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EDITORIAL REVIEW

Highly active antiretroviral treatment in countries with very limited resources: do we have cheaper alternatives?

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Introduction

Since the introduction of highly active antiretroviral treatment (HAART) in 1996, a lot of progress has been made in the treatment of HIV infection and the AIDS-related mortality has dramatically decreased[1] in developed countries. In contrast, in most of the developing countries, where over 90% of the persons infected with HIV live, these treatments are not available to a large majority. Several obstacles make management of HIV infection in developing nations very challenging, e.g. low resources, insufficient healthcare infrastructures (clinics and hospitals), shortage of trained personnel and laboratory capacity, unreliable clean water and electricity supply, and insufficient political will of governments to see this crisis as a national priority. One obstacle that can be influenced by the international community is the availability of funds to allow developing countries better access to antiretroviral medication. Discussions between national governments, multilateral organizations such as UNAIDS, and various private groups are ongoing, but are making slow progress. The Global Fund to Fight AIDS, Tuberculosis and Malaria has so far managed to collect only a fraction of the projected $10 billion annual need. Although some generic antiretroviral combinations are available at $350 per person per year, a further reduction in price to $50 per year would make treatment affordable in many more countries[2]. One strategy is to continue to fight for price reductions and mobilization of international funds. Another strategy is to identify effective alternatives to these relatively expensive HAART regimens we are using today. This paper explores some of these alternatives.

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Structured treatment interruptions (STI)

STI is the planned cyclic interruption of all antiretroviral drugs followed by a resumption of the treatment at regular intervals[3]. The cost of antiretroviral therapy through STI is reduced, as the total amount of medication consumed is less. Many patients appreciate the relief from the inconvenience of taking antiretroviral medication every day and the associated reduction in potential side effects. Other arguments for STI include a possible increased HIV-specific immune response[4], which is currently under study in several trials, and an increase in adherence to treatment due to shorter treatment periods, although this still needs confirmation.

A randomized clinical trial by Lori *et al.*[5] comparing STI (three weeks on and three weeks off treatment) to continuous treatment showed no significant differences in plasma viral load or CD4+ lymphocyte count between these two treatment strategies at 36 weeks. Viral load rebounded in the STI group at each therapy interruption, in most cases similar to the level seen at baseline, and control of the viral replication was achieved with reintroduction of therapy. At the end of 36 weeks when treatment was discontinued for all study participants, plasma HIV1 RNA rebounded to similar levels for patients in both the STI arm and the continuous treatment arm.

Selection of HIV-1 resistant mutants[6] and cases of treatment failure[7] during STI have been described. Non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing HAART regimens are probably less good candidates for STI because NNRTIs have a much longer half-life than the nucleoside reverse transcriptase inhibitors (NRTIs). This difference in half-life could facilitate resistance. Additionally, during the interruption periods a higher transmission rate of HIV may be seen in absence of safe sex practices due to rebound of the HIV viral load.

Current HIV treatment guidelines do not recommend STI[8,9] but more randomized clinical trials are under way. A large multicentre study, called the Strategies for Management of AntiRetroviral Therapy (SMART) study, is being conducted in the US and Australia, and compares continuous HAART guided by viral load results with STI (HAART treatment deferral till CD4+ lymphocyte count drops below 250×10^9/L and discontinuation of HAART when the CD4+ lymphocyte count rebounds over 350×10^9/L regardless of viral load levels) (www.smart-trial.org). A similar study is being conducted in Abidjan, Ivory Coast. Results from these studies will help define the place of the STI strategy in the treatment of HIV.

HAART only during the acute HIV infection

It has been suggested that starting HAART at the time of acute HIV infection could improve the prognosis[10–14]. What has not been studied, but would be worth knowing, is whether a limited period of HAART initiated at the time of seroconversion and stopped after six to 12 months, delays disease progression. To study this, one would need to improve the ability to diagnose acute HIV infection. Symptoms associated with acute HIV infection are non-specific, if present at all, and many other diseases such as malaria, dengue and many other viral infections present with similar clinical manifestations in tropical areas. Despite new laboratory tools to diagnose acute HIV infection[15–16] only a small number of new infections are diagnosed at that time. Neonates are an exception, as the majority of the vertical transmissions occur in the perinatal period. At present, treatment guidelines in developed countries recommend initiating antiretroviral therapy in all HIV infected infants age <12 months at the time of diagnosis, regardless of clinical of immunological status or viral load[16]. On the other hand, according to the recently published WHO treatment guidelines, '*Scaling up antiretroviral therapy in resource limited settings*', HAART is only recommended in symptomatic children with WHO paediatric stage III or with CD4+ lymphocyte count $<20\%$[17]. A randomized trial comparing different short-term HAART regimens for the treatment of acute neonatal HIV infection as a strategy to defer the onset of clinical AIDS in children in resource-limited countries could be considered.

Induction–maintenance regimens

This strategy consists of using a highly potent HAART combination at initiation, followed by a less toxic but maybe less potent maintenance combination. This approach is current practice in the treatment of tuberculosis and cancer. Could this work in the treatment of HIV? A sustained suppression of viral replication was not observed[18–19] in a small number of trials. However, the efficacy of this strategy may improve with more potent initial regimens. The cost-saving potential of these regimens is obvious[20].

Delay the start of HAART

The optimal time to start HAART is not known as no clinical trials have addressed this issue[21–22]. The emphasis on the use of HAART has shifted from 'hit hard, hit early' to 'hit hard, but only when necessary'[8]. The international recommendations to start HAART are now more conservative and recent cohort studies suggest that the start of HAART can be delayed until the CD4+ lymphocyte counts drop below 200×10^9/L[23]. The above-named SMART trial will review outcome of the conservative initiation of therapy, but results will not be available for several more years.

Use of less expensive drugs in the antiretroviral treatment regimen

1 *Hydroxyurea*

Hydroxyurea (HU) does not have direct antiretroviral activity, but inhibits cellular ribonucleotide reductase, resulting in decreased intracellular deoxynucleoside triphosphates that are required for DNA synthesis[24]. *In vitro* studies have shown that HU is synergistic with didanosine[5] and that HU reduces the viral load. However, this is a cytostatic agent that reduces the CD4+ lymphocyte count[5], and can increase the toxicity of didanosine leading to a higher incidence of peripheral neuropathy and pancreatitis[25]. HU should not be used in pregnant women or women who may become pregnant. Randomized clinical trials have not demonstrated a clear clinical benefit of the use of HU. One randomized trial (the ACT65025 study) was prematurely stopped due to higher rates of drug toxicity in the HU arm, including three deaths due to pancreatitis[26]. Based on these studies, use of HU should not be advocated.

2 *Chloroquine*

Chloroquine inhibits HIV replication *in vitro*[27–28] and exerts an additive anti-HIV effect when combined with didanosine and HU[28]. Chloroquine has a direct inhibitory effect on HIV-1 replication in human lymphocytes with an EC_{50} of 15 μM, which approximates the chloroquine plasma concentration generated in the treatment of acute malaria[29]. In order to achieve this *in vivo*, high doses of chloroquine would have to be given continuously with concerns for toxicity in addition to the known immunosuppressive effect[30] of the product. The appeal of cloroquine is that it is very cheap, easily available in developing countries, not stigmatizing and it has an inhibitory effect on several opportunistic pathogens *in vitro*. Chloroquine limits the deposition of iron in the reticulo-endothelial system,

leading to a reduction of excessive iron; tissue iron accumulation may have a negative effect on HIV infections[31–32]. Plasma HIV viral load increases during malaria infection and decreases during treatment with anti-malaria medication[33]. In HIV-infected pregnant women, chloroquine may be beneficial as it has been shown that HIV diminishes a pregnant woman's capacity to control *Plasmodium falciparum* parasitaemia[34]. In most tropical countries chloroquine is recommended as prophylaxis against malaria in pregnancy, but this prophylaxis seems less effective in HIV-infected women[35]. Studies are needed to evaluate if a further reduction of the vertical perinatal transmission rate of HIV can be obtained by adding chloroquine to an antiretroviral treatment combination. Use of chloroquine by breast-feeding women reduces the HIV viral load present in the breast milk[36], so the benefit of the use of chloroquine on reducing vertical transmission through breast-feeding should also be evaluated. A further increase of chloroquine-resistant plasmodia species is, however, a valid concern. The combination of HU 500 mg, hydroxychloroquine 200 mg, and didanosine 125–200 mg, twice daily was recently studied in a small group of patients in Singapore[37]. The mean reduction in viral load was 1.3-log10 copies/mL and the mean CD4+ lymphocyte count was maintained (percentage increase 2.9%). The interpretation of these results is, however, difficult because the didanosine by itself may increase the CD4+ lymphocyte count. Therefore didanosine+HU+chloroquine should not be considered as a safe alternative for HAART.

3 *Boosting antiretrovirals by less expensive drugs*
Use of inexpensive booster drugs can reduce the overall cost of a treatment regimen. Allopurinol increases didanosine levels[38]. Ketoconazole increases indinavir levels with 68%[39] allowing for a reduction of indinavir doses to 600 mg three times a day. Continuous ketoconazole treatment may protect against fungal infections but also could lead to resistance of these infections against azoles[40]. Further exploration of use of these and other booster drugs is useful.

Other approaches

1 *Combining antiretrovirals with immune therapy*
Combination of one of the modified HAART strategies, discussed above, with immune therapy may reduce toxicity and may preserve or enhance efficacy, particularly if used at the time of acute HIV infection[41–42]. Several immune therapies have been investigated, including vaccination with HIV antigens[41], use of interleukin-2[43–44], cyclosporin A[42], and mycophenolic acid[45]. Mycophenolic acid was shown to increase the *in vitro* antiviral activity of abacavir[45]. These immune therapies are generally still quite expensive and clinical trials have been disappointing, making this a less interesting option at this time.

2 *Reducing immune activation*
Replication of HIV in CD4+ T-cells is dependent on cellular activation. There is now evidence that immune activation by pathogens and pathogen-derived products leads to increased HIV replication[46] and this could lead to HIV disease progression if the activation is chronic (as with chronic infections). For instance, chronic helminthic infections cause a Th2 type immune activation that favours HIV progression[47]. Therefore, the treatment of these helminthic infections may decrease progression rates. While this is, strictly speaking, not HAART, more clinical trials are needed to evaluate to what degree multi-drug chemoprophylaxis including co-trimoxazole, isoniazid, antifungal therapy, antiparasitic treatment and chloroquine could improve survival[48].

Ethical considerations

The cause of the unavailability of HAART in developing countries is multifactorial. The implementation on a large scale of the same treatment strategies in developing and developed countries in the near future seems unlikely, especially when we think of second line regimens containing ritonavir-enhanced protease inhibitors and salvage regimens after multiple treatment failures. Some alternatives discussed in this paper may appear less efficacious than current strategies generally in use, but could be very valuable in regions where HAART is simply not available due to its cost. Ethical concerns about less efficacious therapy are certainly valid, but are of little solace to the many succumbing to AIDS without any access to therapy at all. The argument made is not in favour of substandard therapy, but is clearly in favour of improving access to HIV therapy that may not be as potent, but that is sufficiently efficacious to beat the current reality of no therapy at all. More clinical trials that are ethically acceptable to both local and international standards[49] should be conducted in research centres in developing regions.

Conclusions

There is a need to improve access to HAART in resource-limited countries where the bulk of the HIV infected people live. One strategy can be clinical trials looking at the efficacy of lower cost HAART regimens. For the moment there are no cheap alternatives to HAART with proven efficacy that could be used safely in resource-limited settings. Therefore, if we want HAART to become affordable beyond the current generic first line regimens, there is an urgent need for cheap boosted protease-inhibitor regimens.

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