Is Average Adherence to HIV Antiretroviral Therapy Enough?

In this edition of the *Journal of General Internal Medicine*, Golin et al. report on adherence behavior to antiretroviral therapy in 140 HIV-infected people using electronic medication monitors, pill counts, and patient report.¹ The use of multiple adherence measures is an unusual strength of this study and provides important insight regarding our view of normal adherence behavior. Consistent with a small number of other studies using objective measures of adherence,²⁻⁷ Golin et al. found that patients receiving combination HIV antiretroviral therapy took 71% of prescribed doses on average. Remarkably, only 6% of patients took 95% of their medications, the minimum level of adherence believed to be necessary for durable viral suppression.³ Does this mean that HIV antiretroviral therapy is doomed because it will lead to incomplete viral suppression, the selection of drug-resistant HIV, and eventual disease progression in the majority of people treated?

Golin et al. correctly state that “Nonadherence is widely viewed as a risk factor for drug-resistant virus...” Two frequently cited editorials articulated the early biologic relationship between adherence and antiretroviral drug resistance.^{8,9} Many investigators, however, interpreted this conceptual framework to mean that nonadherent patients will both fail to derive benefit from therapy and also pose a public health threat vis-à-vis the development and spread of drug-resistant HIV. Although conceptually sound, early data linking nonadherence to the emergence of HIV drug resistance was limited to a few studies with small numbers of patients and/or imprecise measures of adherence.^{10,11}

More recent data suggest that the relationship between resistance and adherence is far more complex than initially assumed, and that resistance to protease inhibitor combination therapy is uncommon at levels of adherence below the 70% average. For example, we found that protease inhibitor resistance was limited to patients with 65% to 100% adherence. Resistance to reverse transcriptase inhibitors was also more common in highly adherent patients.² Because there were several alternative explanations for this finding, this observation was interpreted cautiously. Further data are accumulating, however, to support the interpretation that protease inhibitor resistance requires above-average levels of adherence. In 2 studies using electronic medication monitors, Walsh et al. found that the number of drug resistance mutations increases linearly with improving adherence in viremic patients,¹² and Howard et al. found that resistance was more common in the most adherent patients with detectable viremia.¹³ Similarly, Gallego et al. found that indinavir resistance was limited to patients reporting >90% adherence.¹⁴ During longitudinal observation, we have observed that the rate of accumulating drug resistance mutations increases with improving adherence in

viremic patients.¹⁵ Taking into consideration higher rates of viral suppression with higher levels of adherence, resistance to non-ritonavir-boosted protease inhibitors may be most common in the 80% to 90% adherence range.¹⁶ Although speculative, the lack of drug resistance among patients with below-average adherence may be due to the fact that resistance mutations often reduce replicative capacity (“viral fitness”), and that wild-type virus may be relatively more fit than the replication-impaired, drug-resistant virus in the presence of low drug concentrations. This also suggests that the adherence-resistance relationship may be entirely different for non-nucleoside-based regimens.¹⁷

Although incomplete adherence, partial viral suppression, and drug resistance are common, clinical failure (defined as disease progression and/or death) remains uncommon.¹⁸⁻²¹ Furthermore, high levels of adherence may be associated with both protease inhibitor drug resistance^{2,13-16} and delayed progression to AIDS and death.²²⁻²⁴ Several factors may contribute to this apparent “disconnect” between virologic failure, drug resistance, and clinical success. First, antiretroviral drug resistance is rarely complete. Most antiviral drugs exert some degree of anti-HIV activity against the drug-resistant variant. Those patients who remain on some therapy despite the presence of drug-resistant virus are likely to derive some treatment benefit. Second, the mutations associated with drug resistance result in virus that replicates less efficiently than wild type, perhaps because drug-associated mutations result in reduced efficiency of the target enzyme.²⁵ This results in a virus that replicates at a lower titer,²⁵ spares thymic function,^{26,27} and perhaps is less cytopathic.^{28,29} Finally, reductions in the degree of viral replication or alterations in the inherent pathogenicity of the virus may shift the delicate balance between the host and the virus, resulting in an immune system that is better able to control viral replication immunologically. Selective drug pressure in the setting of high but imperfect levels of adherence suppresses wild-type HIV such that the less-fit drug-resistant variant persists. This is consistent with preliminary observations that CD4 cell increases (a better marker for disease progression than HIV viral load) occur at levels of adherence lower than those required for complete viral suppression.³⁰

While it is both epidemiologically and biologically plausible that patients with incomplete adherence derive durable clinical benefit from therapy, this does not suggest that incomplete adherence is equivalent to perfect adherence. Several studies have demonstrated that adherence is the strongest predictor to progression to AIDS and death after CD4 cell count.²²⁻²⁴ Higher levels of adherence and greater degrees of viral suppression will lead to better outcomes. Theoretically, complete adherence with potent therapy will prevent any viral evolution, thus assuring that

drugs will work indefinitely. Thus, complete adherence and viral suppression should remain the goal of therapy. As shown by Golin et al., incomplete adherence, often leading to incomplete viral suppression, is common and should be viewed as normal human behavior rather than a disease in need of a cure. If patients are treated, they will do better. And if they improve their adherence to near perfect levels, they will do even better. Ongoing declines in AIDS-related mortality suggest, however, that average adherence to combination antiretroviral therapy, even if incomplete, is sufficient to profoundly impact the natural history of HIV infection. —**DAVID R. BANGSBERG, MD, MPH**, *Epidemiology and Prevention Interventions Center, Division of Infectious Diseases, San Francisco General Hospital, UCSF and Positive Health Program, San Francisco General Hospital, UCSF*; and **STEVEN G. DEEKS, MD**, *Positive Health Program, San Francisco General Hospital, UCSF, San Francisco, Calif.*

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