fight against AIDS should be rapid mass access to HAART in communities hardest hit by HIV, a rational development of antiretroviral treatment guidelines is needed that takes into account the infrastructure and the financial and healthcare resources of a country. In accordance with improvement of infrastructure, monitoring could be carried out more accurately. We propose a three-tier scheme for HAART administration programmes in the public sector (Table 1).

In high-income countries (e.g. Western Europe, North America), adult prevalence of HIV infection is generally low (<1%) and HIV spreads predominantly in well defined high-risk groups. In these countries, HIV is generally diagnosed in early stages of infection because of the elaborate healthcare systems that are already well established. Treatment decisions are taken in close consideration between a patient and the physician, and are based on an assessment of short-term disease progression and the patient’s willingness to initiate and adhere to a demanding therapy. The costs of HIV treatment are high, but can be covered by health insurance and the wealth of the individual patients.

In middle-income countries (e.g. former Soviet Union, South America), adult prevalence of HIV infection is still low (<1%), but incidence rates are often high, raising the alarming possibility of HIV spread to the general population. These countries have existing infrastructures and some form of health insurance, which can be used for implementation of HIV treatment programmes. In these settings, active case-finding of recently infected individuals is important for early diagnosis of infection and reduction of transmission. Limited monitoring of HIV infection would in any case require an assessment of CD4 cell count, and viral load measurement, if affordable, is recommended to achieve an efficient supply of HAART. Potential development of antiretroviral drug resistance should be monitored on a population level, because close monitoring of each patient individually is too costly. The rapidly rising prevalence of HIV infection warrants good surveillance before the epidemic reaches an unmanageable scale in these countries.
Finally, in low-income countries, the state of the epidemic should
determine the type of HAART administration programme that is to
be installed in the public sector. If adult prevalence is stably low and
incidence rates do not suggest an exploding epidemic (e.g. North
Africa, Middle East), HAART administration programmes can be
hospital-based and HIV monitoring could be limited to assessment of
HIV antibody status and HIV antigenaemia, if the sensitivity of p24
testing can be increased, or else CD4 cell count, if affordable methods
for lymphocyte testing become available, in order to introduce efficient
HAART eligibility criteria. On the other hand, if adult prevalence is high
and/or HIV spreads rapidly through the general popu-
lace (e.g. sub-Saharan Africa, India), HAART administration
programmes should be community-based, seeking active involve-
ment of the people and early diagnosis of HIV infection. Monitoring
would not require more than HIV antibody testing, and community
health workers could be trained to ensure treatment adherence. In
order to facilitate the resulting large-scale demand for HAART,
sensitive HIV antigen tests could be used to discriminate between
individuals at high and at low risk of short-term disease progression.
Low-cost drugs, either trademark or generic, should be supplied
through support from governments and industries of high-income
countries. Drug resistance surveillance systems should be set up in
collaboration with the global HIV drug resistance surveillance
network, an initiative by the WHO and partner organizations. 7
HAART policies can be optimized when proper healthcare systems,
including laboratory infrastructure and insurance schemes, are
installed.

Temporary unrestricted HAART supply to HIV-infected people
in resource-poor settings perhaps seems grandiose in light of the vast
numbers of individuals that would be eligible for HAART, but it
could well be more cost-effective compared with selective HAART
supply—it certainly requires less time to install such a programme.
Safety and adherence are serious issues and must not be overlooked,
but must not be overstressed either. If one-quarter of a country’s adult
population is expected to be dead in 10 years time, safety really seems
a luxury issue. Perhaps the fear of the Western world of being con-
fronted with transmission of drug-resistant HIV plays too large a role.
Whether these concerns could be overcome if triple-drug therapy is
concurrently introduced in developing countries remains to be seen,
but it seems inconceivable to let people die of AIDS because of pre-
conceived risks and side effects of treatment.

By the end of 2001, an estimated 500000 people worldwide
received antiretroviral therapy, almost exclusively in high-income
countries. Over 2002, an estimated 3.1 million people died of AIDS,
almost all in resource-poor countries. The fast spread of HIV in the
developing world warrants new treatment goals and innovative
methods to achieve them. If 15000 people a day initiated HAART,
we would just keep pace with the number of new infections that occur
every day. 8 But we should do much better than that, if we are to with-
stand the deadliest pandemic since the Black Death in the late Medie-
val ages.

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