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Letters to the Editor

HIV Transmission After Suspension of Highly Active Antiretroviral Therapy

To the Editor: Since the introduction of highly active antiretroviral therapy (HAART) in 1996, survival and clinical status of infected individuals have changed dramatically. The improved life expectancy, changes in the public perception of the seriousness of HIV infection, as well as the widespread opinion that the transmission risk is low, when HAART has suppressed plasma viremia, may have resulted in an increased risk behavior in some populations. In the Swiss HIV Cohort, 13% of HIV patients living in a stable relationship with an HIV-negative partner report having unprotected sex. Preliminary data from an anonymous poll in the same cohort indicate that this information, obtained by the treating physicians, may underestimate the true incidence of unprotected sex.

Given that HAART implies indefinite treatment duration, novel strategies to improve the HIV-specific immune response, including temporary suspension of therapy, are currently being evaluated. In addition, some patients decide to discontinue treatment for a "drug-free holiday" of a few weeks or months. We would like to report a case of HIV transmission during a temporary interruption of treatment.

A 32-year-old woman was enrolled in the Spanish-Swiss intermittent therapy trial (SSITT), which aims at the induction of HIV-specific immune response by repeated suspension of treatment of 2 weeks' duration in patients with previously suppressed plasma HIV-RNA under HAART. At the time of the first drug-free period, the patient had been receiving HAART (stavudine (d4T), lamivudine [3TC] and nelfinavir) for 22 months and had a CD4 cell count of 630/μl. At 2 weeks after the first drug-free interval, her blood viral load rose from less than 50 to 130,000 cp/ml (by Roche Amplicor, Roche Molecular Systems, Rotkreuz, Switzerland) and treatment was reintroduced according to the protocol.

For the previous 6 months, the patient had lived in a monogamous sexual partnership with a 27-year-old healthy HIV-negative man. Despite repeated counseling, the couple continued to practice unprotected vaginal sex. Sixteen days after reintroduction of HAART in the index patient, her partner developed fever, headache, and fatigue, followed the next day by a disseminated maculopapular rash. A diagnosis of primary HIV infection was made, based on the clinical presentation, a positive p24-antigen assay, the presence of a few faint bands in the Western blot (gp160, p25, p68), and an HIV-RNA load of 16,000,000 copies/ml. The absence of any other exposure to HIV in the seroconverting partner and the sequence of the described events strongly suggest transmission of HIV during the short period of suspension of treatment.

Based on markedly decreased HIV-RNA and DNA shedding in genital secretions during HAART, we and others have previously hypothesized that the risk of transmission is reduced during therapy (1,2). As this case tragically illustrates, the HIV-RNA rebound during suspension of treatment reflects a rapid change from a stable situation with low risk of transmission to a highly infectious state, similar to the increased risk of sexual transmission during primary infection (3). In fact, shortly after the suspension of HAART, some patients develop a clinical picture indistinguishable from that of primary HIV infection, as was observed in another patient in the SSITT trial who rebounded from less than 10 to 930,000 copies during the first drug-free period. High blood viral load is clearly associated with an increased risk of sexual transmission (4) and with increased viral shedding in the genital tract (5). As indicated previously, interruption of treatment might occur more frequently in the future. Patients need to be advised about the increased infectivity immediately after the suspension of HAART.

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Pharmacokinetic Parameters of Protease Inhibitors and the Cmin/IC_{50} Ratio: Call for Consensus

To the Editor: The use of highly active antiretroviral therapy (HAART) including protease inhibitors (Pls) and reverse transcriptase inhibitors (RTIs) is associated with marked improvements in the clinical outcome of patients with HIV infection, even at advanced stages of the disease (1). Nonetheless, it has become increasingly clear that significant challenges remain if we are to extend the benefits of HAART to a greater proportion of patients infected with HIV. These include achieving adequate potency for antiviral activity, limiting toxicities and side effects, improving patient adherence, and preventing and treating drug resistance.

Some PIs achieve high peak concentrations, which may be associated with increased toxicity (2), and low trough concentrations (Cmin), which may result in insufficient drug exposure and an increased risk of viral breakthrough. Ritonavir can be used to inhibit the cytochrome P450 enzyme CYP3A4, resulting in significant increases in plasma concentrations including Cmin (3). Additional benefits resulting from this strategy include simplifying the therapeutic regimen by reducing pill burden, removing food restrictions, and/or reducing dosing frequency. Because it is likely that the Cmin of the PIs may correlate with antiviral efficacy (4), increasing Cmin concentrations and, consequently, overall drug exposure, may provide improved activity against the virus, including drug-resistant strains. The clinical application of this principle is reflected in the growing acceptance of the concept of pharmacokinetic enhancement of PIs by ritonavir, represented most notably by the recent approval of the fixed dose combination of lopinavir/ritonavir, as well as by data associated with amprenavir (5), indinavir (6), and saquinavir (7) in combination with low-dose ritonavir.

The clinical potency of a drug against a given viral population may be expressed as the ratio of the Cmin to the minimum inhibitory concentration (IC_{50}), (the concentration of drug necessary to inhibit virus replication by 50% in vitro). As the concept of pharmacokinetic enhancement of PIs has become more widely studied, various methods have been used to calculate and compare IC_{50}s and trough drug concentrations. The IC_{50} is preferred more than IC_{90} or IC_{95} because it lies in the middle of the concentration response curve and is the more precise measurement.

A number of factors may confound comparisons among various pharmacodynamic parameters. These include: 1) whether the inhibitory concentrations are measured in the presence of human serum and what concentration of serum is used; 2) what strain of virus is used to measure inhibition; 3) what cell type, and what time point after infection; 4) whether the trough concentrations are calculated or measured in healthy volunteers versus HIV-infected individuals (HIV-infected individuals may have higher levels of proteins such as α_1 acid glycoprotein (AAG), which can alter unbound drug concentrations) (8); and 5) what dosing regimen of drug is used to assess Cmin. To make valid comparisons among the agents, it is necessary to compare data generated using identical techniques.

Molla et al. (9) have used the term *inhibitory quotient* (IQ), which is Cmin/EC_{50} ratio. Their method, the EC_{50} (that is, effective concentration), is an in vitro measure of virus inhibition determined in the presence of 50% human serum, which has lower concentrations of plasma proteins such as AAG compared with 100% human serum. Many PIs bind with high affinity to AAG, which becomes diluted in anything less than 100% serum. Unfortunately, most tissue culture cells do not survive in higher serum concentrations and HIV viral replication is inhibited by the presence of high serum. One problem with this technique is that the slopes of the increases in protein binding of the various PIs with increasing serum content are not identical. Thus, highly protein bound PIs probably have much steeper increases in protein binding when going from 50% to 100% serum than less protein bound PIs.

A second method of evaluation uses a Cmin/IC_{95} ratio. Here, the IC_{95} is an in vitro measure for a single isolate (NL4–3, ViroLogic) where the effect of protein binding is estimated based on foldchange using the IC_{50} of three wild-type isolates (HXB2, IIIB, NL4–3) (9). A third method uses a Cmin/IC_{50} ratio, in which the IC_{50} is based on 334 patient isolates from the PRO3006 trial for amprenavir (10). This method estimates the free drug concentration of each PI by using the published mean protein binding data for each drug (indinavir, 60%; amprenavir, 90%; saquinavir, 97%–98%; nelfinavir, 98%; ritonavir, 98–99%; and lopinavir, 98%–99%). Nonetheless, even this technique has a significant error rate for the highly protein bound drugs, because there is variability in protein binding around the mean. Thus, a protein binding of 98% versus 99% yields a twofold difference in plasma-free concentration at an equivalent total plasma concentration.

There are few data to support the predictive value of any of these methods, although the first method has been shown to have some association with antiretroviral response to lopinavir/ritonavir in patients failed by a previous protease inhibitor—containing regimen and also received efavirenz therapy (11). Each of these calculations uses a different method for determining the IC_{50}, a different method to adjust for protein binding, and different numbers for the achievable drug concentrations. Although each method has some measure of validity on its own terms, the lack of standardization among the techniques makes comparisons extremely difficult.

Clinicians need to recognize that therapeutic success or failure is the consequence of many factors, not just drug potency and pharmacokinetics. Drug tolerability, toxicity, and adherence to therapy all play important roles. Most importantly, there is a need for clinical trials that will assess the validity of the ratio of protease inhibitor trough concentration to inhibitory concentration as a predictor of clinical efficacy. Although there is a strong theoretical rationale for the use of such measures, long-term controlled clinical trial data are needed to demonstrate how these calculated values can be used most effectively in therapeutic decision making.

Much of the success in antiretroviral therapy in recent years has been the result of improvements in our understanding of how to tailor therapies to individual patients based on the specific characteristics of particular agents and combinations, and how to best sequence therapies over time. The exploration and validation of pharmacologic parameters will provide clinicians with additional data that may contribute to improved clinical outcomes. Although it is clear that clinical effectiveness is never the result of one isolated pharmacologic feature of a drug, as we improve our knowledge of how agents act and interact,

we will be better equipped to make the complex treatment recommendations that are critical to effective antiretroviral therapy.

It is our opinion that, where possible, standardization of the measurement of pharmacokinetic and pharmacodynamic parameters of antiretroviral drugs is needed to provide useful information for HIV clinicians, allowing clinically relevant comparisons aimed at improving patient outcomes.

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