

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

Genes, Ethnicity, and Efavirenz Response: Clinical Pharmacology Update from the 11th CROI

By Adriana Andrade, M.D., M.P.H. and Charles Flexner, M.D.

Race, Ethnicity and Pharmacokinetics

Pharmacokinetics, therapeutic response, and side effects have been shown to vary in HIV-infected patients from distinct ethnic backgrounds [Barrett JS, et al. *Int J Clin Pharmacol Ther* 2002;40:507; Pfister M, et al. *Antimicrob Agents Chemother* 2003; 47:130]. A recent study found a statistically significant association between polymorphism in the human multidrug resistance-1 (*mdr1*) gene, efavirenz (EFV) plasma concentrations, and CD4 changes during treatment [Fellay J, et al. *Lancet* 2002 5;359:30] suggesting a role for host genomic diversity in explaining these differences. However, the results of this study are controversial, as several later studies failed to confirm this association (Flexner C, *Topics HIV Med* 2003;11:40). During the 11th CROI in San Francisco, two studies investigated a possible role for genetic differences as the basis for developing EFV toxicity. Both abstracts presented data from Adult AIDS Clinical Trials Group (AACTG) Protocols 5095/5097, in which HIV-infected antiretroviral-naïve subjects were randomized to receive either efavirenz (EFV) plus zidovudine/lamivudine/abacavir (*Trizivir*) or *Trizivir* alone.

In the first study, Heather Ribaldo from Harvard discussed the findings from ACTG 5097, a sub-study of the ACTG 5095 protocol which investigated the relationship between EFV pharmacokinetic parameters, CNS side effects, weight, race, virologic response and treatment discontinuation [Abstract 132]. From the 202 subjects randomized to take an EFV-containing regimen, 81% were males (53% white non-Hispanic, 32% black-non-Hispanics, 12% Hispanics, and 3% other). The investigators found significant associations between drug clearance and weight, and between drug clearance and race. EFV clearance was 24%

lower in blacks and Hispanics (9.4 L/hr) compared to whites (12.4 L/hr), while EFV area under the concentration-time curve (AUC) was 24% higher in black and Hispanics (64 mg x h/L) compared to whites (48 mg x h/L). There was a trend towards an increased rate of EFV discontinuation with decreasing EFV clearance and increasing EFV concentration, but no apparent association between EFV clearance and CNS toxicity. Analysis of virologic response is underway.

The second study evaluated the relationship between genetic variants of the cytochrome P450 2B6 (CYP 450 2B6), CYP450 3A4/5 and MDR-1 genes and EFV pharmacokinetics, CNS toxicity and therapeutic effect. EFV is primarily metabolized by the CYP2B6 and 3A4/5 pathways, and genetic polymorphisms in these genes have been described. Using real-time PCR, Haas and colleagues evaluated six allelic variants from patient DNA samples obtained from the AACTG DNA repository: CYP450 2D6 (G516T, C1459T), CYP450 3A4 (A-392G), CYP450 3A4/5 (A6989G), and *mdr1* (G2677T, C3435T) [Abstract 133]. Pharmacokinetic sampling of EFV and assessment of CNS side effects were done at weeks 1, 4, 12, and 24. Of the 157 subjects included in the final data analysis, 57% were white, 32% were black and 10% were Hispanic. Median EFV AUC was significantly greater in blacks (58 µg.hr.mL⁻¹) and Hispanics (66 µg.hr.mL⁻¹) than in European Americans (46 µg.hr.mL⁻¹). All 6 identified allelic variants were significantly associated with EFV plasma concentrations among all

subjects. Twenty percent of the African Americans were T/T homozygous at the CYP450 2B6 516 position compared to only 3% of European Americans. The median AUC was 3-times higher with the 516 T/T genotype relative to G/G. Overall, G/G and T/T homozygotes were associated with lower and higher EFV plasma concentrations, respectively, while those who were heterozygous (G/T) at this locus had intermediate levels. CYP450 2B6 G516T and CYP450 3A45 A6986G were significantly associated with EFV clearance. No apparent association was found between race and clearance after adjusting for these allelic variants.

With regard to EFV-associated CNS toxicity, the CYP450 2B6 position 516 TT genotype was significantly associated with risk of CNS effects only at week 1 (P=0.036). No associations were observed between the allelic variants and immunologic and virologic response.

The findings from these two studies corroborate the notion that drug metabolism may be affected by racial background, and suggest that CYP450 2B6 polymorphisms may explain some of the reported differences in EFV exposure and therapeutic effect. The 516 T/T genotype, more frequently found in African Americans, was associated with higher plasma EFV concentrations, slower clearance, and increased CNS toxicity at week 1. However, the association with CNS toxicity was no longer evident by week 4, so the clinical significance of this association is unclear. Furthermore, while the associations

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described are statistically significant, drug concentrations overlapped substantially amongst the two genotypes. It remains to be seen whether similar associations occur with other antiretroviral agents. Though these observations need to be confirmed in other large databases, they will renew interest in the potential role of the individual genome and treatment of populations with diverse racial/ethnic backgrounds. The extent to which polymorphisms will impact tolerability and virologic suppression is still unclear.

The Impact of Sex, Weight and Race on the Pharmacokinetics of Antiretrovirals Agents

Much effort has been spent characterizing the effects of sex, weight and race on the pharmacokinetics of anti-retroviral agents. There have been reports suggesting that drug metabolism may differ between sexes and among racial groups [Flexner C, *HHR*2003; 15(3):7] and that body weight could influence the pharmacokinetic parameters of antiretroviral drugs [Keiser P, et al. Abstract 927, 10th CROI, 2003, Boston]. These are potentially important observations since significant variations in the pharmacokinetics of antiretroviral drugs could affect virologic response and/or increase the risk of drug toxicity.

Hitti and colleagues explored these topics in a retrospective analysis of pharmacokinetic data from six studies from the AACTG (ACTG 368, 372, 384, 388, 389 and 5055) [Abstract 604]. These investigators assessed individual pharmaco-kinetic data for EFV, indinavir (IDV), nelfinavir (NFV) and M8 (the primary active metabolite of NFV) in plasma samples from 38 females and 233 males from diverse racial backgrounds. Body weight and body mass index (BMI) were also included in the multivariate logistic regression model. The authors found that female subjects (15 samples) had a 25% higher mean EFV AUC than their male counterparts (82 samples) [see Table, right]. This association remained statistically significant after adjusting for weight, racial group and co-administered medications (amprenavir[APV]; ritonavir [RTV]; and any NNRTIs). No significant differences in

systemic exposure to IDV, NFV or M8 were found between males and females. Of note, women were more likely than men to belong to a racial minority group, which could have confounded the study results.

With respect to race, blacks had significantly higher IDV AUCs and lower NFV and M8 AUCs. In contrast to the studies by Ribaudo and Haas, EFV AUC was indistinguishable between blacks and subjects from other racial backgrounds,. These results were independent of sex, weight and BMI.

Finally, body weight was a significant predictor of AUC for EFV and IDV but not for NFV or M8. Weight remained a statistically significant determinant of this pharmacokinetic parameter even after adjusting for sex and concurrent medications. It is important to note that body

weight was not statistically different between women and men.

These study findings underscore the complex influences of race, gender and weight on the pharmacokinetics of individual antiretroviral agents. A number of studies have described differences in treatment efficacy and antiretroviral-induced toxicity between women and men that may now be explained by sex-based differences in drug concentrations. The positive association between female sex and higher plasma concentrations of some antiretroviral drugs has been previously described [see Flexner C, *HHR* 2003;15(3):7]. One possibility is that sex-based differences in P-glycoprotein expression may explain this association. P-glycoprotein is the product of the *mdr1* gene and is a membrane drug efflux transporter that pumps out of the cell

Table. Sex, Weight and Race-Based Differences in the Mean AUC of Efavirenz, Indinavir, Nelfinavir, and M8*

	Efavirenz 600 mg QD Mean AUC ₀₋₂₄ µg x hrs/mL (range)	Indinavir 400-1200 mg bid Mean AUC ₀₋₁₂ µg x hrs/mL (range)	Nelfinavir 1250 mg bid Truncated AUC ₀₋₆ µg x hrs/mL (range)	M8
Sex				
Males	39.9 (31.3-50.8)	37.1 (22.7-60.6)	14.1 (10.7-18.5)	2.3 (1.3-4.0)
Females	51.8 (46.7-57.5)	35.1 (27.9-44.3)	13.9 (12.5-15.5)	2.4 (1.9-2.9)
P=Value	P=0.050	NS	NS	NS
Race				
African American	50.2 (40.5-62.2)	51.0 (35.5-73.1)	11.3 (9.6-13.3)	1.7 (1.2-2.3)
Other	49.7 (44.5-55.4)	30.1 (23.6-38.4)	15.6 (13.8-17.5)	2.9 (2.3-3.7)
P-Value	NS	P=0.018	P=0.002	P=0.011
Weight				
Change/10 Kg (from 75-85 Kg)	-3.3	-6.6	0.2	0.2
P-Value	P=0.050	P=0.016	NS	NS
BMI				
Change/5 units (from 25-85 units)	-6.9	-3.5	0.2	0.4
P-Value	P=0.007	NS	NS	NS

*Adapted from Hitti, et al., Abstract 604.



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some antiretroviral agents [see Andrade and Flexner, *HHR* 2001;13(2):12]. In some studies, females were shown to express less P-glycoprotein than males [Cummins CL, et al. *Clin Pharmacol Ther* 2002;72:474] which could theoretically affect the plasma concentrations of antiretroviral agents that are P-glycoprotein substrates. However, other potential mechanisms may figure into this relationship, since plasma concentrations of IDV, a P-glycoprotein substrate, were equivalent in male and females in this and one previous study [Fletcher CV, et al. Abstract 128, 2nd IAS, 2003, Paris].

Gastrointestinal motility, plasma protein levels, and CYP450 enzyme function and

excretion activity are examples of other potential factors that could theoretically contribute to the sex-based variations of antiretroviral pharmacokinetics. Gastric emptying is influenced by sex hormones and is reportedly slower in females [Hutson WR, et al. *Gastroenterology* 1989;96:11]. A trend was found towards a higher CYP450 3A4 metabolic rate in females while sex-based differences are thought to be the result of weight difference between men and women [Gandhi M, et al. *Annu Rev Pharmacol Toxicol* 2004;44:499]. Although, sex-determined variations in drug metabolism have been identified for a number of commonly prescribed drugs, it remains unclear whether these differences can significantly affect the

efficacy and toxicity of antiretroviral agents. To date, there are no compelling data to justify antiretroviral dosing modifications based on sex-related metabolic and pharmacokinetic differences.

Some have questioned the practice of using fixed antiretroviral doses with no regard to body weight. Results from this and other retrospective studies suggest that weight is a predictor of plasma concentrations for some but not all antiretroviral agents [Keiser P, et al. Abstract 927 10th CROI, 2003, Boston]. However, the isolated effect of weight on pharmacokinetics is difficult to discern because in most

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studies investigating this association women tended to have lower body weights and BMIs than males. In the current study, weight did not differ between men and women but remained a predictor of AUC for EFV and IDV, and for NFV and M8, even after adjusting for sex. These results conflict with findings from a previous study that found a positive association between lower body weight and therapeutic success in patients treated with NFV-containing regimens [Keiser P, et al. Abstract 927, 10th CROI, 2003, Boston]. The lower proportion of women in the current study and differences in study population could explain these discrepancies. Thus, questions remain about the relevance of body weight to the efficacy of antiretroviral drugs.

Generic Antiretrovirals: How Good Are They?

The production of generic versions of brand name antiretroviral agents continues to increase in countries such as Thailand, Brazil, and India. However, there is ongoing concern about the quality of generic formulations. Penzak and colleagues addressed this issue in a quality control and bioequivalence study of six antiretroviral agents: saquinavir (SQV), IDV, lopinavir/ritonavir (LPV/r), ritonavir (RTV), amprenavir (APV) and EFV from six manufacturers from various international sources [Abstract 581]. Using the United States Pharmacopeia (USP) Uniformity of Dosage Units Test (which specifies that drug content be between 85% to 115% of label claim) the investigators found that, with the exception of RTV, the active ingredient of each drug was within USP specifications. Of note, RTV was not continuously refrigerated which could explain the lower concentration of the active compounds found in this formulation.

These encouraging findings should not dissuade investigators from conducting further bioequivalence studies to continue monitoring the quality of generic drugs, especially in light of recent reports of counterfeit antiretroviral products in the developing world [Apoola A, et al. *Lancet* 2001;357:1370].

Drug Interactions

• Extended-Release Stavudine and Tenofovir DF

Stavudine extended-release (d4T XR) and tenofovir DF (TDF) are potential components of once-daily HAART regimens and thus, it is important to establish how concomitant administration of these two agents might affect their pharmacokinetics. Previous investigation revealed that TDF had no significant effect on the pharmacokinetics of d4T XR [Kaul S, et al. Abstract 534-W, 10th CROI, Boston 2003]. In this study the same team of investigators evaluated the effect of d4T XR on TDF steady-state pharmacokinetics [Kaul S, et al. Abstract 602]. In this Phase 1, open-label study, 18 healthy volunteer went through three treatment phases:

- Period 1** d4T XR 100 mg QD for 1 day
- Period 2** TDF 300 mg QD for 7 days
- Period 3** d4T XR 100 mg QD + TDF 300 mg QD for 1 day

The authors reported that d4T XR had no significant effects on TDF pharmacokinetics and co-administration of TDF and d4T XR was safe and well tolerated. Although the lack of drug interaction and toxicity in this short term study is reassuring, the main concern continues to be possible long-term toxicity associated with d4T XR. In a separate study presented at this meeting, extended-release d4T appears to be less toxic than standard d4T [see Cofrancesco J, *HHR* 2004;16(2):12]. This was a post-hoc analysis of two different studies and did not compare the d4T XR safety profiles with that of other NRTIs.

Effect of Hepatic Impairment on Tenofovir Metabolism

Hepatic impairment is a common finding in the HIV infected population, especially in the setting of hepatitis B or C co-infection. The pharmacokinetics of TDF, an agent with activity against HIV and hepatitis B, have not been studied in patients with hepatic impairment. Even though TDF is primarily excreted unchanged by the kidneys, 20% to 30% of this drug is eliminated by non-renal mechanisms [*Viread Disoproxil Fumarate* (Tenofovir) tablets product monography. Gilead Sciences, Inc., Foster City, CA, 2002]. It is unknown whether TDF affects the pharmacokinetics of other drugs used to treat hepatitis B infection (adefovir dipivoxil [ADV]) and hepatitis C (ribavirin [RBV]). To address these questions, a group of investigators from Gilead conducted three pharmacokinetic studies [Kearney PB, et al. Abstract 600]. Using the Child-Pugh-Turcotte Score (CPTS), the first study compared single dose TDF pharmacokinetics (300 mg QD) in subjects with unimpaired hepatic function (8 subjects; CPTS 5.0±0) to those with moderate (7 subjects; CPTS 8.0±.8) and severe (8 subjects; CPTS 10.8±1.0) hepatic impairment. The second and third studies evaluated potential pharmacokinetic

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interactions between ADV (10 mg QD alone for 1 day)/TDF (300 mg QD for 7 days) and RBV (600 mg QD for 1 day)/TDF (300 mg QD for 21 days). The authors reported that TDF concentrations were not significantly altered by moderate or severe hepatic impairment, and ADV and RBV plasma concentrations were indistinguishable when dosed with or without TDF. These findings are consistent with the fact that TDF is not primarily metabolized by the liver, and thus hepatic impairment should have a limited impact on the pharmacokinetics of this drug.

• **Efavirenz and Statins**

PIs are inhibitors of cytochrome P450 3A4 (CYP450 3A4), the same enzyme responsible for the metabolism of a number of HMG-CoA reductase inhibitors (statins). Consequently, there is a considerable potential for pharmacokinetic drug interactions when these agents are combined. It is known that inhibition of the CYP450 3A4 by ritonavir/saquinavir (RTV/SQV) greatly increases simvastatin and atorvastatin concentrations, which could potentially lead to serious drug toxicity such as rhabdomyolysis [Fichtenbaum CJ, et al. *AIDS* 2002;16:569]. Conversely, a significant reduction in pravastatin plasma concentrations occurred when it was combined with NFV and EFV, raising concerns about a possible reduction in the effectiveness of this drug [Gerber JG, et al. Abstract 870, 2nd IAS, Paris, 2003].

EFV is a mixed inducer/inhibitor of the CYP450 3A4 and might affect statin metabolism. This issue was addressed in the ACTG 5108 study, in which 28 healthy volunteers were treated 14 days of EFV 600 mg QD and then for 3 days with either simvastatin 40 mg QD (14 subjects) or atorvastatin 10 mg QD (14 subjects) alone [Gerber JG, et al. Abstract 603]. EFV reduced simvastatin and atorvastatin $AUC_{0-24 \text{ hrs}}$ by 58% and 43%, respectively. Neither simvastatin nor atorvastatin altered the plasma pharmacokinetic parameters of EFV. It remains to be determined whether the reduction observed in simvastatin and atorvastatin concentrations has any clinical significance in the treatment of hyper-

lipidemia, and whether the recommended doses for these statins will have to be increased in an attempt to offset this pharmacokinetic interaction.

• **Atazanavir and Saquinavir/Ritonavir**

Investigators from the Chelsea and Westminster Hospital in London conducted an open label, single arm, pharmacokinetic study to determine the optimal dosage of concomitant atazanavir (ATV) and SQV-hcg (*Invirase*)/RTV [Boffito M, et al. Abstract 607]. These investigators reported that addition of ATV 300 mg QD to SQV-hcg/RTV 1600/100 mg QD at steady-state, resulted in a statistically significant increase in SQV geometric mean ratios (GMR) of 112% in C_{trough} , -42% in C_{max} , and 60% in $AUC_{0-24 \text{ hrs}}$. ATV pharmacokinetic parameters were comparable to those observed with RTV boosting (300/100 mg QD) without SQV. No significant changes in trans-aminases, glucose, cholesterol, or triglycerides were observed, although one third of the 20 HIV-infected participants developed clinically relevant hyperbilirubinemia.

The significant boosting effect on SQV/RTV pharmacokinetics may be secondary to additional CYP450 3A4 inhibition by ATV. Additional studies are needed to further explore the long-term safety, tolerability, and virologic effects of this regimen and to determine how it compares to other ATV-dual PI combinations.

Lopinavir/Ritonavir and Fosamprenavir

Systemic concentrations of LPV and APV are markedly reduced when lopinavir/ritonavir (LPV/r) and fosamprenavir (FPV) are combined [Kashuba ADM, et al. Abstract H-855a, 43rd ICAAC, Chicago 2004]. Two studies presented at CROI explored strategies to counteract this deleterious drug interaction. Corbett and others presented the results of a prospective, non-blinded, randomized, cross-over healthy volunteer pharmacokinetic study investigating whether temporal separation of FPV and LPV/r by 4 and 12 hours, or addition of an extra 200 mg of RTV, could prevent the reduction of FPV and LPV

concentrations [Abstract 611]. Study subjects were randomized into 3 groups:

- Treatment A:** FPV 700 mg bid + LPV/r 400/100 mg bid for 7 days (simultaneous administration)
- Treatment B:** FPV/r 700/100 mg bid + LPV/r 400/100 mg bid for 7 days (dosed 4 hours after FPV/r)
- Treatment C:** FPV/r 1400/200 mg QD + LPV/r 800/200 mg QD for 7 days (dosed 12 hours after FPV/r)

The authors reported that staggering administration of FPV and LPV/r did not ameliorate this pharmacokinetic interaction, since only LPV concentrations improved.

Investigators from GlaxoSmithKline also assessed dosing strategies to overcome the pharmacokinetic interaction between LPV/r and FPV [Wire MB, et al. Abstract 612]. In a randomized, open-label, steady-state, cross-over pharmacokinetic study, healthy volunteers were treated with either a regimen containing a higher dose of LPV/r (FPV 1400 mg bid + LPV/r 533/133 mg bid) or with standard doses of FPV and LPV/r with an additional RTV 100 mg dosed twice-daily (FPV 1400 mg bid + LPV/r 400/100 mg bid + RTV 100 mg bid). The authors found higher LPV plasma concentrations in the group treated with increased doses of FPV and LPV/r when compared to those treated with extra RTV. Nevertheless, APV concentrations were still below the levels observed in other boosted APV pharmacokinetic studies. LPV/r concentrations were higher with extra RTV, but variability was also increased. FPV and LPV/r combinations were poorly tolerated by these healthy volunteers leading to a high discontinuation rate (36% and 44% in the first and second regimens, respectively). Because of the high plasma concentration variability and discontinuation rate, the authors were unable to make dosing recommendations for this triple PI regimen.

Fact or Fiction: Transformation of AZT to D4T-TP

Last year, Becher and colleagues reported that lymphocytes taken from HIV infected

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HIV Superinfection: Can Patients Be Infected Twice?

By Joel N. Blankson, M.D., Ph.D.

How does one counsel two HIV-infected individuals who are in a monogamous relationship? Do they really need to still use condoms? The answer to this complicated question depends in part on whether or not an HIV-infected patient can be infected with another HIV strain. It is now known that dual HIV infection, defined as the presence of two distinct HIV strains in a patient, can occur. The best evidence for this phenomenon is the existence of recombinant viruses that contain genetic material from two different parental strains. Recombinant viruses can only be created by the simultaneous replication of the two parental strains in the same patient. There are two potential mechanisms by which dual infection can occur: coinfection, in which a host is infected by two distinct HIV strains at or around the same time, and superinfection, in which there is sequential infection of a patient by two different viral strains. Distinguishing between these possibilities has been an area of intense research. The evidence for and against these possibilities will not only affect how physicians counsel patients, it also has major implications for vaccine development.

Evidence of Coinfection

A case report in 1995 from David Ho's laboratory demonstrated that HIV coinfection can occur [Zhu T, et al. *J Virol* 1995;69:1324]. An acute seroconverter with exposure to multiple sexual partners was shown to be infected with multiple distinct HIV clade B isolates. The degree of genetic difference between two of these strains strongly suggested that the patient had been infected by different partners. Superinfection was ruled out by a negative HIV Western blot at the time of presentation. Interestingly, there was evidence of recombination between two of the strains. A second report demonstrated coinfection in an infant who received transfusions from two different HIV-infected donors [Diaz RS, et al. *AIDS Res Hum Retroviruses* 1996;12:1291]. Recombination between the two distinct strains was also observed. This was direct evidence

that coinfection could occur and could lead to recombinant viruses.

An elegant animal model of HIV infection has demonstrated that coinfection occurs more readily than superinfection. Macaques could be easily infected with two distinct strains of HIV-2 if the animals were inoculated with both viruses at the same time. However, if the animal was inoculated with one virus first, then, following a two-week window, it became progressively more difficult to infect the animals with a second virus [Otten RA, et al. *J Infect Dis* 1999; 180:673]. The reason for this difference is unclear, but one hypothesis has been that the immune response generated to the first virus provides protection against infection by a second virus. This may seem counterintuitive at first, given that the immune response of many HIV-seropositive patients doesn't seem to confer protection against the replication of autologous virus. But the inoculating dose of a second virus in most cases will be relatively small, and thus even a partially effective immune response may be able to prevent superinfection.

Evidence of Superinfection With Viruses from Different Clades

Seven years after the initial reports of coinfection, three reports of superinfection were published. The first two studies involved cases where the initial virus and the superinfecting virus were from different HIV clades. Ramos and colleagues demonstrated superinfection of two injection drug users who were enrolled in prospective cohort study in Thailand [Ramos A, et al. *J Virol* 2002;76:7444]. Clades AE and B viruses are the predominant isolates in this region. The subjects were screened for the presence of recombinant clade AB virus at different time points. Two patients were initially found to be infected with virus from a single clade. Approximately one year after seroconversion, only recombinant AB virus was found, suggesting that superinfection had occurred and had led to recombination.

Jost and colleagues reported a case of a patient who had been placed on HAART

during primary infection [*N Engl J Med* 2002;347:731]. He was on a supervised treatment interruption 2 years later when he was noted to have a rise in his viral load and symptoms of fatigue and fever. Analysis of his plasma virus at this time revealed clade B, virus whereas only clade AE virus had been detected at earlier time points. The patient had had a high-risk sexual exposure three weeks earlier in a country where clade B virus is endemic. Phylogenetic analysis of the 2 viruses confirmed that they were distinct strains, leading to the conclusion that super-infection had occurred.

In a recent study of highly exposed, HIV-positive commercial sex workers from Kenya with chronic infection, one individual who was initially infected with clade A virus was found to have only recombinant clade A/C isolates 10 years after seroconversion [Fang G, et al. *AIDS* 2004;18:153]. This patient had experienced a febrile illness and a drop in her CD4 count a few years before this. A detailed analysis revealed no evidence of clade C virus shortly after seroconversion, suggesting that superinfection had occurred with a clade C isolate leading to the formation of the recombinant AC isolates.

Evidence of Superinfection With Viruses From the Same Clade

Viruses from different clades have significant differences in their genetic composition. Therefore, it is not surprising that an HIV-specific immune response to the initial virus was not able to prevent superinfection by the second isolate. More concerning are two reports of superinfection by viruses from the same clade. The first involved another patient who had been treated with HAART during primary infection and who was then placed on a supervised treatment interruption [Altfield M, et al. *Nature* 2002;42:434]. Superinfection was detected when he experienced a sudden rise in his viral load and a significant drop in his CD4 count after having demonstrated excellent immune control of viral replication for close to a year. Phylogenetic analysis revealed that the circulating virus was genetically distinct



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from the isolate the patient had originally been infected with 3 years earlier. The patient had a high-risk sexual exposure 2 to 3 months prior to the rise in his viral load and had experienced symptoms consistent with the acute retroviral syndrome. Of note, he had a very broad CD8 T-cell mediated response to the first virus prior to superinfection, yet his immune system was unable to prevent infection with a second virus from the same clade. Subsequent studies, however, have shown that the assay used to analyze the CD8 T-cell responses in their study may not be a good predictor of HIV specific immunity [Addo MM, et al. *J Virol* 2003;77:2081].

Another noteworthy study demonstrated superinfection by a wild type clade B virus in a treatment-naïve person who was initially infected with a multidrug-resistant clade B isolate [Koelsch KK, et al. *AIDS* 2003;17:F11]. The wild type isolate predominated shortly after superinfection, but surprisingly, subsequent studies showed that the two viruses had similar replication capacities as determined by the virologic assay [Daar E, et al. Abstract 394, 11th CROI, San Francisco, 2004]. This illustrates the point that “viral fitness” is determined by more than just mutations in the protease and reverse transcriptase genes. In both cases of clade B superinfection, it was found that the superinfecting virus differed genetically from the initial virus in key regions or epitopes that were targeted by the immune system. This may have allowed the viruses to evade the immune response and thus to out-compete the initial virus.

It should be noted that all of these studies have failed to definitively rule out coinfection as the cause of dual infection. The inability to track the second virus could simply be due to a sampling error. A change in selective pressure could lead to preferential replication of one isolate and this could explain why the second virus was detected at a later date. The fact that some of these individuals had high risk exposures and symptoms of the acute retroviral syndrome shortly before the second virus was detected makes it more likely that superinfection had indeed occurred.

How Frequently Does Superinfection Occur?

There have only been five case reports of HIV superinfection in the literature, but it is possible that superinfection occurs much more frequently and is simply not detected. Two recent large studies would argue against this possibility. Gonzales and colleagues looked at the protease and reverse transcriptase genes of HIV isolates obtained from 718 individuals [*J Infect Dis*. 2003;188:397]. The sequence of these genes was followed longitudinally to screen for superinfection. Major genotypic changes were seen in some subjects, but this was mostly due to the loss or gain of drug resistant mutations associated with changes in antiretroviral therapy (ART). Sequence from *tat* and *gag*, genes not affected by changes in ART, were not significantly different in these cases. Thus superinfection was highly unlikely. They found no cases of superinfection during 1072 person-years of observation.

In a similar study, Tsui and colleagues performed longitudinal analyses of the *gag* and *env* genes from isolates obtained from 37 injection drug users [Tsui R, et al. *J Virol* 2004;78:94]. They found no evidence of superinfection over 215 person-years during which there was continued high risk exposure. They estimated that based on the reported exposure, there should have been 3.4 episodes of superinfection. They thus concluded that existing HIV infection conferred a significant degree of protection against infection with an isolate from the same clade. Both of these studies are limited by the relatively low sensitivity of the methods used to screen for superinfection. Neither assay would routinely pick up an isolate that accounted for less than 20% of the circulating virus. Thus if a superinfecting virus did not out compete the existing virus, it would probably not be detected.

In a preliminary report, Smith and colleagues used similar techniques to look at 54 patients with early HIV infection who had deferred treatment with ART [Smith D, et al. Abstract 21, 11th CROI, San Francisco, 2004]. Curiously, three cases of superinfection were detected in 46 person-years

of follow up. One patient, who was initially infected with a wild type strain, later became infected with a drug-resistant isolate. Superinfection generally was associated with an increase in viral load (mean of 1.6 log) and a decrease in CD4 count (mean 132 cells/mm³). It's unclear why there is such a discrepancy between this study and the prior two larger studies. It should be noted that people with early HIV infection have a more homogeneous population of isolates than chronically infected persons, and thus a new viral isolate might be easier to detect. Alternatively, individuals with early infection may be more susceptible to superinfection, possibly because their HIV-specific immune response is still evolving.

Summary

There are now sufficient data suggesting that superinfection can occur. Significant drops in CD4 counts and transient increases in viral loads often accompany superinfection. Furthermore a recent retrospective analysis showed a very rapid progression from seroconversion to clinical AIDS in five untreated patients with dual HIV infection (range of 1.0 to 3.4 years) [Gottlieb GS, et al. *Lancet* 2004; 363:619]. It should also be noted that patients on HAART with undetectable viral loads may be at increased risk of superinfection, as the levels of HIV-specific neutralizing antibody and effector CD8 T-cells have been shown to decline over time when viral replication is suppressed [Morris MK, et al. *J Acquir Immune Defic Syndr* 2001;28:405, Casazza JP, et al. *J Virol* 2001;75:6508]. There is also the danger of infection with drug-resistant viruses, which would have a selective advantage over wild type virus in patients on effective antiretroviral therapy. Based on these findings, HIV-infected people should be advised to practice safe sex with other HIV-infected partners in order to prevent HIV superinfection and all of its associated consequences. Additionally, safe sex practices are indicated to prevent transmission of other sexually transmitted infections. ▲



Syphilis Rates Climb Again

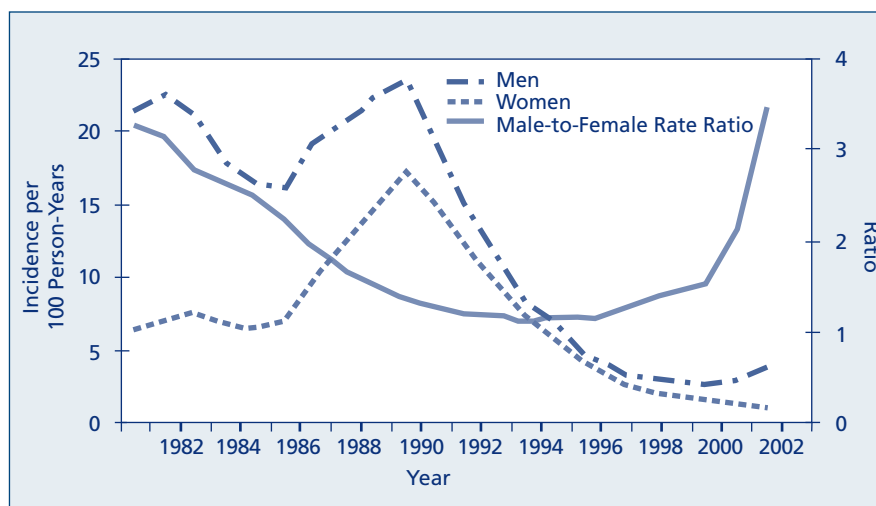
By Emily J. Erbelding, M.D., M.P.H.

Rates of primary and secondary (P&S) syphilis in the United States have risen for the third straight year since hitting an all-time low in 2000. Projected rates for the United States as a whole were presented at the CDC 2004 STD Prevention Conference in Philadelphia this past March [Heffelfinger J, Symposium A-07]. Though surveillance reporting from all jurisdictions is not yet final for 2003, there are likely to be over 7,000 reported cases of P&S syphilis in the US, at least a 3% increase over 2002. Emerging pockets of syphilis transmission have historically served as sentinel indicators of new patterns of HIV spread. As such, they provide clues that may indicate where HIV prevention services fall short of HIV prevention needs. This article will describe recent US epidemiologic trends in syphilis and their relationship to HIV, and what HIV treatment providers can do to detect syphilis and assist public health agencies in reversing these trends.

Syphilis Elimination

In 1999, CDC officials noted that the biologic characteristics of *Treponema pallidum* would make syphilis uniquely vulnerable to an elimination strategy: it lacked an animal reservoir; its fairly long incubation period following exposure allowed sufficient time for contact investigation and successful epidemiologic treatment; and it has remained highly susceptible to penicillin over decades of use. The fact that other industrialized countries had eliminated syphilis by the late 1990's provided further evidence that elimination could be a feasible goal for the US. The heavy impact of syphilis among impoverished minority communities in the US and its contribution to costly health outcomes (pregnancy loss, infant morbidity and mortality, and HIV transmission) made elimination an even greater public health priority for reasons of social justice. *The National Plan to Eliminate Syphilis from the United States* (accessible at <http://www.cdc.gov/stopsyphilis/Plan.pdf>) was formulated, which set the national goal to reduce P&S syphilis cases to less than 1000 by 2005. However, rises in P&S

Figure. Reported Rates* of Primary and Secondary Syphilis, by Year and Sex, and Male-to-Female Rate Ratios – United States, 1981-2002 [MMWR 52(46): 1117-20, 2003]



*Per 100,000 population.

syphilis over the past 3 years indicate that this goal will not be achievable by next year.

Syphilis Epidemiology: Recent Trends

In 1998, most US cases of syphilis were concentrated in Southern States (69%), and within this region, most were in larger metropolitan areas (50%). The burden of disease affected African Americans most heavily, with the black:white P&S syphilis rate ratio of 34:1. This ratio had declined to 8:1 by 2002, evidence that implementation of the national plan did effectively address one glaring example of a race-based health disparity in the US [MMWR, 52(46):1117]. However, from 2000-2002, P&S syphilis cases increased substantially among men while decreasing among women (see Figure), indicating that new epidemics were occurring among men who have sex with men (MSM). The male:female rate ratio of P&S syphilis has continued to widen, suggesting an urgent need for intensification of syphilis prevention efforts among MSM. In many cities, the majority of early syphilis cases are occurring among MSM with known HIV infection, underscoring the importance of continued vigilance among HIV treatment providers for early signs and symptoms of syphilis among patients in their practice.

What HIV Treatment Providers Should Know and Do

Medical providers have important responsibilities for recognizing syphilis when it presents clinically and for reporting cases quickly to public health authorities to facilitate effective community-based disease control efforts. Given the intersecting epidemics of HIV and syphilis, HIV treatment providers have larger responsibilities than other private sector providers in this effort. Because syphilis can cause inflammatory destruction of any organ system, syphilis has enjoyed the reputation of "The Great Imposter" or "The Great Imitator" of other diseases, and thus it can always present as a diagnostic puzzle. However, the most common clinical manifestations are ulcerations ("chancres") at the site of first inoculation, often in the anogenital region or as a rash, typically involving the palms and soles. Oral sex may be a more frequent sexual activity among high risk sexual networks given the perception of its lower risk of HIV transmission. Therefore oral chancres may be a more common presentation of primary syphilis in the current era. In HIV clinical practice, syphilis is often identified through annual serologic screening as "latent" stage syphilis. Though serologic screening for



Syphilis Rates Climb Again

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syphilis at annual intervals has been the recommended practice standard, screening at more frequent intervals in the HIV clinic (even as frequently as every 3-6 months) might be appropriate for some patients based on the local syphilis epidemiology and on the provider's findings on sexual risk assessment. Current practice recommendations for HIV clinical practice include discussion of sexual risk behavior at every regular medical visit [Erbelding E, *HHR* 2003;15(5):11].

Knowledge of basic *T. pallidum* pathogenesis and observations from clinical practice have both provided a rational basis for the theory that syphilis takes a more destructive clinical course in those co-infected with HIV. In a recent large cross-sectional analysis of persons with syphilis undergoing lumbar puncture, HIV infection, CD4 cell depletion (<350 cells/mm³), and RPR titer $\geq 1:32$ were independent predictors of neurosyphilis [Marra CM, et al. *J Infect Dis* 2004;189:369]. Providing patients with accurate information on the health risks of exposures to high risk sexual networks, including the consequences of syphilis acquisition and superinfection with new or drug-resistant strains of HIV, is also a responsibility of HIV medical providers and HIV care systems. The importance of early syphilis detection and treatment should be continually emphasized to patients.

Summary

Once again, syphilis has proven itself to be a formidable foe for public health. Enhanced syphilis control efforts as part of the national elimination effort have been successful in reducing the burden of disease among African Americans and women in the US, but these gains have been largely offset by new syphilis epidemics among MSM. Syphilis control and prevention efforts among MSM should be intensified. Current trends indicate that syphilis will persist as an important clinical problem in the HIV treatment setting for many years to come. ▲

Travel Advice For HIV-Infected Individuals

By Robin McKenzie, M.D.

A growing number of HIV-infected individuals are traveling to developing countries for vacations, business, or visits with friends and family. This article discusses ways to reduce the risk of travel for immunosuppressed patients.

Vaccines

Pre-travel preparation includes updating routine vaccines and administering "travel" vaccines that are specific for the regions to be visited. Since most of the pre- and post-marketing data for these vaccines were obtained in healthy individuals, there are concerns about safety and efficacy when vaccines are given to immunocompromised travelers. In general, vaccines that are not "live" can be given safely to HIV-infected persons, but their immunogenicity may be reduced, roughly in proportion to the reduction in CD4 count.

A summary of vaccine recommendations is contained in the Table, p 11. Before travel all routinely recommended vaccines should be up-dated. Each traveler should be fully immunized against tetanus-diphtheria, which requires booster injections every 10 years. If available, an annual influenza vaccine should be given, since influenza occurs year-around in the tropics. While pneumococcal infection is not considered to be a travel-related illness, HIV-infected individuals are at greater risk for pneumococcal disease and should be vaccinated, probably with a booster every five years. Even though hepatitis B virus (HBV) infection is more common in developing countries, HBV infection is not commonly acquired by travelers. HBV vaccine is recommended, however, for those who will be exposed to blood products, those who will have sexual contact or daily physical contact with the local population, and those who may receive medical or dental care while abroad. Additionally, HBV vaccine is standard-of-care in non-immune HIV-infected individuals. For travel to areas with high levels of endemic HBV infection, the longer the trip and the greater the contact with the local population, the greater the risk. The hepatitis B vaccine is given in 3

doses at 0, 1 and 6 months. In young, healthy adults antibody develops in about 60%, 80% and 95% of vaccinees after the first, second and third dose respectively. For HIV-infected individuals these rates are probably lower. Even though one dose may give some protection, it is clearly preferable to complete the series. Occasionally vaccination is completed abroad.

Measles occurs commonly in developing countries and in some developed countries in Europe and Asia. In general, individuals born in the US before 1957 are naturally immune. Healthy travelers born after 1957 should have confirmation of immunity, either based on a history of two doses of measles, mumps, and rubella vaccine (MMR, the first dose of which is usually given at 12-15 months of age) or a laboratory test showing antibodies. Even though MMR is a live vaccine, measles can be severe in HIV-infected individuals, and the CDC recommends MMR vaccination for all asymptomatic non-immune HIV-infected individuals. (Asymptomatic children do not need to be tested for HIV.) Adults with CD4 counts <200 cells/mm³ or CD4% $<14\%$ should not be vaccinated with MMR but can consider receiving immune globulin.

In addition to the routinely recommended vaccines, specific travel vaccines may be needed. Hepatitis A is one of the most common vaccine-preventable illnesses among travelers. The inactivated vaccine is given as two doses. The first dose produces an antibody response in $\geq 95\%$ of healthy adults and should be administered to all persons who travel to developing countries. The second dose, given 6 to 12 months later, promotes long-term protection. If the second dose is delayed, the series does not need to be restarted. The two brands, *Havrix* and *Vaqta*, can be interchanged. Hepatitis A and B vaccines is also available in a combined formulation (*Twinrix*), which is given as a series of 3 injections (months 0, 1, and 6). HIV-infected individuals with low CD4 counts may not develop antibody after

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vaccination and may need intramuscular immune globulin instead of, or in addition to, vaccine.

Polio has been eradicated from most of the world except parts of Africa and Asia. Most transmission occurs in five countries: Afghanistan, India, Pakistan, Nigeria, and Niger. In addition, outbreaks of vaccine-derived polio occurred recently in Haiti, the Dominican Republic, and the Philippines. Before traveling to endemic areas, adults should have completed the primary vaccine series (usually completed by age 6 years) and have one booster as an adult of inactivated polio vaccine. (Oral, live polio vaccine is no longer available in this the United States.)

Typhoid fever is not a common illness in travelers, but vaccination is recommended for those planning to eat adventurously, to stray off the five-star tourist track, or to travel longer than three weeks. Risk is greater in some areas, especially the Indian subcontinent. HIV-infected individuals should receive the inactivated rather than the live typhoid vaccine.

The quadrivalent ACYW-135 vaccine for meningococcal disease is indicated for travel during the dry season (December through June) to the “meningitis belt” of Africa, which stretches from Senegal to Ethiopia. In addition, vaccination is required for those visiting Mecca during the Hajj.

Two other vaccines are recommended under certain circumstances. Rabies vaccine should be given to those who will be working with animals, to spelunkers, and to those who are visiting endemic areas long-term, especially remote areas where post-exposure prophylaxis with both rabies immune globulin and a safe, effective vaccine may not be available. Japanese encephalitis (JE) vaccine is indicated for expatriates and some long-term travelers to certain Asian countries. Risk of infection with JE virus increases with evening and nighttime outdoor exposure, especially in rural areas. Thus, vaccination might be recommended for campers or others with long-term exposure to mosquitoes in rural areas, but generally not for short-term trips or trips to urban areas. There may be some confusion about the availability of JE

vaccine. Fortunately, it is and has been available. Alternatively, the vaccine for tickborne encephalitis, which occurs mainly in Europe and the former USSR, is not available in this country.

Since the above “travel” vaccines are not live, they present no increased risk for HIV-infected persons. The same is not true, however, for yellow fever vaccine. Yellow fever, a mosquito-borne illness, is endemic in large parts of tropical South America and sub-Saharan Africa. Some countries require proof of vaccination for entry. An official stamp is provided by clinics that are approved yellow fever vaccine centers. Since the yellow fever vaccine is a live vaccine, immunocompromised persons may be at risk for dissemination of the vaccine strain. In Thailand a 53-year-old man with a low CD4 count developed fatal myeloencephalitis [Kengsakul K, et al. *J Med Assoc Thai* 2002;85(1):131]. On the other hand, two HIV-infected individuals with high CD4 counts (674 and 1000 cells/mm³) were successfully immunized [Receveur MC, et al. *Clin Infect Dis* 2000;31:e7-8]. In a French study, 44 HIV-infected persons with CD4 counts >200 cells/mm³ were given yellow fever vaccine without adverse events [Goujon C, et al. *J Travel Med* 1995; 2:145]. Since the risk for dissemination of the vaccine strain varies with the degree of immunosuppression, those with CD4 counts <200 cells/mm³ should not be vaccinated and should avoid travel to endemic areas if possible. If travel to an endemic area is unavoidable and the CD4 count is high, vaccination is an option. The CDC does not encourage vaccination but states that those with “adequate immune system function” who “cannot avoid potential exposure to yellow fever virus” should be offered the choice of vaccination (<http://www.cdc.gov/travel>). Otherwise, HIV-infected persons who must travel to an endemic area should be instructed in ways to avoid mosquito bites and should obtain a waiver letter from their physician, or, better yet, a travel physician with an official stamp, stating the contraindication to vaccination. This letter should be cleared by the embassy or consulate of the country to be visited.

For travelers, the risk of acquiring cholera is very low and currently, cholera vaccine is no longer available in the US. Two vaccines are available in other countries: Dukoral made by Active Biotech in Sweden and Mutacol manufactured by Berna in Switzerland. Previously, cholera vaccine was required by some countries, but now, no country or territory requires vaccination for entry or exit.

The possibility of reduced immunogenicity is an additional concern for all vaccines given to HIV-infected persons. Antibody levels following vaccination may be lower than for HIV seronegative individuals, especially for those with low CD4 counts. In some instances passive antibody is an alternative. Immune globulin, for example, can be given instead of or in addition to hepatitis A vaccine.

Malaria Prophylaxis

Malaria transmission occurs in large parts of Africa, Asia, and Central and South America. Chloroquine remains effective only in parts of Mexico, Central America, Egypt, and some countries in the Middle East. Chloroquine occasionally causes skin eruptions, pruritus, and gastrointestinal symptoms; it is contraindicated in individuals with psoriasis.

For malaria prophylaxis in countries with chloroquine-resistant *Plasmodium falciparum*, four medications are available in the US: mefloquine (*Lariam*), atovaquone/proguanil (*Malarone*), doxycycline, and primaquine. While mefloquine has the advantage of weekly dosing, it has the disadvantage of possible CNS side effects, prolongation of the QT interval, and bradycardia. Mefloquine is contraindicated in those with active depression, anxiety, other major psychiatric disorders, and seizures. Atovaquone/proguanil is a more expensive alternative with fewer side effects. Doxycycline is less expensive but increases the risk of sun sensitivity, gastrointestinal symptoms, and *Candida* vaginitis. Primaquine is usually recommended only for someone unable to take the other prophylactic medications and requires documentation of a normal G6PD level.



Travel Advice for HIV-Infected Individuals

Table: Vaccinations for HIV-Infected Travelers to Underdeveloped Countries

Disease	Recommendation/Comment
Routine vaccines	Update routinely recommended vaccines.
Tetanus-diphtheria*	Give booster every 10 years.
Influenza	Give annually. Influenza occurs year-around in the tropics.
Pneumococcus	Give initial vaccine and booster 5 years later.
Hepatitis B	Immunize if exposure to blood, high-risk activity, or long-term stay anticipated.
Measles (live vaccine)	Confirm immunity or vaccinate if CD4 count is not low. (See text.)
Travel vaccines	Give for travel to specific areas or for high-risk exposure.
Hepatitis A	Immunize all travelers.
Polio*	Administer an adult booster if traveling to an endemic area.
Typhoid fever	Give inactivated vaccine if trip is long or exposure risk is high. (See text.)
Meningococcus	Give for Hajj or travel to meningitis belt of Africa.
Rabies	Vaccinate if risk is high and access to post-exposure vaccine and rabies immune globulin is unavailable. (See text.)
Japanese encephalitis	Vaccinate before long-term travel to rural, endemic areas of Asia.
Yellow fever (live vaccine)	Not generally recommended. Consider only if CD4 count is high. (See text.)

* Primary series should be given if not given previously.

One or two doses of the prophylactic medication should be taken before entering a malarious area. The daily medications, atovaquone/proguanil, doxycycline, and primaquine, should be started 1-2 days before possible malaria exposure; and the weekly medications, chloroquine and mefloquine, 1-2 weeks before arrival. Whereas atovaquone/proguanil and primaquine can be stopped a week after leaving the malarious area, chloroquine, mefloquine and doxycycline should be continued for a month.

A major concern for HIV-infected persons is drug interactions. For mefloquine and chloroquine, a potential interaction exists with other medications that might prolong the QT interval, such as trimethoprim-sulfamethoxazole, fluconazole, and clarithromycin. Ritonavir may decrease atovaquone and proguanil levels. Atovaquone/proguanil increases AZT levels by about 30%. In subjects at risk for bone marrow suppression, the AZT dose could be lowered by 1/3. Specific advice from the CDC can be obtained from the Malaria Hotline at 770-488-7788.

Diarrhea Treatment

All travelers to developing countries should practice dietary discretion by avoiding raw vegetables and fruits unless peeled by the traveler, unpasteurized dairy products, rare meat, raw seafood, and prepared food kept at room temperature for several hours. Water should be bottled or boiled. Ice is risky unless known to be prepared from clean water.

In spite of ample dietary advice, travelers' diarrhea is still very common. In general, treatment has replaced prophylaxis. Prophylaxis may be indicated for some special occasions, for instance, a short trip with an important presentation or meeting. Otherwise, travelers to developing countries should carry antibiotics for self-treatment. A fluoroquinolone such as ciprofloxacin (500 mg bid for 1-3 days) is often given to immunocompetent travelers. HIV-infected individuals may need a longer course of 5-7 days. For travel in Thailand, which has high rates of fluoroquinolone-resistant *Campylobacter* spp., azithromycin is

preferred. Short-term treatment with loperamide or another antimotility agent is acceptable when there is no fever or blood in the stools. Dehydration, the main consequence of severe diarrhea, can be prevented and treated with oral rehydration salts. Packets are usually available at travel clinics and are easy to carry. If there is no improvement in several days, medical attention should be sought.

Other Travel-Related Issues

DEET is essential for the tropics. Insect repellents with DEET help protect against malaria and other arthropod-borne illnesses, such as dengue, leishmaniasis, yellow fever, Japanese encephalitis, and rickettsial infections. Permethrin, an insecticide applied to clothing, provides additional protection from mosquito bites and is more effective against ticks.

At altitudes >9,000 feet, acetazolamide may help prevent altitude sickness. In areas with schistosomiasis, fresh-water swimming

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patients taking AZT frequently contained the intracellular triphosphate of stavudine (d4T-TP), suggesting that human cells contained an enzyme capable of converting AZT to d4TTP [Becher F, et al. *AIDS* 2003;17:555]. These findings, if true, could provide one explanation for the extensive cross-resistance between AZT and d4T [see Flexner C, *HHR* 2003;15(5):5].

To verify these results, investigators from the University of Puerto Rico used HPLC to measure d4T-TP concentrations in 100 plasma samples and d4T-TP and AZT-TP concentrations in 450 plasma samples from HIV-infected subjects who were on stable d4T and AZT therapy, respectively [Melendez M, et al. Abstract 597]. They also used an *in vitro* system to detect d4T-TP in CEM_{ss} cells treated with high concentrations of AZT (up to 100 μ mol). The authors reported that d4T-TP was not measurable in any of the 450 samples collected from patients taking AZT, nor from the CEM_{ss} cells, even though d4T-TP was detected in all samples of patient treated with d4T. These findings suggest that the initial observation reporting intracellular conversion of AZT to d4T-TP could represent a laboratory artifact, and provides some reassurance that exposure to one NRTI may not inadvertently produce exposure to two. ▲

Travel Advice for HIV-Infected Individuals

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should be avoided. Sunburn should be prevented with the use of sunscreen, hats, and sunglasses. Since animals may not be vaccinated against rabies, contact with domestic and wild animals should be avoided. If a potentially rabid animal bite occurs, the wound should be washed thoroughly and medical attention obtained immediately to determine whether rabies immune globulin and vaccine are indicated.

Other Special Advice for HIV-Infected Travelers

- Persons carrying antiretroviral medications may be denied entry to some countries. Moreover, some countries screen for HIV infection in incoming travelers, especially travelers arriving for prolonged work or study. An unofficial list can be found at the following address: <http://www.travel.state.gov/HIVtestingreqs.html>, but individuals planning a prolonged visit should contact the country's consul in advance.
- When possible, avoid changes in medications shortly before travel. Bring an adequate supply of medication along with copies of prescriptions. Refrigeration of medication may be difficult to obtain.
- Since medical insurance plans often do not cover travel-related illness, additional travel insurance may be needed. Pre-existing conditions, however, may not be covered. Medical facilities in areas to be visited should be identified in advance.

- Vacations may encourage sexual activity. To avoid transmitting HIV infection to others and to avoid acquiring additional HIV strains or other sexually transmitted diseases, HIV-infected individuals should, as always, only engage in safer sexual practices. Condom quality is not guaranteed in all countries; it's best to take them along.

The Yellow Book, CDC's Health Information for International Travel, available online at <http://www.cdc.gov/travel>, contains information on vaccines, malaria prophylaxis, and other topics, including "HIV and Travel". Advance planning and consultation with a travel health practitioner can minimize risks.

Summary

In conclusion, vaccines may be less immunogenic in HIV-infected persons. Live vaccines should be avoided, especially when the CD4 count is low. The need for malaria prophylaxis is based upon travel destination and the agent should be chosen based on side effects, convenience, cost, and medication interactions. Insect precautions, including application of both DEET and permethrin, will diminish the risk of acquiring yellow fever, malaria and other insect-transmitted diseases. Medication for treatment, rather than prophylaxis, of travelers' diarrhea is usually preferred. ▲

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