Running with Scissors: Using Antiretroviral Therapy without Monitoring Viral Load

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(See the article by Marconi et al. on pages 1589–97)

“As viral loads are not normally available in resource-limited settings it is recom-

mended that programmes primarily use clinical, and, where possible, CD4 count

criteria, in order to define treatment fail-

ure,” the World Health Organization

stated in 2004 [1]. As antiretroviral ther-

apy is rolled out to resource-limited set-

tings, will clinicians remember what has

been learned?

In the beginning of the HIV/AIDS pan-

demic, clinicians and researchers were be-

hind the curve. Unabated, AIDS ravaged

communities, families, and individuals

until clinicians, researchers, and HIV-

infected volunteers were mobilized. Seven

years after the first published reports of

the disease that the world would come to

know as AIDS, monotherapy with azido-

thymidine showed promise [2], but

within 2 years, HIV drug resistance was

found [3]. With dual-drug therapy, the de-

velopment of drug resistance was delayed,

and clinical benefits were somewhat en-

hanced [4, 5], but not until at least 3 an-

tiretroviral medications from at least 2 dif-

ferent classes were combined did HAART

emerge, providing greater virologic sup-

pression, a broader barrier to the devel-

opment of drug resistance, and longer-

term clinical benefits [6, 7]. Researchers

found that preventing viral evolution of

drug resistance required suppressing viral

RNA replication to undetectable levels in

the peripheral blood using sensitive mo-

lecular techniques [8, 9].

Giving prescriptions to a patient does

don’t guarantee that the patients will achieve

an undetectable viral load. Incomplete

medication adherence [10], insufficient

drug levels [11], drug and food interac-

tions [12], and acquisition of drug-resis-

tant virus are among the many factors that

can contribute to treatment failure [13–

15]; therefore, HAART is not a “start-it-

and-forget-it” treatment. It requires mon-

toring for optimal outcomes. Currently,

the standard of HIV care in resource-

wealthy settings relies on laboratory mon-

itoring of the immune system using CD4
cell counts, of viral suppression using viral

loads, and of the development of drug re-

sistance using genotypic or phenotypic

testing [16]. These approaches to moni-

toring therapy emerged in the context of

clinical trials, and a delay in the clinical

use of each technique occurred, because

clinicians and scientists argued that pa-

tients did well clinically without these “ex-

pensive” studies. Eventually, each moni-
toring method was found to improve

patient outcomes and to be cost-effective

[17–22]. As the challenges of vaccine de-

velopment became increasingly apparent,

researchers found that HAART coupled

with behavioral strategies was perhaps the

only real tool to stem the tide of the epi-

demic for a long time [23–26]. Therefore,

understanding and preventing drug resis-
tance wherever HAART is used is essential

to maintaining the value of HAART in the

future.

In this issue of Clinical Infectious Dis-

eases, Marconi et al. [27] add to the un-
derstanding [28–31] that, whether the set-
ing is rich or poor in resources and

whether HIV is subtype B or C, HAART

failure and HIV drug resistance can still

occur. Similar to other reports [32], Mar-
coni et al. [27] demonstrate that subtype

C virus can develop mutations that de-

crease susceptibility to HAART; however,

the genetic changes that develop in sub-
type C virus are not always the same as

those that develop in subtype B virus. Be-

cause of its prevalence in the developed

world, subtype B is the best characterized

of all HIV subtypes [33–36]; thus, most

of what is known about the development

of drug resistance is based on subtype B

HIV [37]. However, subtype B virus ac-

counts for only 10% of the burden of HIV

infection worldwide, and subtype C is the

most common subtype worldwide [38].

Because subtype C virus may differ from

subtype B virus with regard to the devel-
development of drug resistance [39–42], researchers will need to be diligent in documenting the genetic determinants of drug resistance among circulating HIV genetic backgrounds (subtypes and recombinant forms) for the surveillance of transmitted drug resistance and to guide the clinical selection of HAART regimens.

Optimal clinical outcomes require maximal suppression of viral replication with combination therapy, and current World Health Organization recommendations to assess adherence, clinical findings, and changes in CD4 cell count cannot predict virologic HAART failure [43, 44]. In addition, drug-resistant HIV infection represents a real public health threat, because the transmission of such infection limits the usefulness of certain HAART regimens. Therefore, clinicians’ thinking must shift from HAART being an emergency intervention in resource-limited settings (used until a vaccine is developed) to HAART being an intervention that must be sustained. Failing to use laboratory tools that monitor treatment success is like running with scissors; it is all quick and easy until someone falls down. Over a decade ago, researchers discussed whether to incorporate viral load monitoring in clinical care in resource-wealthy settings, because patients who were not monitored were less likely to achieve viral suppression and contributed to the substantial amount of drug-resistant viruses being transmitted in these locations. This experience should not be repeated. If a choice must be made between monitoring viral load or CD4 cell count during HAART, we believe that it would be more useful to monitor viral load than CD4 cell count. Monitoring CD4 cell count is important for determining when to start prophylaxis for opportunistic infection and HAART [45, 46], but HAART has a direct effect on viral replication, not on CD4 cell count.

Access to HAART must be expanded in the most sustainable fashion. Marconi et al. [27] provide compelling evidence for concrete recommendations to attain this goal. As HAART is introduced throughout the developing world, we recommend that (1) drug access plans should proceed rapidly and should not be delayed by the false perception that a successful vaccine will soon be available, (2) local laboratory and technical capacity to monitor HAART (including viral load and drug resistance testing) be developed, (3) the availability of second-, third-, and fourth-line HAART regimens be increased, (4) resources for the scientific discovery of cost-effective methods to deliver high-quality HIV care (such as monitoring for viral replication [47]) be developed, (5) surveillance for both acquired HIV drug resistance and transmitted drug resistance within treated populations be performed, and (6) the cost-effectiveness of all aspects of HIV care in resource-limited settings (including monitoring CD4 cell count, viral load, and drug resistance) over the short and longer term be determined to better inform the allocation of limited resources. While HAART is introduced to the developing world, researchers should follow the advice of Santayana [48] and remember history.

Acknowledgments

We thank Drs. Constance Benson, David Butler, and Miguel Goicoechea, for their critical insights, and Laureen Cogter, for technical assistance.

Potential conflicts of interest. R.T.S. has served as a consultant to Gilead Sciences, Merck, GlaxoSmithKline, Bristol-Myers Squibb, Roche, Pfizer, Vertex Pharmaceuticals, Achiilion, Koronis Pharmaceuticals, Tibotec, and Monogram Biosciences and has stock or stock options in Monogram Biosciences and Achiilion Pharmaceuticals. D.M.S.: no conflicts.

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