Resistance Testing in Drug-Naive HIV-Infected Patients: Is it Time?

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(See the article by Sax et al. on pages 1316–23)

Early recommendations for the use of antiretroviral drug resistance testing in 1998 cautiously endorsed its use for persons who have experienced treatment failure, with a possible role for persons identified with recent HIV infection [1]. More recent recommendations now include clear recommendations for resistance testing in persons with treatment failure and in those with HIV infection of <2 years' duration, and suggest considering resistance testing for drug-naive patients in areas with a prevalence of resistance of ⩾5% [2]. In this issue of the journal, Sax et al. [3] present a cost-effectiveness analysis that supports the use of genotypic drug-resistance testing for all drug-naive patients in most settings. Is it time to make this change?

Initial recommendations to perform antiretroviral drug resistance testing in recently HIV-infected persons but not in those with chronic HIV infection were based on an assumption that, within 1–2 years, most drug-resistance mutations would be overgrown by wild-type virus [1]. Resistance testing for patients with chronic infection might provide little but false assurance that resistance was not present in those with low levels of drug-resistant virus that could emerge rapidly when treatment was initiated. Although some resistance mutations do revert to wild-type virus within a year [4, 5], recent studies of persons with primary drug resistance (i.e., resistance acquired through transmission of virus from a source with drug resistance) indicate that most resistance mutations persist at detectable levels considerably longer and may be stable for many years [5–7]. Early assumptions that drug-resistance mutations would be lost more quickly were based in part on experience with persons who acquired drug-resistance mutations while receiving antiretroviral therapy. In these individuals, drug-susceptible virus usually has a fitness advantage, and cessation of antiretroviral therapy often leads to overgrowth of drug-resistant virus that obscures the detection of mutations within months [8]. In persons with primary HIV drug resistance, viral evolution appears to have a different pattern: evidence of primary resistance is lost more slowly and typically involves reversion of mutations one-by-one, rather than larger viral genetic shifts involving decreased frequency of several mutations at the same time. This pattern is consistent with transmission of only a few HIV-1 variants such that no drug-susceptible virus is present to compete with the drug-resistant virus, and the emergence of wild-type virus depends on a much slower process of backward mutations to the wild-type genotype.

This likely explains why recent reports indicate that the prevalence of drug resistance in drug-naive patients is relatively high regardless of whether they are recently or chronically infected. In a study of >1000 drug-naive individuals in 10 US cities enrolled during the period of 1997–2001, Weinstock et al. [9] found that 8.3% had at least 1 resistance mutation. This makes sense in light of data on the persistence of transmitted drug-resistance mutations and the frequency of transmission of drug-resistant HIV, which has varied over time and population, but which has consistently been ⩾8% during the past decade in the United States [9–11] and elsewhere in the developed world [12–16].

The cost-effectiveness analysis by Sax et al. [3] provides a third piece of important information that supports the use of antiretroviral drug-resistance testing for all drug-naive patients. This analysis found that the cost-effectiveness ratio for resistance testing of drug-naive patients before commencement of antiretroviral therapy remained less than $50,000 per quality-adjusted life-year, a commonly accepted threshold below which medical interventions are agreed to be cost-effective, as long as the prevalence of drug resistance was ⩾1%. This remained true in sensitivity analyses that varied factors, such as the cost of assays and the benefit of resistance

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testing in improving outcomes, over wide ranges.

We believe that there is now sufficiently strong information to recommend genotypic resistance testing for all drug-naive patients at the time of diagnosis. Because HIV drug-resistance testing has little risk of causing harm to patients (other than the anxiety caused by knowledge that one has a drug-resistant variant), cost-effectiveness considerations are key. The analysis by Sax et al. [3] suggests that such testing will be well within accepted parameters of medical interventions believed to be cost-effective over most plausible scenarios. The baseline assumptions in the model are appropriately conservative and may underestimate the benefit of drug resistance testing in drug-naive persons. For example, the model bases the utility of resistance testing on trial data from patients with treatment failure. The utility of drug-resistance testing may be greater in drug-naive persons because partial resistance is more common, leaving effective drug regimens that can be selected with the right information. In contrast, some patients in trials of these assays have been infected with highly drug-resistant HIV and have had no highly effective regimen choices that can be selected using resistance data. Furthermore, in situations involving salvage therapy, the ability of experienced clinicians to use antiretroviral history to select optimal regimens competes with the utility of resistance testing. In contrast, the treatment history of transmission partners is not usually available to guide regimen selection in drug-naive persons.

There are several questions that remain. Accepted levels of cost-effectiveness in well-resourced regions may not apply to resource-poor areas where investments in job development, clean water, and provision of basic HIV/AIDS treatment are urgently needed. Development of novel and less-costly strategies for drug-resistance testing will be important. In addition, there is emerging information that, although many drug-resistance mutations remain detectable after several years of infection, there are others that wane below the limit of detection of standard resistance assays but remain detectable using novel minor variant assays. Application of assays capable of detecting minor drug-resistant variants in chronically infected persons appears to increase detection of primary resistance in a significant number of patients [17, 18]. Validation of these assays for clinical use is going to be challenging, because normal viral variation at primer-binding sites has complex effects on assay performance. Furthermore, there will be questions about whether the additional cost is justified.

For now, this work addresses a perplexing problem faced by clinicians. Prior recommendations and current reimbursement in many programs restrict resistance testing for drug-naive persons to those who are recently infected. In most patients, however, the duration of infection cannot be discerned from the history or clinically available laboratory tests. Current suggestions to perform resistance testing when the prevalence in drug-naive patients is expected to be $\geqslant$5% assumes that this information is available to clinicians, which in most communities is not true. The recommendation of genotypic resistance testing for all drug-naive persons with HIV is more easily implemented, and the article by Sax et al. shows that it is also cost-effective.

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