Antiretroviral therapy in sub-Saharan Africa: myth or reality?

Anthony Kebba*

Medical Research Council Programme on AIDS in Uganda, Uganda Virus Research Institute, Entebbe, Uganda and Department of Immunology, Imperial College London, Chelsea & Westminster Hospital, 369 Fulham Road, London SW10 9NH, UK

Keywords: HIV-1, antiretroviral therapy, Uganda

Introduction

Antiretroviral therapy (ART) in the management of HIV-1 infection is associated with significant reductions in morbidity and mortality.1 Until recently, access to such life-saving therapy in sub-Saharan Africa, a region that bears 70% of the HIV-1 burden,2 has been severely limited. Thanks to the intervention of various individuals, organizations and governments and the resulting price reductions, ART is becoming a possibility for increasing numbers of AIDS patients.

However, many issues remain to be resolved, some real and others myths. When is it appropriate to initiate ART and with which drugs? Are the drugs available at a reasonable price? Should monitoring follow the same approach as in the developed world or should Africa develop its own monitoring protocols? Is ART equally efficacious against non-B subtypes that predominate in Africa? How will the management of opportunistic infections (OIs) be addressed? How should adherence and the associated non-structured treatment interruptions be dealt with? Perhaps the most important question concerns the under-resourced health sector: will it be able to deliver and regulate access to ART and will this divert attention from other important healthy priorities like malaria?

It is, however, not realistic to expect or demand that all requirements be fulfilled before access initiatives are implemented. Much has been learned about ART from the experiences in treatment centres like the Joint Clinical Research Centre (JCRC) in Kampala, Uganda, and reinforced during the UNAIDS Drug Access Initiative (DAI). ART in Africa is now a reality. This personal perspective attempts to review the current situation and anticipate future directions.

Health infrastructures and ART in Africa

There are concerns about existing health infrastructure in sub-Saharan Africa and its capacity to ensure sustainable distribution and proper use of antiretroviral drugs. Giving legitimacy to these concerns is the fact that essential antibiotics and antimalarials are often not available in smaller health facilities, and that regulation of their use is somewhat lax. Treatment access programmes will have to determine at what level within the health system ART should be made available.

Pilot programmes like the UNAIDS DAI demonstrated that by strengthening existing facilities, an effective central system for drug procurement, distribution and accountability could be implemented and ensure an uninterrupted supply of drugs to support sustainable management of AIDS patients. It is thus likely that in the implementation phase, expanded access to ART in sub-Saharan Africa will start with utilizing and strengthening existing central health infrastructures. However, because provision of ART on an expanded scale involves more than distributing antiretroviral drugs, other health infrastructure requirements will need to be addressed. These are likely to include reviewing best practices, developing standard operating procedures for all components involved, establishing quality assurance programmes, training of health care personnel and planning for staff retention, and renovating physical structures. Of paramount importance will be the need to strengthen drug control mechanisms so as to provide a means of supervision, especially for the informal sector. Although an emotive issue, there will eventually be a need to control unregulated access to antiretroviral drugs and discourage practices such as making antiretroviral drugs available ‘on the street’ and the selling to patients of single pills, even without prescription.

When to start ART and with what first-line regimen?

Does ART work in Africans?

The issue of when to initiate ART is especially relevant in resource-limited settings to avoid wastage of already scarce resources. Long-term toxicity and efficacy also need to be considered. A decision on initiation of therapy is often clear-cut since the majority of patients seek ART with advanced disease.3,4 Of the ~500 HIV-1-infected patients presenting for their first time each year at the JCRC, 57% have baseline CD4+ T cell counts <200 cells/mm3 and plasma viral load (VL) >105 copies/mL. Sixty per cent have either a past history of, or an active, OI and are WHO stage II, III or IV (A. Kebba, unpublished observations). Decisions to initiate ART are, however, complicated by the fact that patients incur all costs. Thus decisions are not based solely on clinical grounds, but also on economic considerations. Not uncommonly, already advanced patients have opted to delay initiation of ART, a dilemma treatment-access programmes will encounter.

*Correspondence address. Medical Research Council Programme on AIDS in Uganda, Uganda Virus Research Institute, PO Box 49, Entebbe, Uganda. E-mail: anthony.kebba@mrcuganda.mimcom.net

DOI: 10.1093/jac/dkg453
Advance Access publication 16 October 2003

JAC vol.52 no.5 © The British Society for Antimicrobial Chemotherapy 2003; all rights reserved.
In those who initiate ART, choice of the first-line regimen is mainly governed by cost. This partly explains the significant shifts in treatment practices in Uganda following the introduction of non-nucleoside reverse transcriptase inhibitors (NNRTIs), which, in combination with two NRTIs, are less costly than either triple nucleosides or two NRTIs plus protease inhibitors. To date, the leading antiretroviral regimen prescribed (nevirapine, lamivudine and stavudine, dispensed as the generic Trionum) is also the cheapest (I. Takwuba, personal communication). Approximately 11% of patients develop pulmonary tuberculosis during the first 12 weeks of ART (A. Keba, unpublished observations) and would require switching or stopping therapy shortly afterwards to avoid potential drug interactions. Importantly, the choice of first-line antiretroviral regimen may significantly influence all subsequent ART. Countries scaling up access to ART should therefore adopt an approach that rationally sequences antiretroviral drugs in order to preserve future treatment options for as long as possible, but again cost will often compromise this recommendation.3,4

Concerns also exist as to the efficacy of ART against Africa’s predominantly non-B HIV-1 subtypes, particularly subtype D.5 ART has not been carefully evaluated against these subtypes. A retrospective analysis showed that 80% of antiretroviral-drug-naive HIV-1-infected Ugandans initiated on zidovudine, 3TC and efavirenz at the JCRC achieved and maintained optimal virological suppression associated with significant quantitative immunological reconstitution.6 The ‘Lazarus’-like improvement in clinical condition is also observed. This suggests that subtypes A and D, which predominate in HIV-1-infected Africans,7 are susceptible to ART. ART does work in HIV-1-infected African patients.

Unfortunately, between 6% and 11% of patients are antiretroviral-drug experienced, usually in an unsupervised and irregular manner, prior to their first visit to a treatment centre (A. Keba, unpublished observations). This figure will rise, because price reductions of antiretroviral agents will inevitably increase uncontrolled access. This carries with it the risk of drug resistance, which will have an impact on therapeutic responses to ART in the future.

Monitoring ART amidst limited resources

The need to monitor CD4+ T cell counts, VL and toxicity during ART is obvious, but because of cost, monitoring in sub-Saharan Africa will generally be infrequent or even non-existent as patients give preference to procuring medication. Monitoring schedules will probably differ from those in the developed world. It is postulated that in the majority of cases, clinical criteria with or without the measurement of immunological parameters such as CD4+ T cell counts and/or lymphocyte counts will be employed to monitor ART. However, changes in clinical parameters indicating treatment failure occur much later, after virological and immunological failure. Intervention in such situations may be late. Cheaper monitoring is being developed but will not be available outside of the major urban areas for some time. Treatment-access programmes will need to strengthen existing laboratories or even build new ones, train technicians and ensure quality control.

Ironically, monitoring schedules used in the ‘Western’ world may be best suited for Africa, considering the following behaviours that are said to be typical: patients interrupt therapy in a haphazard way, reduce dosages or change administration schedules because of lack of funds to maintain a steady supply of medications; they switch regimen when prices of antiretroviral drugs change or drug stocks run out; and many also take herbal preparations the content and interaction with antiretroviral agents of which is largely unknown. These would affect adherence and bioavailability of antiretroviral drugs and compromise achieving optimal virological outcomes. Complete and sustained virological suppression are of great importance for clinical success.8–10

Patient adherence to ART amidst limited resources

Treatment interruptions because of drug intolerance, pulmonary tuberculosis, surgery or other reasons are not uncommon in routine clinical practice at the JCRC; it is the chaotic interruptions because of financial constraints that are of concern. In such circumstances, an attractive option is to structure interruptions. This approach is appealing because the duration of drug exposure, risk of long-term adverse events and especially financial burden are reduced, and this can potentially improve adherence during the treatment phase. Adherence correlates with optimal virological suppression,11 so given the inevitability of treatment interruptions in sub-Saharan Africa, there is an urgent need to evaluate structured treatment interruptions (STIs).

However, caution needs to be exercised. STI should be avoided when ART is unsuccessful, which is likely in advanced patients in whom immune reconstitution may not occur despite optimal virological suppression.12–14 STI requires that patients are under careful medical supervision, and their VL and CD4+ T cell counts regularly monitored, which is costly. Caution is also required when dealing with antiretroviral drugs that have long half lives. Although earlier studies had suggested that STI does not reduce overall efficacy of ART,15,16 it can still delay reduction of VL and increase in CD4+ T cell counts on re-initiation. Furthermore, STI may have immunological consequences.17–19 It is appropriate to mention here that STIs are unlikely to result in enhanced immune control of virus in chronically infected Africans. Lastly, the optimistic view that no drug selection would be applied if interruptions were carried out safely has been brought into question by studies in which the emergence of resistance mutations occurred in closely monitored patients.20 Notwithstanding these concerns, treatment interruptions are inevitable for a substantial number of patients given the existing financial constraints in sub-Saharan Africa. If current conditions remain, STIs will be inevitable in order to make interruptions ‘safer’.

What does the future hold?

Although primary HIV-1 prevention strategies have yielded success in countries like Uganda, in this country and the rest of sub-Saharan Africa, people continue to become infected with HIV-1. Prophylactic HIV-1 vaccines are not going to be available for many years, and in any case these will not address the plight of the large numbers already infected. Although reservations exist as to introducing ART in Africa’s current circumstances, these fail to recognize the reality that antiretroviral drugs are already available in many African countries, ART works in African AIDS patients, cost is forcing patients to interrupt treatments in a non-structured way, and that, in time, Africa will be one of the biggest users of antiretroviral drugs. There is optimism, and some evidence to the effect, that by strengthening central health infrastructures, ART can be provided in a sustainable manner to increasing numbers of AIDS patients in Africa. Acceptably, much may be required to ensure its regulated and proper use.
Acknowledgements

I would especially like to thank Dr Robert Downing for help in preparing and critically reading the manuscript. His comments and support were invaluable.

References