Opportunities and Options for Treatment Research in Resource-Constrained Settings

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HIV clinical research faces limitations even in research-rich settings. Even though important questions remain unanswered, clinical trials will probably never be conducted that address, prospectively, when treatment is optimally indicated, for example. In resource-constrained settings, large, prospective clinical trials are also unlikely. On the other hand, ones with a more observational design or that compare cohort experiences may well be feasible and able to provide information important in those settings, as well as in regions with abundant financial resources.

Antiretroviral therapy regimens can increasingly be both potent and compact. Combinations of ≥3 drugs may require as few as 2–4 pills daily, with fewer dietary or storage restrictions. Furthermore, some side effects, such as diarrhea, are less common, whereas others, including some of the metabolic changes so discussed recently, seem either unavoidable or associated more with the HIV infection itself. With current antiretroviral regimens, virological response rates of >80% are now being reported after ≥1 year of therapy. This therapy is so potent that excellent immunological, virological, and clinical response can be expected, even when drugs are initiated well into the course of HIV disease. Because the first regimen used is likely to be used for a prolonged period, choosing its components is obviously of central importance. Because the treatment toxicities may be cumulative, deferring initiation would seem to be an appropriate strategy as long as that does not compromise virological or immunological outcomes.

The central questions of HIV therapy are, then, easy to delineate—when should treatment begin and which drugs should be used. Other considerations in the field, such as salvage therapy for resistant virus, are less immediately important and more difficult to define. Because the causative virus and the resulting disease are common regardless of the local resources available for treatment, these treatment issues are truly the same in both the more economically developed and less developed areas of the world.

In the United States and in other countries where treatment decisions are minimally affected by resource constraints, published guidelines address the key issues of when to treat and what regimens initially to use. In these guidelines, the recommendations acknowledge an absence of firm data based on prospective controlled trials, the usual expectation of evidence-based medicine. Several factors have limited such evidence, often a product of the high success rate of therapy itself. For example, given the comparable potency of many different drug combinations, prospective trials would need to be very large and continued for long periods to establish meaningful differences. And because these trials would use drugs otherwise readily available in resource-rich settings, patients would have little incentive to participate. Finally, the drug industry would have little reason to support the enormous cost of these trials unless there was the strong belief that one specific choice was clearly the best—unlikely in the opinion of many physicians.
Difficulties in conducting prospective trials to define the optimum starting point for treatment are even more challenging than finding the best drug combination. Such trials would, again, require thousands of previously untreated persons in an even larger trial with an even more uncertain outcome and with even less attraction for support from the pharmaceutical industry. Finally, because many providers and infected persons lack equipoise on the question of treatment initiation—either when to begin or which drugs to use—large trials seem even less likely to be mounted.

If prospective trials addressing the optimum initiation of antiretroviral therapy are highly unlikely in those countries with abundant financial resources, what is the role, if any, of such research in countries that do face such restraints? If this question is limited to conventional randomized, prospective, clinical trials, the answer seems clear. The resources needed for these trials would be even larger—much larger, in fact—because their conduct would first require a health care infrastructure unavailable for many affected areas in the foreseeable future. Given this, clinical trials are highly unlikely.

Yet, resource-constrained countries facing a devastating epidemic have a clear stake in answering the questions of initial therapy. Moreover, these questions are increasingly real as the decreasing cost and complexity of antiretrovirals increase their availability and use. These countries also have, perhaps paradoxically, an asset in the size of their epidemic and in previous lack of access to these agents. Trials that require thousands of previously untreated persons who are difficult or impossible to accrue in countries such as the United States may, from the perspective of eligible populations, be feasible in resource-constrained settings. “Resource constrained” is also too simple a term that does not reflect wide variations in health care expertise, infrastructure, and resources in countries and regions.

At least 2 broad models of research might be imagined in developing economies that could better inform treatment decisions in all settings. Broadly, these might include carefully designed prospective trials addressing issues specific enough to limit sample size, conducted with external funding in settings with less striking economic and infrastructure limitations. The other approach, potentially feasible even in those more constrained settings, might collect noncomparative and nonrandomized outcome data from cohorts of persons treated under national or regional guidelines with locally available antiretroviral medications.

**PROSPECTIVE TRIALS IN RESOURCE-LIMITED SETTINGS**

Even with nearly limitless numbers of potential trial subjects, it remains improbable that a single clinical trial would directly establish the optimum point at which to initiate antiretroviral therapy. Such a trial would demand the carefully coordinated care and outcome assessment of thousands of persons and would be hugely expensive. Yet, some aspects of the central treatment questions may be approached by smaller and more focused efforts. For example, one concern with treatment deferred is the possible incomplete immune reconstitution that might occur when therapy begins. If such a problem were sufficiently real, those initiating therapy at a very low CD4 cell count (for example, 100 cells/mm$^3$) might develop opportunistic diseases even after receiving antiretroviral therapy, unlike those starting with a higher CD4 cell number (for example, 350 cells/mm$^3$). This type of trial, relying on more clinically verifiable outcomes, might be feasible in countries such as Botswana, Thailand, or South Africa, where resources are less severely limited, at least in some regions. Similarly, trials in such settings might allow direct comparison of specific toxicities among commonly used drug regimens in previously untreated populations. Together, such trials might yield data useful even in countries with ready access to all approved drugs and might even be simultaneously enrolled in those countries.

**COHORT COMPARISON TRIALS**

Another type of research, possibly conducted in more economically limited settings, would not specify treatments but would simply follow their outcomes. Although uncontrolled and thus subject to more potential bias, this work would still yield important and useful information. For example, if a country introduces a given combination of locally produced, generic, or conventional pharmaceutically developed agents, one might collect data on how long that regimen was able to be continued, subsequent rates of mortality, or resulting employment status of the treated person. Such data might be crudely adjusted for initial disease stage and compared with data from other countries or regions obtained with use of other drugs or drug combinations. Taken together, this data collection could give insights into varying strategies and would help develop the infrastructure needed for more carefully designed trials. It is even conceivable, if the size of treated populations expands, that data surveillance may enable estimates on the relation between antiretroviral therapy and the scale of ongoing transmission.

It should be obvious that conducting research in any setting is difficult and that this is particularly true in countries with limited resources. The issues are also not just economic. Local cultural approaches to health and disease may vary, as might the set of ethical principles requiring resolution. Many appropriately fear a form of medical and pharmaceutical imperialism in which externally imposed standards prevent more cost-effective local strategies or in which poor countries are exploited for the data that might allow rich countries to further improve...
their own standards without directly benefiting local infected populations. These are real and critically important concerns. Yet there is no doubt that antiretroviral therapy will be increasingly used in otherwise resource-limited settings and that many important questions remain on how these drugs are best used, regardless of the setting. Because those economies that are not constrained financially stand to benefit from any research conducted, this work should be constructed as a true bilateral partnership in which the responsibilities of all parties are explored and defined in advance. If this can be done, the resulting information might better illuminate the many remaining questions concerning initiation of HIV treatment.