Update in HIV Care

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INTRODUCTION

This update in the care of individuals with HIV reviews key research publications from the past year relevant to General Internal Medicine practitioners. Specific topics that we have covered include new developments in the understanding of HIV transmission, risk behavior among injection drug users, baseline resistance testing, choice of initial treatment regimens, and controversies in treatment interruption. Our selection process was based on MEDLINE review of key journals by all authors and recommendations of experts in this field. The original MEDLINE review encompassed January 1, 2005 to March 1, 2006 and has been updated to September 1, 2006. Key phrases used in the search included “HIV,” “AIDS,” “heterosexuality,” “antiretroviral treatment (ART)/highly active antiretroviral therapy (HAART),” “drug resistance,” and “risk behaviors.”

HIV TRANSMISSION

Epidemiologic studies suggest the risk of HIV infection per heterosexual (coital) encounter (HIV infected to uninfected partners) is approximately 1 in 1,000. However, this risk rate seems low, given the spread of HIV during the past 20 to 30 years. As risk predictions are based on computer simulations rather than observation in real populations, this population-based study was undertaken to identify the risk of contracting HIV during heterosexual coital sex.

In Rakai, Uganda, the researchers attempted to identify the determinants of HIV transmission among monogamous, HIV sero-discordant heterosexual couples. They retrospectively identified 235 such couples where the HIV-uninfected partner reported being monogamous. These data were analyzed from a large, community-based randomized clinical trial previously conducted from 1994 to 1999 involving 15,127 adult participants. The original study evaluated the efficacy of treating sexually transmitted infections on the reduction of new HIV infections. The researchers collected a large amount of behavioral data and biological specimens from the participants during in-home surveys conducted at 10-month intervals for up to 40 months.

The median number of reported coital acts reported per couple was 8.3 per month. There was no reported anal intercourse, injection drug use (IDU), injected medication, or transfusions. Only 29% of couples reported any condom use, and none used condoms consistently. Overall, 68 of the 235 (29%) index partners transmitted HIV to their initially uninfected partner. The risk of transmission was higher among those with very early HIV infection and those with late-stage disease compared to those with chronic infection. In fact, almost half (43%) of the index partners acquiring HIV during the study transmitted the virus to their partner during the acute HIV infection (the first 2.5 months after their seroconversion). In addition, 37% of new infections were acquired from index partners with late stage HIV disease (within 35–61 months before death). The risk factors associated with HIV transmission in an adjusted model were early/incident HIV infection (aRR 4.98), late-stage HIV infection (aRR 3.49), high HIV viral load (aRR 7.06), genital ulcer disease (aRR 2.03), and younger age of the index partner (aRR 2.38). No significant association was seen with the gender of the index partner, circumcision status (of male index partners), AIDS-defining symptoms, symptoms of discharge or dysuria, or laboratory evidence of sexually transmitted infections (STIs).

This study presents the first observational data to confirm the validity of earlier computer simulations that predicted the greatest period of risk for viral transmission is during the period of acute HIV infection. These results strongly suggest that those with early HIV infection are a leading source of the sexual spread of this infection. Although late-stage HIV disease was also associated with an increased transmission risk, individuals with more advanced disease reported fewer coital acts, had fewer partners, and were more likely to have HIV infected (not sero-discordant) partners.

This study has a number of limitations. It was performed in rural Uganda and only evaluated monogamous, heterosexual couples who did not report anal intercourse. Despite these limits, the study findings have tremendous public health implications and underscore the need to develop strategies to identify people experiencing acute HIV infection so that we can intervene to reduce their risk of transmitting the virus to others.
**HIV TRANSMISSION AMONG INJECTION DRUG USERS**

Previous studies have demonstrated that HIV-positive injection drug users (IDUs) in clinical care may harbor and transmit drug-resistant HIV. Even those who are aware of their HIV status may still share needles and/or injection equipment (“works”). Few studies have examined the number of needle-sharing events involving HIV drug-resistant strains and provided information about the number and perceived HIV serostatus of sharing partners. Therefore, to characterize the relationship between injection–drug risk behavior and drug resistance and to estimate the likelihood of transmission of resistant HIV, Kozal et al. performed a cross-sectional study of resistant HIV, to estimate the prevalence of drug-resistant HIV, and to identify the number and perceived serostatus of needle-sharing partners. Thus, to characterize the relationship between injection–drug risk behavior and drug resistance and to estimate the likelihood of transmission of resistant HIV, Kozal et al. performed a cross-sectional study of resistant HIV.

Patients from 19 European countries seen during 1996–2002 were studied with genotype resistance assays. Of the 2,208 patients in the sample, about 1/3 (N=777) were recently infected (less than 1 year). 607 had over a year of chronic infection, and for the rest, the duration of infection was unknown. By the International AIDS Society-USA mutation definitions, about 10% of antiretroviral-naïve patients had at least 1 resistance mutation. Resistance was more common in recently infected patients (13.5%) than in those who had been infected for more than a year (8.7%), or for an unknown amount of time (8.7%; P=0.006), suggesting that longstanding infections may have taken place at a time when resistance was rarer, or alternatively that there may be reversion to wild type in at least some patients over time. In the 777 recently infected patients, nucleoside reverse-transcriptase inhibitor-related resistance decreased from 13.4% in early years (1996–1998) to 6.3% in later years (2001–2002), likely owing to the improved effectiveness of antiretroviral therapy over time. However, non-nucleoside reverse-transcriptase inhibitor (NNRTI)-related resistance increased from 2.3% to 9.2% in later years when they were more commonly used. Protease-inhibitor resistance was less than 5% and did not change over time. When drug susceptibility interpretations were done from genotypes using commonly available algorithms, predicted high-level resistance was most common for drugs with low genetic barriers to resistance development such as NNRTIs and lamivudine.

Drug resistance was common in these European antiretroviral-naïve patients, as it has been shown in studies in the U.S. Overall, resistance rates may be increasing. This study was large and geographically diverse, but still may not reflect rates that would be seen elsewhere. Nevertheless, it suggests that baseline genotyping may well be justified in many clinical settings in patients with chronic or unknown duration of infection and those with acute infection. The risk of transmission of resistant strains should be considered when starting new regimens and in selecting empirically based postexposure prophylaxis regimens. These and other data have led to a change in Department of Health and Human Services (DHHS) guidelines to recommend “performance of genotypic resistance testing prior to initiation of antiretroviral therapy in patients with acute or chronic HIV infection (BIII).”

**PREVALENCE OF BASELINE RESISTANCE**

Effective, sustained management of HIV infection with antiretroviral medications is limited by the fact that drug resistance is common, and resistance to some drugs may confer cross-resistance to other antiretrovirals, making regimen selection a great challenge. Transmission of resistant HIV from therapy-experienced individuals to others has been documented for a broad range of drug-resistant variants, so that clinical concern about resistance exists for patients new to therapy and for those who have been treatment-exposed. Patterns of resistance could influence selection of initial treatment regimens, postexposure prophylaxis regimens, and whether to perform resistance testing in those seeking therapy for the first time. The SPREAD Programme investigators studied HIV patients from across Europe not previously exposed to antiretrovirals to determine the prevalence and patterns of transmitted drug resistance.

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**SELECTION OF INITIAL ANTIRETROVIRAL REGIMEN**

Treatment of HIV-infected, antiretroviral naïve patients continues to evolve, as new medications and fixed drug combinations emerge. The DHHS guidelines recommend efavirenz or lopinavir/ritonavir in combination with a backbone of 2 nucleoside reverse transcriptase inhibitors. In the efavirenz-based regimen, the currently recommended nucleoside analogs are zidovudine or tenofovir paired with lamivudine or emtricitabine. With a lopanivir/ritonavir-based regimen, the preferred nucleoside backbone is zidovudine plus either lamivudine or emtricitabine. The recently released Interna-
ional AIDS Society-USA Panel recommends the use of the combination pills zidovudine/lamivudine, tenofovir/emtricitabine, or abacavir/lamivudine, used with either an NNRTI (efavirenz or nevirapine) or a protease inhibitor (PI) (lopinavir, atazanavir, fosamprenavir or saquinavir) boosted with ritonavir. Studies published this year are likely to impact future DHHS recommendations.

Gallant and colleagues conducted a study to evaluate the choice of nucleoside analog backbone. The open-label, randomized study of 517 HIV infected, treatment-naïve patients, compared tenofovir and emtricitabine once daily to the fixed-dose zidovudine/epivir twice daily. Each nucleoside pairing was given with once daily efavirenz. Subjects were primarily white (60%) and male (86%). Approximately 50% of subjects in each arm had baseline HIV polymerase chain reaction (PCR) quantifications of greater than 100,000 copies/mL, and approximately 40% had CD4 counts <200 cells/mm$^3$ at enrollment. Although initially designed to test non-inferiority of tenofovir to zidovudine, a 48-week data demonstrated that significantly more patients in the tenofovir–emtricitabine group reached the primary end point of HIV RNA quantification of <400 copies/mL (84% vs 73%, $P = .002$) and <50 copies/mL (80% vs 70%). In addition, patients receiving tenofovir–emtricitabine had greater increases in CD4 cell count (190 vs 158 cells/mm$^3$, $P = .002$) compared to zidovudine/lamivudine. Some of the results can be explained by the higher drop out rate for patients in the zidovudine/lamivudine arm (9% discontinuation zidovudine/lamivudine vs 4% for tenofovir–emtricitabine), primarily because of anemia. Interestingly, no patients developed the K65R mutation, suggesting that there may be a difference in resistance to one or more of the drugs in the combination pill needs to be considered (see above). Overall, one pill does not fit all: therapy should still be tailored to the individual patient.

**CONTROVERSIES IN CD4-GUIDED INTERMITTENT THERAPY**

Concerns over adverse effects of continuous antiretroviral therapy such as development of resistance, side effects, long-term toxicity, decreased quality of life, and cost have contributed to the consideration of CD4-guided treatment interruption. In this paradigm, once the CD4 count is above a predetermined level, antiretroviral therapy is discontinued. The CD4 count is then followed and therapy resumed once the CD4 declines to a designated threshold value. In this manner, the patient cycles on and off therapy. Previously, small studies using CD4-guided therapy have shown that patients can remain off therapy for an average of 8–12 months, do not develop significant resistance, and although there is a rapid increase in viral load to pretreatment levels after stopping therapy, patients have a good response when therapy is resumed. However, these trials were small and did not have hard clinical outcomes.

This year, data from a larger study of CD4-guided therapy, the Strategies for Management of Antiretroviral Therapy (SMART) trial, were reported. In this trial, 5,472 patients from a variety of international sites were randomized to either continuous treatment with a goal of maintaining full viral suppression or to the CD4-guided drug conservation arm with a goal of limiting exposure to antiretroviral therapy. In the latter arm, antiretroviral therapy was given intermittently depending on the CD4 count: therapy was discontinued if the CD4 count was above 350 cells/mm$^3$ and resumed when the CD4 count fell to below 250 cells/mm$^3$.

The primary end points were defined as HIV progression or death. The baseline characteristics in the two groups were well matched for baseline and nadir CD4. Patients had a median baseline CD4 of 600 cells/mm$^3$ at enrollment, and the median lifetime nadir was 250 cells/mm$^3$. Overall, 25% of each group had been AIDS defined, and 70% had viral suppression at baseline. Very few patients were treatment naïve, and the median time on antiretroviral therapy was 6 years.

The SMART study was stopped early because the CD4-guided intermittent therapy arm had significantly higher number of events (HIV progression and death) than the viral suppression arm. The overall event rate in the drug conservation arm was 3.7 events per 100 patient years versus 1.5 in the continuous treatment arm, a relative risk of 2.5 ($P < .0001$). In addition, severe complications (myocardial infarction, stroke, progression of liver and kidney disease) were also
found to be increased in the treatment interruption group (RR 1.62). Subgroup analysis did not find any correlation with CD4 nadir or baseline CD4 count: the relative risk of discontinuing therapy was approximately equivalent for all groups examined.

One potential explanation of the results may be because of differences in CD4 counts during the trial. The CD4-guided therapy group spent over 30% of the time at CD4 counts below 350 cell/mm$^3$ and below 250 cell/mm$^3$, greater than 10% of the time compared to 9% and 2%, respectively, for the continuous treatment arm. An alternative possibility is that the results may be explained by the level of HIV viremia. Although the viral load data have not been reported, in the continuous therapy arm, patients were on therapy 93% of the time, whereas in the treatment interruption arm, patients were on therapy only 33% of the time. Thus, HIV viremia may possibly explain some of the findings, particularly the increase in non-HIV-related complications.

The main limitation to this study is the concern that the restart level of 250 CD4 cells/mm$^3$ may have been too low. Both SMART and the smaller Trivican study, which used this threshold, have reported increased mortality and morbidity. Another small study, STACATTO, which used a CD4 threshold of 350 cell/mm$^3$, reported this strategy to be safe and effective. Thus, it remains to be seen whether CD4-guided intermittent therapy may be feasible with a higher threshold for restarting therapy.

In conclusion, in the SMART trial, CD4-guided intermittent therapy was associated with increased risk of clinical AIDS, severe complications, and death. Currently, the DHHS expert guidelines "cautions patients and clinicians that treatment interruption should only be done in the setting of a clinical trial and under close observation."

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