Universal Antiretroviral Therapy for HIV Infection: Should US Treatment Guidelines Be Applied to Resource-Limited Settings?

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(See the Editorial Commentary by Lundgren and Wood on pages 888–90.)

US treatment guidelines now recommend antiretroviral therapy (ART) for all persons infected with human immunodeficiency virus (HIV), regardless of CD4 count, both for the benefit of infected individuals and to prevent HIV transmission. In an effort to meet the critical goal of treating all HIV-infected persons worldwide, there is movement toward extrapolating these guidelines and the data supporting them to resource-limited settings. While economic and practical barriers to universal ART are widely recognized, there has been little discussion of the ethical considerations resulting from global disparities in the safety and efficacy of universal ART in these settings. We argue that the risk-benefit considerations for initiating ART are not the same worldwide due to limitations in the ART regimens used, laboratory monitoring, and consistent availability of ART, which raises ethical questions about universally applying US guidelines in resource-limited settings at the present time.

**Keywords.** HIV; antiretroviral therapy; ethics; guidelines; resource-limited settings.

Guidelines issued in the United States in 2012 advocate treatment of all HIV-infected patients regardless of CD4 cell count [1, 2]. This is clearly a landmark in the history of the AIDS epidemic. Although there is considerable enthusiasm for generalizing these recommendations globally, both for the benefit of infected individuals and as a means of curtailting the epidemic, there are clinical, practical, and ethical reasons to do so only with caution and creativity.

The treatment of HIV-infected individuals reduces HIV transmission to others [3–5]. Mathematical models suggest that universal testing and immediate treatment of HIV-infected patients could reduce or even end the epidemic [6], although these models have been criticized for using overly optimistic assumptions about program coverage, adherence, and rates of virologic suppression. In addition, antiretroviral therapy (ART) reduces morbidity and mortality in HIV-infected individuals. In patients with high CD4 cell counts, observational data suggest a survival benefit with early ART [7]. There is also growing evidence that HIV-related morbidity and mortality are due to more than just immunosuppression. Uncontrolled viral replication causes immune activation and inflammation that may increase the long-term risk of complications such as coronary heart disease, stroke, neurocognitive impairment, malignancies, and osteoporosis [1]. Furthermore, HIV viremia is a risk factor for death independent of CD4 cell count [8].

Even those who disagree with the US guidelines accept that HIV infection is not benign in patients with normal CD4 cell counts and low viral loads. However, they point out that current US guidelines are based
mostly on expert opinion, that not all cohort studies show a survival benefit [9], that patients at early stages of HIV infection are at low risk of dying or developing AIDS-related complications, and that by starting ART early, patients are susceptible to toxicity and drug resistance without hard evidence supporting individual benefit. However, modern ART is now well tolerated and not associated with the toxicity of older regimens, and cohort studies not demonstrating a survival advantage to early ART have not shown evidence of harm, making the risk-benefit ratio of early ART highly favorable.

Not surprisingly, there has been growing global enthusiasm for this approach. In settings where the burden of the epidemic is greatest, the potential prevention and treatment benefits of universal ART are promising. Many of the arguments favoring early ART in the United States can be applied anywhere. The prevention benefit has been demonstrated primarily in resource-limited settings, and clinical benefits should also apply there. In fact, early ART may be even more beneficial in areas where tuberculosis is endemic [10, 11].

Nevertheless, before generalizing the US treatment guidelines, it is critical to evaluate and weigh the risks and benefits in particular settings. In the United States, the benefit of ART is high and the risk to most patients is low based on the safety, tolerability, and efficacy of current treatment regimens as delivered in resource-rich settings. In current clinical trials, efficacy of 85%–90% is commonplace, with excellent tolerability. Observational data from clinical settings also demonstrate outstanding efficacy, safety, and tolerability [12]. In resource-limited settings, the benefit of ART relative to risk is high among persons with advanced disease. However, the risk-benefit ratio may be less favorable among those with asymptomatic, early-stage disease because of the limitations in (1) the antiretroviral agents used, (2) laboratory monitoring, and (3) access to uninterrupted ART.

ANTIRETROVIRAL DRUG REGIMENS

The Nucleoside Analogue “Backbone”

Initial regimens in resource-limited settings typically include stavudine or zidovudine. Current World Health Organization (WHO) guidelines no longer recommend stavudine [13], but it is still widely used despite its known toxicities. Zidovudine is safer, but in addition to causing fatigue and nausea, it can cause anemia, leukopenia, blunted CD4 response to ART, lipoatrophy, hepatic steatosis, and lactic acidosis. Because some of these toxicities are cumulative, earlier initiation of ART might increase the prevalence of conditions such as peripheral neuropathy and lipoatrophy. Both drugs select for thymidine analogue mutations that can cause broad cross-resistance to other nucleoside reverse transcriptase inhibitors (NRTIs), including tenofovir, the most commonly used NRTI in second-line therapy. Moving toward safer, tenofovir- or abacavir-based regimens in resource-limited settings would improve the risk-benefit ratio associated with early ART. These agents are not associated with mitochondrial toxicity, and they select for predictable NRTI mutations that do not cause cross-resistance to zidovudine. Tenofovir is more effective than zidovudine [14] and less toxic than both zidovudine and stavudine [14, 15].

The “Third Agent”

Virtually all first-line regimens used in resource-limited settings include a nonnucleoside reverse transcriptase inhibitor (NNRTI): nevirapine or efavirenz. These are highly effective agents that are also used in resource-rich settings, but they have potential limitations in some patients. Nevirapine is associated with early hepatotoxicity and severe skin reactions in patients with high CD4 counts. US guidelines recommend that it be started only in women with CD4 counts <250 cells/μL and men with CD4 counts <400 cells/μL, making it a less attractive option for early initiation of ART, especially in women. Efavirenz causes early neuropsychiatric side effects and is not recommended in the first trimester of pregnancy or in women likely to become pregnant because of teratogenicity. NNRTI resistance emerges readily with interruptions in NNRTI-based regimens. Furthermore, hepatotoxicity is more common in patients coinfected with viral hepatitis, which is more prevalent in resource-limited settings. Thus, there are patients for whom NNRTI-based regimens are not optimal. Efforts should be made to expand options for initial therapy to include protease inhibitors and/or integrase inhibitors for selected patients in resource-limited settings.

Availability of Second-line and “Salvage” Therapy

Whereas some resource-limited settings now offer second-line therapy, usually consisting of tenofovir, lamivudine, and lopinavir/ritonavir, other drugs such as darunavir, etravirine, maraviroc, and integrase inhibitors, which have completely changed the outlook for patients with highly resistant virus in resource-rich settings, are rarely available in resource-poor settings.

LABORATORY MONITORING

Efficacy Monitoring

Viral load is typically monitored 2–4 times per year in stable patients on ART in resource-rich settings, but monitoring is performed infrequently or not at all in resource-limited settings, where the decision to switch to second-line therapy is often based on CD4 count alone. The CD4 count is both insensitive and nonspecific as a measure of virologic failure [16, 17]. This can result in (1) virologically suppressed patients being switched unnecessarily to second-line therapy, and (2) continuations of first-line therapy despite virologic failure. The interval between the onset of virologic failure and CD4 cell count...
decline has been estimated to be as long as 3 years [16]. By the
time treatment failure is recognized, patients in resource-
limited settings have significantly more drug resistance mu-
tations than those in resource-rich settings, including resistance to
tenofovir, a widely used component of second-line therapy [18].
Development of low-cost viral load assays will improve the
risk-benefit ratio of early ART in resource-limited settings.

**Toxicity Monitoring and Management**

Monitoring and management of drug toxicity, such as anemia,
hepatotoxicity, nephrotoxicity, hyperlipidemia, and hypergly-
cemia, is more readily available in resource-rich settings. Drug
toxicity can become more severe in resource-limited settings,
either due to delayed diagnosis or lack of other treatment
options [19], and management options, such as use of lipid-
lowering agents, oral hypoglycemic agents, erythropoietin, and
nonopiate analgesics to treat peripheral neuropathy, are often
unavailable in resource-limited settings.

**Resistance Testing**

Because resistance testing is rarely available in resource-limited
settings, second-line therapy is chosen empirically. As dis-
cussed above, patients failing first-line regimens may have de-
veloped resistance to tenofovir by the time they are switched to
second-line therapy, at worst compromising the efficacy of the
second-line regimen, and at best resulting in the unnecessary
use of this agent. The implications of resistant virus in commu-
nities and populations are unclear, but transmission of resistant
virus in resource-limited settings is increasingly being reported
[20]. Because baseline genotypic testing is not performed, resis-
tance will not be detected. Patients will be started on NNRTI-
based regimens, which are likely to fail, possibly resulting in
accumulation of further resistance. Second-line therapy is then
required, with no further treatment options available in the
event of second-line treatment failure. In contrast, people in-
fected with resistant virus in developed countries almost always
have many effective treatment options.

**ACCESS TO ART**

Recommendations for universal treatment in the United States
are predicated on the assumptions of good adherence and un-
interrupted access to ART. Although individual-level adherence
has been demonstrated to be high in many resource-limited set-
tings, structural challenges in resource-limited settings such as
clinic distances, long waiting lines, and drug stockouts may
hinder adherence even among motivated patients, necessitating
the development and implementation of creative approaches to
ART delivery [21]. Without sufficient infrastructure, initiating
ART may be harmful to patients, as well as to communities, as
it may increase the likelihood of viral resistance.

**CONCLUSIONS**

In resource-rich countries, evidence of the benefit of early ART
continues to accumulate, while the cost of therapy in terms of
quality of life and toxicity has declined. In resource-limited set-
tings, there is a clear prevention benefit associated with earlier
initiation of ART, and there is also likely to be clinical benefit.
Whereas the limitations described above apply whether ART is
initiated early or late, in symptomatic patients or patients with
low CD4 counts, the reduction in morbidity and mortality due
to ART outweighs these concerns. However, the risk to patients
with high CD4 counts in terms of side effects, toxicity, drug re-
sistance, and elimination of future treatment options may be
high compared to the incremental clinical benefit of very early
treatment. For that reason, current US recommendations
should not yet be directly generalized to the rest of the world,
as early therapy could do more harm than good. The central
ethical obligation of clinicians is to benefit patients while not
causing harm. Although it might be argued that as a matter of
justice, universal treatment is necessary to meet the needs of
HIV-infected individuals in resource-limited settings, prematu-
rely implementing US guidelines using inadequate resources
and suboptimal agents could be harmful. In addition, in set-
tings where resources are limited, preventing universal access to
ART, there is arguably a moral claim for treating those with ad-
vanced disease before treating those with early infection. Such a
claim is justified by the fact that the clinical and preventive ben-
efits of ART are greatest for persons with lower CD4 counts
because the risk of morbidity/mortality and risk of HIV trans-
mission are greater for those with more advanced disease.
When the number of patients who can be treated is finite, the
treatment of patients at early stages of HIV infection may
prevent patients with more advanced disease from being
treated.

Nonetheless, this does not mean that the move toward early
initiation of ART should be abandoned in resource-limited set-
tings. Universal treatment should be the long-term goal, both
for the benefit of those infected and for its effect on slowing
and ultimately stopping the epidemic. But in the enthusiasm
for the benefits of ART, we must not lose sight of the glaring
disparities among nations that stand as obstacles to the ethical
implementation of early ART. There are many shorter-term
goals that should take priority. These include fostering political
commitment at a country level to sustain HIV treatment pro-
grams, with reduction in dependence on external donor
support; development of low-cost viral load assays to assess ad-
herence and detect virologic failure; increased use of less toxic
regimens for first-line therapy; expansion of options for first-
and second-line therapy, including integrase inhibitors and less
toxic protease inhibitors; development of less demanding deliv-
ery systems that simplify provision of ART for patients and that
reduce treatment interruptions; and public education about the rationale for initiation of therapy before the onset of symptoms. Recognizing the critical differences in risk and benefit considerations between resource-rich and resource-poor settings, we strongly support the recent proposal for a randomized controlled trial addressing the question of when to start ART in resource-limited settings [22]. In the meantime, we should strive to implement existing WHO treatment guidelines worldwide, and to apply proven methods of HIV prevention.

Notes

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