

# HIV Is Putting Up Less Resistance

Douglas D. Richman<sup>1,2</sup>

<sup>1</sup>Departments of Pathology and Medicine and the Center for AIDS Research, University of California, and <sup>2</sup>VA San Diego Healthcare System

(See the Major Article by Scherrer et al on pages 1310–7.)

**Keywords.** HIV drug resistance; antiretroviral therapy.

The development of combination antiretroviral therapy (ART) has been a major achievement of modern medicine, turning a fatal condition into a relatively manageable condition for millions of persons globally. During the past decade, antiretroviral drugs with increased potency, reduced toxicity, and availability as several fixed-dose combinations (1 pill daily) have expanded acceptance by patients and providers. Current guidelines recommend treatment for virtually all persons with human immunodeficiency virus (HIV) infection, including those in low- and middle-income countries [1–3].

One proposed hazard that would result from the broader implementation of ART has been the prospect of increasing both the selection for resistant virus in those being treated and the incidence of transmitted drug-resistant virus in newly infected patients. The article by Scherrer et al [4] from the excellent database of the Swiss HIV Cohort Study documents what has been observed in several smaller cohorts, as acknowledged by the authors, and has been gratifyingly apparent to individual healthcare providers in recent years.

Scherrer et al [4] analyzed HIV genotypic drug resistance tests performed between 1999 and 2013 in plasma from 11 084 patients. This database reflects

the remarkable foresight to establish a prospectively monitored cohort of the majority of patients under treatment in Switzerland, as well as the commendable collaborative efforts of the Swiss providers and investigators. The study subjects were divided into 3 groups based when they started ART: (1) the years before combination ART (before 1999), (2) the early combination ART years (1999–2006), or (3) the years with the current, more potent and tolerable combination ART (after 2006).

The cohort starting therapy before 1999 had the highest prevalence of any drug resistance (56%), and most of these patients had already developed multiple class resistance. This quick acquisition of multiple class resistance can be attributed to the initiation of single- or dual-nucleoside therapy in the 1980s or early 1990s (74%) and the subsequent availability of the earlier less potent and less tolerable nonnucleoside reverse-transcriptase inhibitors and protease inhibitors, many of which were administered as a sequential add-on regimen rather than as combination treatment. These patients also tended to initiate treatment at later stages of HIV infection.

These risk factors for acquiring resistance progressively diminished in each group initiating ART in the subsequent periods. Associated with these reductions in risk factors were substantial reductions in the prevalence of resistance during each time period. With these changing resistance patterns, the treatment options and the rates of successful suppression of virus replication correspondingly improved. Noteworthy and reflecting recent clinical

trials results, only 45 of 2092 patients (1.6%) starting ART since 2006 acquired new drug resistance mutations, and all had effective second-line treatment options.

The expansion of treatment indications is not expanding drug resistance; it is resulting in less drug resistance. This can be attributed to more potent drugs, fewer adverse effects, fixed dose of combinations, and higher treatment success rates in those initiating treatment at earlier stages of disease. Sadly, these reductions are not being seen in low- and middle-income countries [5]. The encouraging observations from the Swiss cohort have not been seen in low- and middle-income countries for several reasons: (1) viral load monitoring is not readily available to promptly identify treatment failure, (2) drug resistance testing is not readily available to identify likely nonadherence or to guide new regimens, (3) protease and integrase inhibitors are not readily available, and (4) limited resources are limiting treatment, for the most part, to patients with later-stage disease.

The reductions in drug resistance documented with the well-analyzed data from the Swiss cohort are dramatic and gratifying. The continuing introduction of more effective and less toxic drugs, such as dolutegravir and tenofovir alafenamide fumarate [6, 7], can only enhance this trend. The imperative in resource-rich countries is now to mitigate the treatment cascade so these drugs are provided to as many HIV-infected persons as possible, with mechanisms to sustain treatment with good adherence. In low- and middle-income countries, the availability of these better drugs, resources to provide them,

Received and accepted 10 February 2016; published online 8 March 2016.

Correspondence: D. D. Richman, Rm 329, Stein Clinical Research Bldg, 9500 Gilman Dr, La Jolla, CA 92093-0679 (drichtman@ucsd.edu).

**Clinical Infectious Diseases**® 2016;62(10):1318–9

Published by Oxford University Press for the Infectious Diseases Society of America 2016. This work is written by (a) US Government employee(s) and is in the public domain in the US. DOI: 10.1093/cid/ciw130

and testing capabilities for HIV load and drug resistance mutations are also needed. There are many obstacles to achieving the ideal of providing universal treatment with the associated benefits of reduced transmission. The data clearly show, however, that the fear of selecting for HIV drug resistance can no longer be invoked as a reason to defer treatment.

#### Note

**Potential conflict of interest.** Author certifies no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the

editors consider relevant to the content of the manuscript have been disclosed.

#### References

1. Gunthard HF, Aberg JA, Eron JJ, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. *JAMA* **2014**; 312:410–25.
2. *AIDSinfo*. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available at: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0>. Accessed 9 February 2016.
3. World Health Organization. Guideline on when to start antiretroviral therapy and pre-exposure prophylaxis for HIV, **2015**. Available at: <http://www.who.int/hiv/pub/arv/policy-brief-arv-2015/en/>. Accessed 9 February 2016.
4. Scherrer AU, von Wyl V, Yang W, et al. Emergence of acquired HIV-1 drug resistance has almost been stopped in Switzerland: a 15 year prospective cohort analysis. *Clin Infect Dis* **2016**; 62:1310–7.
5. TenoRes Study Group. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multi-centre retrospective cohort study. *Lancet Infect Dis* **2016**; doi:10.1016/S1473-3099(15)00536-8.
6. Raffi F, Rachlis A, Brinson C, et al. Dolutegravir efficacy at 48 weeks in key subgroups of treatment-naïve HIV-infected individuals in three randomized trials. *AIDS* **2015**; 29:167–74.
7. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, co-formulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* **2015**; 385:2606–15.