Understanding Primary and Secondary HIV Prophylaxis—
Part 1: Non-occupational Post-exposure Prophylaxis and Antiretroviral Pharmacokinetics in the Male and Female Genital Tracts

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Based on presentations at PRN by Michelle Roland, MD, and Angela DM Kashuba, PharmD

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IN JANUARY OF 2005, THE UNITED STATES CENTERS FOR DISEASE CONTROL and Prevention released its revised guidelines for nonoccupational posttexposure prophylaxis (PEP) of HIV transmission for high-risk sexual contacts. These guidelines have raised many questions about the evidence supporting PEP and the ways in which it is best provided to patients in clinical settings. The idea of using antiretrovirals to prevent transmission is not new, since guidelines for occupational exposures have existed since 1996. For sexual transmission, prophylaxis with antiretrovirals before a potential exposure—pre-exposure prophylaxis (PrEP)—or after the exposure occurs (PEP) is controversial and often leaves clinicians unsure of how to provide the best care to their at-risk patients.

In March of 2006, Michelle Roland, MD, and Angela Kashuba, PharmD, were invited to a PRN meeting to discuss this complex issue. Dr. Roland discussed the challenges and opportunities she has experienced in PEP research, particularly focusing on the broader context of non-pharmacologic interventions that prevent transmission, and the current state of PEP in the United States and internationally. Dr. Kashuba focused on work being done to determine which antiretrovirals are optimal for PrEP and PEP applications, and to provide a rational framework for further policy making.
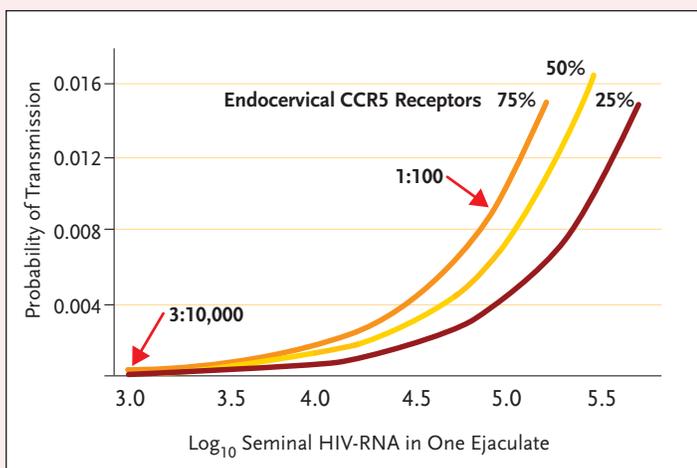

FIGURE 1. **Estimated male-to-female per-sexual contact HIV-1 transmission probability** for different seminal viral load and for different receptor cell counts when 100% of the isolates in the semen are non-syncytium-inducing (NSI). The horizontal axis represents $\log_{10}$ seminal viral load in one ejaculate and the vertical axis represents the male-to-female per-sexual contact HIV-1 transmission probability. Three different lines represent different receptor cells/mm^2 counts; 25th percentile, 50th percentile, and 75th percentile.

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Introduction to Sexual Transmission of HIV and Antiretrovirals

DR. KASHUBA PROVIDED DATA SUPPORTING THE USE OF PrEP AND PEP. Endemic spreads of infection are a function of the size of the inoculum at the site of infection, the contagiousness of the organism, and the duration of infection (Anderson, 1991). In HIV transmission, the size of the inoculum corresponds to the viral burden. For sexual transmission, this specifically applies to the viral load in the genital tract.

In a model of sexual transmission, an Emory University team calculated that male-to-female transmission may vary from 1:100 to 3:10,000 incidences per sex act, depending on the viral load in semen and the number of endocervical CCR5 receptors in the woman (see Figure 1) (Chakraborty, 2001). Adding to this picture of transmission is acute HIV infection, where viral load is very high, and patients may not be aware of the diagnosis and thus be unable to make behavioral changes. The rate of transmission during this time period has been estimated at 1:30 to 1:200 per sex act, depending on the type of exposure (Cohen, 2005). However, as Dr. Kashuba explained, patients all along the continuum of infection contribute to transmission, since HIV viral load increases with concomitant sexually transmitted diseases (eg, syphilis) and increases during late-stage HIV disease. The majority of HIV-infected patients are in the asymptomatic, or drug-controlled, phase of disease, and the number of patients in this group may considerably add to the rate of transmission.

In several studies involving men and women, antiretroviral therapy has been shown to decrease HIV-RNA in the genital tract of an infected individual (Pereira, 1999; Vernazza, 2000; Dumond, 2006). Taken together with the success of occupational PEP and the prevention of mother-to-child transmission, these data provide biologic plausibility for the use of antiretrovirals to prevent nonoccupational HIV transmission.

Animal Evidence for PEP and PrEP

TO TEST THIS THEORY, SEVERAL ANIMAL STUDIES HAVE USED SUBCUTAneous tenofovir before a viral inoculation (PrEP) or up to 24 hours postinoculation (PEP) (Tsai, 1995; Black, 1997; Tsai, 1998). Macaque vaginal exposure models have demonstrated that this is fully effective if used within 36 hours of exposure, and partially effective if used 36 to 72 hours postexposure (Otten, 2000). In these studies, antiretroviral therapy was continued for 28 days post-exposure. Two studies of subcutaneous tenofovir given both four hours prior to oral inoculation with simian immunodeficiency virus (SIV), and again 24 hours later have been effective in preventing transmission; a single higher dose of tenofovir was also tested and found to be effective (Van Rompay, 1998; Van Rompay, 2001).

Oral tenofovir (Viread) has not been as effective as subcutaneous tenofovir for PrEP. Oral tenofovir alone given prior to exposure has not been shown to be effective in preventing transmission in infant macaques

given oral viral inoculations, though the oral doses given were lower than previously tested subcutaneous doses (Van Rompay, 2002). Additionally, data presented at the 12th Conference on Retroviruses and Opportunistic Infection (CROI), held in Boston in 2005, showed oral tenofovir's failure to protect against infection when given prior to repeated rectal challenges (Subbarao, 2005). However, data were encouraging in that the K65R mutation, which is sometimes seen after exposure to tenofovir, was not present in the animals that became infected. Also, infection was delayed in the treated compared with control animals.

At the 13th CROI, held in Denver, exciting new PrEP data were presented regarding the use of an injectable combination of tenofovir and emtricitabine (Garcia-Lerma, 2006). The study evaluated 12 macaques rectally exposed to SIV once per week. Six macaques received subcutaneous injections of tenofovir (22 mg/kg) and emtricitabine (20 mg/kg), starting nine days prior to viral exposure. Six untreated macaques were also rectally challenged with SIV. Among the macaques not receiving the drugs, five of the six were infected with SIV after 14 weeks of SIV exposure. Among the six macaques that received PrEP, none were infected with SIV after 14 weeks of exposure.

A pilot study using an investigational CCR5 inhibitor in a macaque vaginal challenge model showed it was partially effective when given four days prior to exposure and continued for 10 days post-exposure. Six of the 11 animals receiving prophylaxis became infected, compared to 16 of 18 control animals (Veazey, 2005). Treated animals that became infected had lower levels of viremia compared with control animals, perhaps suggesting some attenuation of infection. Animals that only received drug before or after exposure—not continuously—had higher rates of infection, but their rates were still lower than control animals. Although more study is needed, CCR5 inhibitors are interesting compounds with potentially important implications in PEP and PrEP.

Overall, animal data support using antiretrovirals to reduce transmission, when administered prior to or soon after exposure, or both. However, the timeframe of drug administration relative to HIV exposure is critical and, at this time, the optimal agents to use remain unknown. These questions will undoubtedly be the focus of much more intense study in animal models.

PEP Failure and Increased Risky Behavior

DR. ROLAND'S GROUP RECENTLY REPORTED A SEROCONVERSION RATE OF 1%, which represented seven patients out of a cohort of 702 patients who had sought PEP in San Francisco and were available for follow up at three months (Roland, 2005). The oral PEP regimen in this cohort was lamivudine (Epivir) with either zidovudine (Retrovir) or stavudine (Zerit), or stavudine with didanosine (Videx/Videx EC).

Are these seroconversions truly failures of the antiretrovirals or a symptom of another problem? The issue of ongoing risk exposure, both before and after the provision of PEP, was of concern in four of these seven patients. The remaining three patients may have been PEP failures, since they did not report any further risky exposures post-PEP therapy. These seroconversions, along with reports of PEP failure in the occupational setting, are a sobering reminder that PEP is not 100% effective, and likely not the complete answer to preventing HIV infection. Helping patients to avoid the exposures—especially high-risk exposures—in the first place plays an important role in keeping them HIV negative, which is the ultimate goal.

This issue of ongoing risk is also seen among sexual assault survivors in South Africa. PEP presents a huge opportunity to conduct a risk assessment and provide appropriate risk reduction counseling and support, and also quite a challenge for the clinician to provide behavioral intervention along with appropriate medications. As Dr. Roland stated, "PEP is not just a moment in time. It's not just 28 days of medication. These are people who are having exposures before they come to us and they'll have exposures after they come to us."

A major concern surrounding PEP is the potential increase in high-risk behaviors among those who receive it. This, however, has not been documented in studies. Data from the original study of PEP in San Francisco, conducted in the mid-to-late 1990s, demonstrated that participants decreased their high-risk behaviors at six and 12 months following receipt of PEP, compared with behaviors at six months prior to PEP (Martin, 2004).

Because of the concern of bias inherent in patient self-reports, the San Francisco Department of Health's sexually transmitted disease (STD) database was evaluated. No increase in STD diagnoses was seen in these participants from one year prior to receipt of PEP to one year after receipt (Martin, 2004). A study from Brazil, although not designed to answer this question as a primary outcome, also confirms these results in high-risk cohorts (Schechter, 2004).

What can be concluded from these studies is that those individuals who are receiving risk reduction counseling in combination with PEP are for the most part not engaging in increases in their risk behavior. However, it is not known what the outcome may be for non-study patients in the community, who may receive little or no risk-reduction counseling in conjunction with the provision of antiretrovirals.

The effects of behavioral counseling as a component of PEP are underscored in findings presented by Dr. Roland at the 13th CROI. In this study, which was designed to look at behavioral changes, 457 subjects were randomized to receive either two risk-reduction counseling sessions or five risk-reduction counseling sessions along with the provision of PEP. Overall, in this population of mostly white, educated, and insured gay males in San Francisco, both counseling interventions reduced the number of risky unprotected sex acts, the need for additional courses of PEP, and the incidence of HIV infection over the next 12 months (Roland, 2006).

In contrast to earlier findings, fewer subjects knew that their source was HIV positive; this in a population where the incidence of infection is about 40%. However, in subjects with less risk at baseline, there seemed to be no difference in risk reduction between getting two sessions or five sessions of counseling, yet the riskier group of subjects seemed to do much better with the five sessions of counseling. A greater reduction in all of these outcomes was seen in subjects with more than four risky sex acts in the six months prior to receipt of PEP who were randomized to the five-session counseling intervention compared to the two-session intervention. Therefore, assessing prior risk behaviors as a component of PEP counseling may be helpful to provide more intense intervention to those who may benefit the most. As Dr. Roland emphasized, "Overall, the population will do well when we provide two sessions of risk reduction counseling. But if we can do a good risk assessment up front and identify those people who are riskier at baseline, we can target our more intensive risk reduction interventions towards that population." In this study, the highest risk subjects comprised about 25% of the total subject population.

Cost-Effectiveness of PEP

IN THE UNITED STATES, WHEN PROPERLY USED IN PATIENTS WHOSE exposures warrant treatment, PEP has been found to be cost-effective and even cost-beneficial (Pinkerton, 2004; 2004a). In the first of these studies, (Dr. Roland's program in San Francisco, which served patients with varying types of exposures to help them decide if they wanted to undergo PEP, not necessarily based on the inherent risk of the exposure),

data were analyzed for cost-effectiveness. Overall, this program was found to be cost-effective, and in the case of very high–risk exposures, such as receptive anal intercourse with a known HIV-positive partner, PEP is cost saving. In the second study of ninety-six metropolitan areas in the United States, models based on the cost experience in San Francisco were applied to the demographics and HIV prevalence of the particular study area. It was found that, in nearly all the areas, PEP programs would be cost effective if structured in a manner similar to the test program.

Controversies with PEP Guidelines

ALTHOUGH MOST CLINICIANS AND RESEARCHERS SEEM TO AGREE THAT PEP is likely to be a valuable tool in preventing HIV infection, there is little agreement about who should receive antiretrovirals based on the source of the exposure, which drugs and how many should be provided, when they should receive them following an exposure, and what type of follow-up care should be offered. Dr. Roland highlighted these issues, where guidelines vary considerably from state to state and country to country. Time to initiation, the HIV status of the exposure source, the number and type of antiretrovirals to use, and follow-up monitoring recommendations are detailed in Table 1 on page 13 for guidelines produced by the CDC, New York, California, and Rhode Island.

The state of New York is the only guideline-issuing body to limit the use of PEP to the first 36 hours after exposure. It is widely believed that the sooner a PEP regimen is started postexposure, the greater the chances that it will prevent HIV infection. This, as highlighted above, has been demonstrated in animal models. Thus, even though PEP is often offered for up to 72 hours after exposure, it should be initiated as early as possible. After 72 hours, PEP is not effective, and there are gradations in efficacy from 24 hours postexposure, to 36, 48, and 72 hours. This is a complicated message to communicate: most will hear that PEP can be initiated up to 72 hours postexposure, but the true message is that PEP needs to be started as soon as possible for greatest efficacy, and should not be started more than 36 or 72 hours postexposure, depending on the guidelines. Dr. Roland offered her message for trying to decide whether to initiate PEP: "If you're feeling ambivalent about this, we can always go ahead and start it and then you can stop it. It's easy to stop. But you can't even have it started if you decide in two days that this is what you want to do."

The prevalence of HIV infection in the local community is important when deciding if treatment is warranted after an exposure from a source with an "unknown" HIV status. For example, in the gay male population in San Francisco, the prevalence of HIV infection is approximately 30% to 40%. Therefore, says Dr. Roland, any MSM exposure to an "unknown" source should be considered high risk. In areas with a lower prevalence, the decision may not be as clear. In contrast to occupational exposures, rarely, if ever, is the source available for testing. Therefore, applying local demographic information to national recommendations, such as those produced by the CDC, which definitively recommend PEP for known HIV positive exposures and case-by-case judgment for all "unknown" status exposures, is critical for the clinician. The CDC guidelines should not be applied so that PEP is provided only to those with exposures to known infected sources, particularly considering that roughly 25% of infected adults in the U.S. are unaware of their diagnosis.

The guidelines differ as to how many, and which, antiretrovirals are to be used in a PEP regimen. More aggressive three-drug PEP regimens are warranted with a known HIV-infected source harboring drug-resistant virus. In turn, the local viral susceptibility patterns and types of resistance seen in the community may be an important consideration for the clinician when deciding which agents to choose.

Tenofovir in combination with coformulated zidovudine and lamivudine (Combivir) is recommended in the New York guidelines. The CDC and Rhode Island both recommend three drugs, including a protease inhibitor or efavirenz, but differ on the specific agent recommended. Two drugs are recommended in California, unless the antiretroviral history and resistance patterns of the source are known. If that information is available, more than two agents may be required. The drug combination that Dr. Roland is currently looking toward using is tenofovir coformulated with emtricitabine (Truvada), which has promising results in animal studies and is generally well tolerated.

Tolerability of the chosen regimen is an important consideration. Research presented at the 13th CROI suggests that the protease inhibitor–based regimen recommended by the CDC—lopinavir/ritonavir (Kaletra) plus Combivir—may be prematurely discontinued in approximately 25% of patients due to adverse effects (Rabaud, 2006). Alternate regimens had high discontinuation rates as well, ranging from 19% for tenofovir plus zidovudine/lamivudine to 35% for a nelfinavir (Viracept)-based regimen.

Although all guidelines recommend an HIV test at baseline, and again during follow-up, other laboratory monitoring recommendations vary. Generally, PEP regimens last 28 days, and the question of which adverse effects might be expected from the antiretrovirals in the regimen likely can help guide patient care. Dr. Roland's experience in California has been that patients rarely have laboratory abnormalities, and she does not recommend extensive lab follow-up. However, other guidelines, such as those produced by the CDC and New York State, do recommend several screening lab tests at baseline, during treatment, and four to six weeks posttreatment.

Establishing a PEP Service

FUNDAMENTAL CHALLENGES IN ESTABLISHING SUCCESSFUL PEP PROGRAMS include patient access to care and the ability of clinicians to provide the needed services in a timely fashion. From 2001 to 2002, Dr. Roland and her colleagues established a telephone hotline for the purposes of recruiting for a PEP study (Roland, 2003). The program received numerous calls after-hours, and around 75% of the callers were eligible for PEP. Of those, 75% of elected to receive PEP after counseling, either through the study or through referral to a nonstudy service. Because of the lack of an emergency department in which to see patients right away, and the short time frame available, telephone prescriptions were often used to provide PEP, with office visits for laboratory work and the needed counseling sessions occurring within a few days. Dr. Roland's sense is that if national guidelines are in place, they needed to be reinforced with services that can provide technical assistance to clinicians, and perhaps more importantly, instructions to patients, since access to this care is generally not readily obtained.

Highlighting this need for established services is the knowledge gained from the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) in San Francisco (Kindrick, 2006). Dr. Roland explained that 775/918 calls over a 20-month period were in regard to patients with exposures who had not yet begun PEP. Of these, 55% involved exposures more than 24 hours prior and 25% were 72 hours or more postexposure. Approximately 87% of these calls involved patients who had not yet started PEP, yet the majority met the CDC's criteria for consideration of PEP. Moreover, most clinicians who used this service were not experienced in providing PEP.

Clearly, patient and clinician education and further study are needed to identify the barriers to seeking early PEP. Currently, it is not

TABLE 1. Postexposure Prophylaxis Recommendations

	Year	Time to PEP Initiation	Source HIV Status	Number of Drugs	Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)		Protease Inhibitor (PI)*	Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
CDC[1]	2005	72 hours†	Known HIV+: recommend Unknown: case-by-case	3 drugs	Preferred: (lamivudine or emtricitabine) + tenofovir + NNRTI or (lamivudine or emtricitabine) + (zidovudine or tenofovir) + PI Alternative: (lamivudine or emtricitabine) + (abacavir or didanosine or stavudine) + NNRTI or (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or didanosine or tenofovir) + PI or abacavir + lamivudine + zidovudine (only when an NNRTI- or PI-based regimen cannot or should not be given)		Preferred: lopinavir/r Alternative: atazanavir‡ fosamprenavir fosamprenavir/r indinavir/r nelfinavir saquinavir/r	Preferred: efavirenz
New York[2]	2004	36 hours†	Known HIV+: recommend Unknown: recommend	3 drugs	Preferred: zidovudine + lamivudine + tenofovir Alternative: stavudine + lamivudine + tenofovir		Alternative: nelfinavir lopinavir/r	Consider only if patient: cannot tolerate either tenofovir or a PI, or has been exposed to a source with resistant HIV that is sensitive to NNRTI
NY Pediatric[3] (not perinatal)	2004	36 hours	Known HIV+: recommend Unknown: recommend	3 drugs	Preferred: if ≥13 yo zidovudine + lamivudine+ tenofovir	Preferred: if <13 yo zidovudine + lamivudine + PI (nelfinavir)	Preferred: if <13 yo nelfinavir	
California[4]	2004	72 hours	Known HIV+: offer Unknown: offer	2 drugs	Preferred: zidovudine + lamivudine Alternative: (stavudine or tenofovir) + (lamivudine or emtricitabine)		If PI used, Preferred: lopinavir/r	If NNRTI used, Preferred: efavirenz
CA Sexual Assault[5]	2001	72 hours	Known HIV+: recommend Unknown: recommend				Alternative: nelfinavir indinavir atazanavir fosamprenavir others	
Rhode Island[6]	2002	72 hours†	Known HIV+: recommend	3 drugs	Preferred: (zidovudine or stavudine) + lamivudine		Preferred: indinavir nelfinavir	
			Unknown: offer	2 drugs	Preferred: (zidovudine or stavudine) + lamivudine		Alternative: indinavir nelfinavir	

* Protease inhibitor boosted with low-dose ritonavir counts as a single agent (PI/r)   † Recommends offering PEP beyond this time-frame under certain circumstances

‡ boost with ritonavir when used with tenofovir

1 Centers for Disease Control and Prevention. **Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States: Recommendations from the U.S. Department of Health and Human Services.** *MMWR.* 2005;54(No RR-2).

2 The New York State Department of Health, AIDS Institute. **HIV Prophylaxis Following Non-Occupational Exposure Including Sexual Assault**. December 2004. Available at: http://www.hivguidelines.org/GuideLine.aspx?pageID=78&guidelineID=2. Accessed October 4, 2006.

3 The New York State Department of Health, AIDS Institute. **HIV Post-Exposure Prophylaxis For Children Beyond The Perinatal Period**. December 2004. Available at: http://www.hivguidelines.org/GuideLine.aspx?pageID=78&guidelineID=26. Accessed October 4, 2006.

4 The California Task Force on Non-Occupational PEP and the California Department of Health Services Office of AIDS. **Offering HIV Post-Exposure Prophylaxis (PEP) Following Non-Occupational Exposures. Recommendations for Healthcare Providers in the State of California. June 2004**. Available at: http://www.dhs.ca.gov/aids/Resources/pdf/pepguidelinesfinal.pdf. Accessed October 4, 2006.

5 SFDPH and the California HIV PEP After Sexual Assault Task Force in conjunction with the California State Office of AIDS. **Offering HIV Prophylaxis Following Sexual Assault.** Recommendations for the State of California. 2001. Available at: http://www.dhs.ca.gov/AIDS/Reports/PDF/HIVProphylaxisFollowingSexualAssault.pdf. Accessed October 4, 2006.

6 Nonoccupational HIV PEP Task Force, Brown University AIDS Program and the Rhode Island Department of Health. **Nonoccupational Human Immunodeficiency Virus Postexposure Prophylaxis Guidelines for Rhode Island Healthcare Practitioners.** August 2002. Available at: www.brown.edu/Departments/BRUNAP/npepguid. Accessed October 4, 2006.
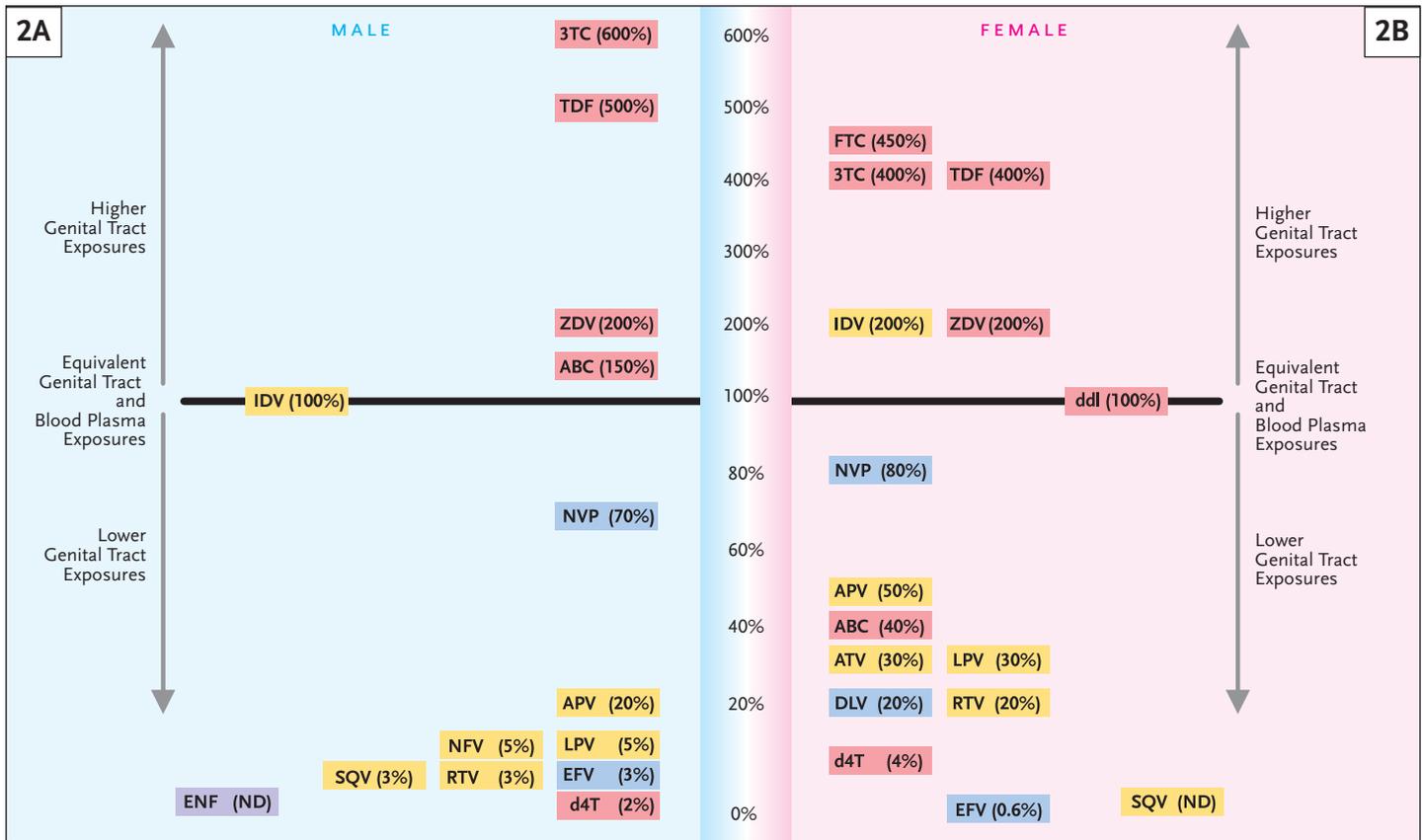
FIGURE 2A AND B. Antiretroviral Exposures in the Male (A) and Female (B) Genital Tracts Compared to Blood Plasma

The solid black line represents 100%, or equivalent exposure in the genital tract and blood plasma. Antiretrovirals are listed by abbreviation with percent exposure. Drugs above the solid black line (100%) have greater genital tract exposures than blood plasma. Drugs below the solid black line (100%) have lower genital tract exposures than blood plasma Drugs on the line have equivalent exposure. Exposure is defined as the area under the time-concentrations curve (AUC) over a dosing interval. To compare exposures, genital tract AUC was divided to blood plasma (BP) AUC to give GT exposure relative to BP.

Male data pooled from: Pereira et al, 1999; Taylor et al, 2000; Van Praag et al, 2001; Chaudry et al, 2002; Reddy et al, 2003; Solas et al, 2003; Ghosn et al, 2004; Vourvahis et al, 2006.

Female data pooled from: Min et al, 2004; Dumond et al, 2006; Vourvahis et al, 2006.

ABC: abacavir	DLV: delavirdine	IDV: indinavir	NRTI: nucleoside reverse transcriptase inhibitor	SQV: saquinavir	**NRTI** / **NNRTI**
APV: amprenavir	EFV: efavirenz	LPV: lopinavir		TDF: tenofovir	**PI** / **FI**
ATV: atazanavir	ENF: enfuvirtide	ND: not detected	NVP: nevirapine	ZDV: zidovudine	
d4T: stavudine	FTC: emtricitabine	NNRTI: non-nucleoside reverse transcriptase inhibitor	PI: protease inhibitor	3TC: lamivudine	
ddI: didanosine	FI: fusion inhibitor		RTV: ritonavir		
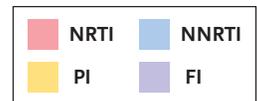
known whether patients are seeking care too late, or clinicians are overwhelmed by the provision of this service, or both. Timing is crucial for optimal outcomes, a message that needs to be reinforced with patients and clinicians, since approximately one-quarter of the calls were received beyond the 72 hours postexposure window.

Pharmacology of Antiretrovirals in the Genital Tract

AS DR. KASHUBA SAID, "ONE THING WE DO KNOW IS THAT THE COMBINATION(s) of drugs that best suppress or eliminate HIV from the genital tract is not known." Without good clinical data to guide policy, Dr. Kashuba and her colleagues are exploring the pharmacology of antiretrovirals in the genital tract to determine which may be most effective for PrEP and PEP. Her working hypothesis is that agents that achieve rapid and high concentrations in the genital tract are the most effective. It is assumed that drugs that concentrate in the genital tract will induce a greater reduction in genital tract HIV-RNA, and thus will have the greatest activity at the site of transmission. No biologic data exist as to whether antiretrovirals differ in this ability, and conducting a clinical

study to test different antiretrovirals, or combinations, would require too large a cohort to be practical. The possibility of selecting for resistant virus based on administering agents with suboptimal genital tract concentrations is also a concern. Some recent data from the ACTG study suggest that males may have increased risk of protease inhibitor mutations in the genital tract, while females may have increased risk of nonnucleoside reverse transcriptase inhibitor mutations (Katzenstein, 2006).

Dr. Kashuba shared the results of a pharmacokinetic study in 25 HIV-infected women at the University of North Carolina at Chapel Hill. This study evaluated blood plasma and cervicovaginal fluid antiretroviral concentrations with the first dose and steady state of a new antiretroviral regimen (Dumond, 2006). She also mentioned several studies that were conducted in males (Reddy, 2002). All investigations demonstrated that there appear to be antiretroviral concentration differences between the male and female genital tracts.

As depicted in Figures 2a and b, the absolute magnitude of a drug's exposure may be different between males and females, but the rank order of exposures is very similar. That is, the drugs that achieve high concentrations in the female genital tract, such as lamivudine, zi-

dovudine, and tenofovir, also obtain high concentrations in the male genital tract. Also encouraging was the finding that drug exposure in the genital tract after a single dose was similar to that after multiple doses.

Generally, drug concentrations are measurable in the genital tract within two hours of taking an antiretroviral dose. Emtricitibine (Emtriva) may be somewhat of an exception, since it takes six hours after a dose to see concentrations in the female genital tract. The drugs that concentrate to the greatest extent in the female and male genital tract are the nucleoside reverse transcriptase inhibitors (NRTIs) lamivudine (Epivir), zidovudine (Retrovir), tenofovir, and emtricitabine. Since these drugs are intracellularly phosphorylated to their active forms, the concentrations inside mononuclear cells in the genital tract should be evaluated. Dr Kashuba stated that to date, intracellular concentration data have only been measured in the male genital tract (Reddy, 2003; Vourvahis, 2006). The results of these studies are interesting, in that there may be particular characteristics of an NRTI that determine its intracellular concentration in the genital tract relative to its intracellular concentration in blood plasma.

Beyond the NRTIs, what other options for PrEP and PEP exist? For the most part, other classes of antiretrovirals do not achieve genital tract exposures similar to blood plasma. With the exceptions of indinavir (Crixivan) and nevirapine (Viramune), exposures to the other PIs and efavirenz are much less than in blood plasma. However, in evaluating the absolute concentrations achieved in relation to viral susceptibility, antiretrovirals with genital tract concentrations that are less than that of blood plasma may still be useful.

Dr. Kashuba's example of this was atazanavir (Reyataz). For subjects receiving boosted atazanvir, blood plasma concentrations for atazanavir are well above the recommended trough concentration of 150 ng/mL, at a mean of 1100 ng/mL and genital tract concentrations are just above this concentration, at a mean of 200 ng/mL. It may be that atazanavir could be useful for PrEP and PEP.

Dr. Kashuba also reviewed the antiretroviral properties that may determine high genital tract penetration. A major factor appears to be the extent of protein binding. She has identified that highly protein-bound drugs do not achieve high drug concentrations in the genital tract. Early reports suggest lower concentrations of drug-binding protein in semen and cervicovaginal secretions (Lizana, 1987; Salas Herrera, 1991). Since unbound drugs have HIV activity, Dr. Kashuba noted that it is important to measure exactly how much active drug is available in the genital tract. Antiretroviral concentrations in tissues in the genital tract may also play an important role in PrEP and PEP activity, but have yet to be explored.

Finally, rectal exposure is an important route of transmission. Particularly for PrEP and PEP applications, it would be helpful to know which antiretrovirals are most active in the lower gastrointestinal tract. Several reported instances of PEP failure, such as those reported by Dr. Roland's group, have been related to rectal exposure. Ongoing work in Dr. Kashuba's lab will evaluate rectal concentrations of various antiretrovirals in order to expand pharmacology knowledge in this area.

Now that some comprehensive pharmacologic data exists in the male and female genital tract, a link between these data and the impact on HIV-RNA and HIV-DNA levels in the genital tract is needed. Dr. Kashuba and her research group will be focusing on this in the future.

PEP and Sexual Assault in Africa

PROVIDING PEP AFTER A SEXUAL ASSAULT IS OF GREAT INTEREST TO providers, both in the U.S. and other countries. Dr. Roland shared some of her experiences providing PEP services to women in Cape Town, South Africa, at a comprehensive rape treatment center. Sexual assault in the con-

text of HIV prevention exposes several links between violence and women's ability to protect themselves against HIV exposures. PEP has provided healthcare workers a means of entering this highly politicized, uncomfortable arena that previously has been considered a psychosocial issue. Although this was a unique experience, many parallels between the provision of PEP in Cape Town and San Francisco were observed.

A challenge highlighted by Dr. Roland is that the literature regarding the provision of post-assault PEP is only from North America and Europe. This body of literature suggests that sexual assault survivors have a very low uptake of PEP and extremely low completion and follow-up rates. It is unclear whether this is a function of healthcare providers not offering or recommending PEP, or if it is a function of the survivor's rational decision-making process. Exposure to HIV in a very low prevalence setting may influence the survivor to decline PEP. Alternatively, it may be the result of an extraordinarily traumatic experience that impairs the decision-making process. Adherence is a challenge and currently, it is not known whether adverse effects of the drugs or symptoms of acute stress disorder as a result of the assault are contributing factors to nonadherence.

Dr. Roland shared data from 335 mostly young women participating in this study in South Africa. Although overall completion rates are relatively high, with the median completion rate being 27 out of 28 days of PEP, four-day recall surveys reveal that doses are often missed. In fact, up to one-third of patients either discontinued or missed at least one dose in the preceding four days. Although nonadherence was initially attributed to adverse effects, shame, and being emotionally overwhelmed because of pill burden, in many cases, it was simply because patients forgot, or they were away from home and did not have their medications with them. This is similar to the adherence barriers of patients in typical clinical situations. In analyzing the adherence data, no predictors of nonadherence were found. This serves to reinforce the notion that every patient should be provided with adherence counseling to enhance the rates of adherence in a population that is not "sick" and may not as fully understand the consequences of missed doses as they would if they had physical signs and symptoms of their disease. Very similar results in adherence and discontinuation were seen in the two populations of Cape Town and San Francisco, with only 79% of patients from San Francisco reporting having taken all of their medications perfectly in the preceding four days.

Another recurring theme previously seen in the San Franciscan MSM population is that of ongoing exposures. More than half of the 135 women seen by Dr. Roland were having unprotected sex prior to their rape, and most did not know the HIV status of their partner(s). This is a previously overlooked aspect of providing PEP to assault survivors: the consideration of what was occurring in their lives apart from the assault. One-third of the subjects were having unprotected sex one month after their assault. After three months, one-half were having unprotected sex, and after six months, two-thirds were having unprotected sex. Controlling for other variables, the only predictor for having unprotected sex after the assault was having unprotected sex prior to the assault. This highlights the need and responsibility to conduct a thorough behavioral risk assessment and to provide counseling to reduce future risk in addition to providing medications. Dr. Roland noted that 4/135 women in this cohort followed for six months seroconverted, two of whom were probably true PEP failures (one due to poor adherence) and two of whom had other exposures that may have resulted in their infections. The contribution of ongoing exposures resulting in seroconversion in both of these populations is the reason that provision of behavioral counseling should be an integral part of PEP.

In this study, the issues of the resources needed to provide PEP in

postassault settings was explored. The results indicate that pro-active follow-up is needed, and Dr. Roland's group accomplished this by hiring nurses to provide home visits, field telephone calls, and provide very proactive follow up rather than passively waiting for patients to come of their own accord. These nurses made 161 tracing attempts for 135 people to provide follow-up care. Several referrals were also made for outside rape counseling services. Overall, this experience showed that providing services such as this one can be quite resource-intensive.

At the international level, the issue of resources is being explored by the WHO. Some of the key issues identified include the fact that PEP services have to be provided as part of a comprehensive prevention package and, generally, should be integrated into existing services rather than developed on their own. Optimal service delivery sites have to be identified in each setting as well, which has clearly been the case in the United States. Dr. Roland's experiences in different systems have shown that, "every system has come up with a different solution based on their unique strengths and opportunities and needs within their community about how and where to provide PEP. Clients must receive appropriate information about the risks and benefits of PEP in order to provide informed consent." Adherence, adverse effect, risk-reduction, and trauma counseling, and available clinical follow up services to provide adverse effect management and follow-up HIV testing need to be part of the PEP package, as do pregnancy testing and emergency contraception.

Ongoing Clinical Research of PrEP

ALTHOUGH SEVERAL TRIALS OF PrEP HAVE BEEN DISCONTINUED FOR --ious reasons, clinical research in this area is ongoing. One trial, sponsored by the CDC and being conducted in Atlanta and San Francisco, is designed to assess the renal and bone safety profile of tenofovir in the MSM population. An additional safety trial of tenofovir in high-risk women is ongoing in Ghana. Each of these trials will evaluate 400 subjects. Several other trials to assess both the safety and efficacy of tenofovir are ongoing in Thailand (IV drug users), Botswana (high-risk subjects), and Peru (high-risk men). In total, these various safety and efficacy trials will enroll approximately 4200 high-risk subjects.

Conclusion

WITH PREP AND PEP COME SEVERAL UNIQUE CHALLENGES AND OPPORTUNITIES. A large body of behavioral, clinical, and animal research is in development in an effort to best care for patients in need of prophylactic treatment for HIV exposures. For the practicing clinician, particularly those with high-risk patients, understanding the current literature, treatment guidelines, and local infection prevalence and drug-resistance epidemiology should assist in selecting appropriate prophylactic regimens for patients. Providing risk-reduction, adherence, and adverse event counseling is also critical in this effort. *prn*

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