

Viewpoint

Antiretroviral treatment in resource-poor settings: clinical research priorities

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The introduction of highly active antiretroviral treatment transformed the AIDS epidemic. In populations with access to these drugs, death rates have plummeted. Until recently, routine use of antiretroviral treatment in regions with few resources such as sub-Saharan Africa was thought to be technically and economically impossible. The world, however, is changing. Regimens that are easier to implement are also highly effective, the cost of some antiretroviral regimens has dropped by 85%,¹ and new resources have become available.² Although expense, feasibility, and effective delivery remain formidable barriers, public health and technical agencies have started to re-examine their assumptions and to discuss use of antiretroviral drugs in poorly resourced environments.³

Data lending support to use of antiretroviral treatment in poorly resourced regions are few. Even in well resourced countries, clinicians still do not have evidence-based answers to simple issues such as: when to start antiretrovirals, how to monitor their therapeutic and toxic effects, and in what sequence to use them. Answers to such issues are greatly needed to speed up delivery of antiretrovirals to the populations most in need of treatment. As a working group convened by the Rockefeller Foundation, we outline an urgent research agenda that attempts to identify gaps in knowledge and to prioritise issues affecting access to treatment for the tens of millions of adults living with HIV/AIDS in poorly resourced regions. Answers to many of these questions will also benefit patients in well resourced regions. We do not address the equally important issues about use of antiretrovirals in infants and children and of prevention of mother-to-child transmission.

When should antiretroviral treatment be started?

Use of antiretroviral treatment is straightforward in adults with symptomatic HIV-1 disease or CD4+ counts of 200 or less,⁴⁻⁶ but whether asymptomatic adults with more than 200 CD4+ cells/mm³ should also begin treatment is unclear.⁷⁻⁹ Guidelines vary, but the pendulum is swinging

away from very early treatment towards a more cautious strategy of deferred therapy.^{10,11} This shift has been fuelled by the desire to strike a balance between the efficacy of treatment and its toxic and adverse effects, and the need to preserve future treatment options. The realisation that, at present, eradication of HIV-1 is not possible and that life-long treatment will be necessary has raised additional concerns about adherence, resistance, cost, safety, and patient convenience.

The issue of when to start treatment is especially relevant in resource-constrained settings, where the cost of drugs, laboratory and clinical monitoring, and management of side-effects is very important. If treatment is started too early, essential resources could be wasted and the risks of unnecessary toxic effects and drug resistance are increased. Treatment started too late leads to excess morbidity and mortality. Not only is the time when treatment should be started unclear, so too is which laboratory tests, if any, should guide such a decision. Many clinicians and most guidelines in resource-rich settings encourage measurement of viral load and CD4+ count to ascertain when to start antiretroviral treatment.¹² In the absence of data to support this strategy, and in view of the expense of such testing, the usefulness of this approach in resource-poor settings has been challenged.

Cheaper, simpler tests of viral burden and immune function are a high priority. Results of pilot studies¹³⁻¹⁵ suggest that total lymphocyte counts correlate with disease progression and survival in symptomatic patients, and some guidelines endorse use of such a measure to help make decisions about when to start treatment.¹⁶ Tests such as the heat denatured p24,¹⁷ Dynabeads,¹⁸ and Cyto-Sphere¹⁹ assays may also be useful, although data for use of these treatments are imperfect. Simplified flow cytometry protocols have also been developed.²⁰ Providers in some resource-poor settings have simply restricted use of antiretroviral treatment to patients with HIV who are symptomatic, an approach that obviates the need for costly laboratory assays altogether.²¹ Panel 1 outlines some of the issues about starting treatment.

Panel 1: Research questions for when treatment should be started

Is there a clinical advantage to starting antiretroviral treatment in asymptomatic patients with a CD4+ count above 200?
 Are there cheaper and simpler methods of measuring CD4+ cell count?
 Are there cheaper and simpler methods of measuring viral load?
 Are there laboratory markers other than CD4+ cells and viral load that can successfully guide decisions about when to start antiretroviral treatment?
 In the absence of laboratory data, are clinical criteria sufficient to guide decisions about when to start antiretroviral treatment?

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Panel 2: Research questions for monitoring of antiretroviral treatment

Is laboratory testing for effectiveness and toxic effects necessary every 3–4 months, or is less frequent laboratory testing appropriate?

What is the minimum laboratory monitoring needed to ensure safety and effectiveness?

Are there less expensive but equally useful methods to measure immune function and viral burden in monitoring of effectiveness of antiretroviral treatment?

Would an algorithm using only clinical variables (weight gain, quality of life, decreased frequency and severity of complications) to assess treatment success or failure be adequate?

How should antiretroviral treatment be monitored?

Antiretroviral treatment has several characteristics suggesting that regular laboratory monitoring is important. Virological and immunological responses and failures are usually asymptomatic. Similarly, although some adverse effects of antiretroviral treatment are associated with clinical symptoms and signs, other adverse events can only be detected by laboratory assays.

Monitoring effectiveness

US guidelines endorse use of CD4+ cell counts and viral load measurement every 3–4 months to assess the continued effectiveness of antiretroviral treatment.¹² Use of these tests at this frequency has not been validated, however, and the assays are prohibitively expensive and technically more complex than what can presently be provided in most resource-poor settings. In Uganda, for example, the cost of routine tests of efficacy (CD4+ cell count and viral load) approaches the cost of a month of antiretroviral treatment (Peter Mugenyi, personal communication). Results of studies in which the best combination of syndromic management, less frequent surveillance, and of cheaper, simpler monitoring tests is assessed should widen the settings in which antiretroviral treatment can be used.

Monitoring for toxic effects

Although many patients tolerate antiretroviral treatment without difficulty, antiretrovirals are associated with short-term and long-term toxic effects. Guidelines from resource-rich countries recommend that asymptomatic patients should be monitored every 3–4 months with laboratory tests (of haemopoietic, renal, and hepatic function) and a medical history and physical examination.¹² None of these strategies has been studied, either individually or in combination, and the expense of such monitoring tests may preclude their use in some environments. Panel 2 summarises some of the issues that need to be addressed in monitoring of antiretroviral treatment.

Selection of antiretroviral drugs (panel 3)

Although safety, effectiveness, and acceptability should govern the choice of antiretroviral treatment, individualised regimens might not be possible in many environments. Standard low-cost regimens and algorithms to guide their use will accelerate the widespread deployment of antiretroviral treatment needed in resource-poor settings where care is provided mainly by nurses and health workers.

Selection of a first-line regimen (or regimens) is a key strategic decision. Objectives include maximising the

Panel 3: Research questions for selection of drugs

Can antiretroviral treatment be safely and effectively prescribed by non-physicians using standard regimens and structured clinical algorithms in resource-poor settings?

What are the most appropriate first-line regimens for resource-limited settings?

How should treatment failure be defined?

When should antiretroviral treatment be stopped or changed?

Should this decision be based on virological, immunological, or clinical indices?

Are structured treatment interruptions, pulse therapy, or treatment-to-safety strategies safe and effective?

duration of clinical and immunological benefits and minimising drug toxic effects and development of antiretroviral resistance. Most guidelines endorse many combinations of antiretrovirals as first-line treatment, since there are no definitive comparisons of potent antiretroviral treatment regimens.

Decisions about whether and when to change treatments are very important to the success of antiretroviral treatment. Changing too soon leads to the risk that antiretroviral options will be exhausted, but continuing with a failing regimen risks viral resistance, which can jeopardise the success of subsequent treatment. Maintenance of viral load below the limit of detection is theoretically appropriate to prevent emergence of resistance, but clinical and immunological benefit can be maintained with a sustained but low level of viral replication.²² Although the guidelines of many developed countries advocate use of viral load testing, viral resistance testing, CD4+ count, and clinical assessment to guide decisions about changing antiretroviral treatment, such an approach may not be feasible in resource-limited settings. Up to now, few investigators have assessed changing treatment solely on the basis of clinical symptoms or low-cost clinical markers, although several trials have been started.

Adherence to antiretroviral treatment

Non-adherence is the Achilles' heel of antiretroviral treatment; it is associated with development of viral resistance,²³ virological failure,²⁴ progression of disease,²⁵ and death.^{26,27} Increasing attention is being paid to helping patients adhere to antiretroviral treatment, and treatment guidelines highlight the topic as essential to successful use of antiretrovirals. Few studies have been published about adherence to antiretroviral treatment in poorly resourced countries and the results of those that have been done show that adherence rates are similar to those seen in resource-rich countries.^{28,29}

Panel 4: Research questions for adherence to treatment

What are the main determinants/correlates of adherence in resource-poor settings?

If there are predictable barriers to adherence in these settings, are they modifiable?

Is fear of disclosure, stigma, or both a barrier to adherence to antiretroviral treatment?

What effect will traditional healers and the parallel health-care system have on adherence to antiretroviral treatment?

What are effective adherence interventions? Do they differ from region to region or could a standard package be developed?

As non-adherence becomes better understood, interventions to promote adherence have been studied with increasing rigor. These interventions fall into four broad categories—patient education, behaviour modification, streamlined regimens, and interpersonal support (including directly observed therapy)—although most programmes are combinations of these approaches. No single best approach has been identified. Panel 4 outlines some of the issues associated with adherence to treatment.

Recommendations

The first 6 years of antiretroviral treatment have led to major health gains in many countries. Answers to fundamental issues on how best to use these agents, however, remain elusive. Experts in resource-rich countries continue to debate when to start antiretrovirals, which drugs to use, how to monitor toxic effects and effectiveness, and how to improve adherence. Use of antiretroviral treatment in resource-limited environments adds additional issues and complexity. Answers are desperately needed to effectively and rapidly extend antiretroviral treatment to millions of people infected with HIV-1 worldwide. Very little antiretroviral research has been done in or addressing the key issues of concern to poorly resourced countries, a situation which must change. The need to answer these questions should not delay provision of HIV care to those who urgently need it. Instead, research can and should be built on to treatment programmes to facilitate wider use of these life-saving drugs.

Contributors

All authors participated in a working group convened by the Rockefeller Foundation. M Rabkin wrote the first draft of the report. All authors contributed to the final text.

Conflict of interest statement

None declared.

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