

# HIV Antiretroviral Postexposure Prophylaxis: A Cautionary Note

Myron S. Cohen, Angela D. M. Kashuba, and Cynthia Gay

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

(See the article by Roland et al. on pages 1507–13)

Antiretroviral therapy can be used in 3 ways to prevent the sexual transmission of HIV infection: (1) to reduce an infected person's viral burden below a critical threshold; (2) as preexposure prophylaxis for people with persistent high-risk behavior(s); and (3) as postexposure prophylaxis (PEP) to be used after occupational needlesticks or sexual or other nonoccupational risks [1]. The first 2 approaches are currently being tested in clinical trials to evaluate their efficacy. However, PEP has already found its way into widespread clinical practice.

Antiretroviral PEP initiated after occupational needlesticks has been used in an attempt to protect health care workers after exposure to HIV. On the basis of historical data, Cardo et al. [2] used a case-control design and reported that zidovudine appeared to reduce the risk of HIV infection by 81%, from ~1 in 200 to 1 in 10,000. But it has been impossible to design case-control or prospective studies to determine the efficacy of the nonoccupational use of PEP against sexual transmission when a partner's HIV infection

status is unknown, and given the poor efficiency of the transmission of HIV infection [3]. Data generated in studies of macaques suggest that therapy for HIV infection initiated within 72 h after genital tract exposure and continued for 28 days can prevent sexual acquisition of HIV infection in the majority of animals [reviewed in 4, 5].

These observations (and their limitations) have led to an explosion of articles about occupational and nonoccupational prophylaxis that focus on the feasibility [6–9] and the cost (and benefit) [10] of such prevention. Feasibility studies have generally demonstrated successful application of the idea [11], although in some studies, toxicity [12–15] or poor adherence [16, 17] became a limiting problem.

In response to biological plausibility and widespread use, many countries (most recently the United States) have established formal guidelines for the administration of nonoccupational PEP. These guidelines all recommend the earliest possible initiation of therapy (within 72 h after exposure) with multiple drugs for 28 days [18–26].

In this issue of *Clinical Infectious Diseases*, Roland et al. [27] offer an important cautionary note. They present the results of a study of 702 subjects exposed to HIV (94.6% of whom had sexual exposure) who received antiviral prophylaxis and were followed up for 12 weeks. Seven men

(1%) in this study acquired HIV infection despite receiving antiviral treatment, all of whom were exposed to HIV through receptive anal intercourse, and 4 of whom knew that their exposure-source partners were HIV infected. Three seroconverters denied any sexual exposure after initiation of nonoccupational PEP, strongly suggesting that the desired protection was not provided.

These results emphasize that we are simply unable to calculate the benefit (if there is any) of nonoccupational use of PEP. There are a number of reasons why nonoccupational PEP might have failed, including a lack of adherence to the PEP regimen (at least 3 seroconverters reported a substantial number of missed doses) and a suboptimal drug regimen (all seroconverters received only 2 nucleoside reverse-transcriptase inhibitors). Animal data suggest that differences in efficacy of prophylaxis may exist between drug classes [28]. In addition, it has been reported that intracellular nucleoside reverse transcriptase inhibitor triphosphate concentrations in other body compartments may be reduced, compared with concentrations observed in PBMCs [29]. Antiretroviral drug exposure in the lower genital tract has not been measured during prophylaxis, but the results may be dissimilar to what is achieved systemically. A broader combination of drugs affecting different stages of HIV infection (preferably parametri-

Received 19 July 2005; accepted 20 July 2005; electronically published 13 October 2005.

Reprints or correspondence: Dr. Myron S. Cohen, 130 Bioinformatics Bldg., UNC-Chapel Hill, Chapel Hill, NC 27599 (mscohen@med.unc).

**Clinical Infectious Diseases** 2005;41:1514–6

© 2005 by the Infectious Diseases Society of America. All rights reserved.

1058-4838/2005/4110-0019\$15.00

zation) may also provide better protection than a combination regimen of 2 nucleoside reverse transcriptase inhibitors. Delayed therapy is another reason why non-occupational PEP might have failed (treatment was initiated at a median of 45.5 h after exposure). Perhaps truly emergent PEP is a better strategy. Animals can acquire HIV infection within 24–72 h after exposures [30–32]. Indeed, in response to this concern, investigators in Brazil have provided persons at high risk with self-administered “first doses” of therapy for use at home [8]. Another reason for failure of nonoccupational PEP is that receptive anal intercourse is a severe test for prevention of HIV infection. Anal intercourse has a high transmission probability [3, 33] and leads to acquisition of a diverse viral swarm that may represent transmission advantages [34]. Indeed, in recent work with macaques, repeated rectal exposure to simian HIV appears to have overwhelmed the efficacy of tenofovir as preexposure prophylaxis [35].

This study provides other interesting information. Because no resistance was observed in the virus recovered from the newly infected subjects, it implies that the index (source cases) might not have received therapy and that nonoccupational PEP itself did not evoke resistance. However, because “bulk sequencing” does not represent the entire viral swarm, resistance in a small number of viral variants could have been missed [36].

These results complement other case reports of PEP failure after needlestick injury [37–39] and sexual exposure [8, 27]. The real question is how should these results affect medical practice. PEP is here to stay, all of the concerns raised notwithstanding. Therapy will become easier and better for patients, given the increasing availability of multiple classes of once-daily drugs and new drugs (e.g., CCR5 inhibitors) with potential biological advantages for infection prevention. But in our opinion, the best chance to improve the efficacy of PEP depends on truly emergent intervention (as soon after exposure

as possible), evolutionary development of therapy guided by ongoing pharmacological studies of antiviral drugs in the genital tract, and continued vigorous exploration with PEP in animals.

### Acknowledgments

**Potential conflicts of interest.** A.D.M.K. has received recent research funding from Abbott Labs and Gilead Laboratories. M.S.C. and C.G.: no conflicts.

### References

- Hosseinipour M, Cohen MS, Vernazza PL, Kashuba AD. Can antiretroviral therapy be used to prevent sexual transmission of human immunodeficiency virus type 1? *Clin Infect Dis* **2002**; 34:1391–5.
- Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. *N Engl J Med* **1997**; 337:1485–90.
- Royce RA, Sena A, Cates W Jr, Cohen MS. Sexual transmission of HIV. *N Engl J Med* **1997**; 336:1072–8.
- Otten RA, Smith DK, Adams DR, et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). *J Virol* **2000**; 74: 9771–5.
- Tsai CC, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl) adenine. *Science* **1995**; 270:1197–9.
- Kahn J, Martin J, Roland M, et al. Feasibility of postexposure prophylaxis (PEP) against human immunodeficiency virus infection after sexual or injection drug use exposure: the San Francisco PEP study. *J Infect Dis* **2001**; 183: 707–14.
- Martin J, Roland M, Neilands T, et al. Use of postexposure prophylaxis against HIV infection following sexual exposure does not lead to increases in high-risk behavior. *AIDS* **2004**; 18:787–92.
- Schechter M, do Lago RF, Mendelsohn A, et al. Behavioral impact, acceptability, and HIV incidence among homosexual men with access to HIV seroconversion following PEP: post-exposure chemoprophylaxis for HIV. *J Acquir Immune Defic Syndr* **2004**; 35:519–25.
- Timsit FJ, Maillard A, Spindler E, et al. Prophylactic antiretroviral therapy after sexual exposure to HIV: 93 cases [in French]. *Ann Dermatol Venereol* **2002**; 129:866–9.
- Pinkerton SD, Martin JN, Roland ME, Katz MH, Coates TJ, Kahn JO. Cost-effectiveness of postexposure prophylaxis after sexual or injection-drug exposure to human immuno-

- deficiency virus. *Arch Intern Med* **2004**; 164: 46–54.
- Limb S, Kawsar M, Forster GE. HIV post-exposure prophylaxis after sexual assault: the experience of a sexual assault service in London. *Int J STD AIDS* **2002**; 13:602–5.
- Rabaud C, Bevilacqua S, Beguinot I, et al. Tolerability of postexposure prophylaxis with zidovudine, lamivudine, and nelfinavir for human immunodeficiency virus infection. *Clin Infect Dis* **2001**; 32:1494–5.
- Parkin JM, Murphy M, Anderson J, El-Gadi S, Forster G, Pinching AJ. Tolerability and side-effects of post-exposure prophylaxis for HIV infection. *Lancet* **2000**; 355:722–3.
- From the Centers for Disease Control and Prevention. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures—worldwide, 1997–2000. *JAMA* **2001**; 285:402–3.
- Centers for Disease Control and Prevention. Updated US Public Health Service guidelines for the management of occupational exposure to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR Morb Mortal Wkly Rep* **2001**; 50:1–42.
- Linden JA, Oldeg P, Mehta SD, McCabe KK, LaBelle C. HIV postexposure prophylaxis in sexual assault: current practice and patient adherence to treatment recommendations in a large urban teaching hospital. *Acad Emerg Med* **2005**; 12:640–6.
- Wiebe ER, Comay SE, McGregor M, Ducceschi S. Offering HIV prophylaxis to people who have been sexually assaulted: 16 months’ experience in a sexual assault service. *CMAJ* **2000**; 162:641–5.
- Almeda J, Casabona J, Simon B, et al. Proposed recommendations for the management of HIV post-exposure prophylaxis after sexual, injecting drug or other exposures in Europe. *Euro Surveill* **2004**; 9:35–40.
- Smith D, Grohskopf L, Black R, et al. 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 Recomm Rep* **2005**; 54(RR-2):1–20.
- 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 health care providers in the state of California. Sacramento, CA:2004. Available at <http://www.dhs.ca.gov/ps/ooa/resources/pdf/pepguidelinesfinal.pdf>.
- Correll P, Smith D, Grulich A. Post-exposure prophylaxis for non-occupational exposure to HIV: experience in New South Wales one year after the introduction of the guidelines. *N S W Public Health Bull* **2000**; 11:113–8.
- Bernasconi E, Jost J, Ledergerber B, Hirschel B, Francioli P, Sudre P. Antiretroviral prophylaxis for community exposure to the human

- immunodeficiency virus in Switzerland, 1997–2000. *Swiss Med Wkly* **2001**; 131:433–7.
23. Rey D, Bendiane MK, Moatti JP, Wellings K, Danziger R, MacDowall W. Post-exposure prophylaxis after occupational and non-occupational exposures to HIV: an overview of the policies implemented in 27 European countries. *AIDS Care* **2000**; 12:695–701.
  24. Rey D, Bendiane M, Moatti J, et al. Policy on non-occupational post-exposure prophylaxis for HIV in 14 European countries [abstract TuPeF5382]. In: Proceedings of the XIV International AIDS Conference, Barcelona, Spain, **2002**.
  25. Kim JC, Martin LJ, Denny L. Rape and HIV post-exposure prophylaxis: addressing the dual epidemics in South Africa. *Reprod Health Matters* **2003**; 11:101–12.
  26. Miro JM, Antela A, Arrizabalaga J, et al. Recommendations of GESIDA (Grupo de Estudio de SIDA)/National Plan on AIDS with respect to the anti-retroviral treatment in adult patients infected with the human immunodeficiency virus in the year 2000 (II) [in Spanish]. *Enferm Infecc Microbiol Clin* **2000**; 18: 396–412.
  27. Roland ME, Neilands TB, Krone MR, et al. Seroconversion following nonoccupational postexposure prophylaxis against HIV. *Clin Infect Dis* 2005; 41:1507–13 (in this issue).
  28. Tsai CC, Follis KE, Grant R, et al. Comparison of the efficacy of AZT and PMEA treatment against acute SIV<sub>mac</sub> infection in macaques. *J Med Primatol* **1994**; 23:175–83.
  29. Reddy S, Troiani L, Kim J, et al. Differential phosphorylation of zidovudine and lamivudine (ZDV/3TC) between semen and blood mononuclear cells (MCs) in HIV-1 infected men [abstract 530]. In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections (Boston). **2003**.
  30. Spira AI, Marx P, Patterson B, et al. Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macques. *J Exp Med* **1996**; 183:215–25.
  31. Stahl-Hennig C, Steinman RM, Tenner-Racz K, et al. Rapid infection of oral mucosal-associated lymphoid tissue with simian immunodeficiency virus. *Science* **1999**; 285:1261–5.
  32. Miller C, Li Q, Abel K, et al. Propagation and dissemination of infection after vaginal transmission of simian immunodeficiency virus. *J Virol* **2005**; 79:9217–27.
  33. Vittinghoff E, Douglas J, Judson F, McKirnan D, MacQueen K, Buchbinder SP. Per-contact risk of human immunodeficiency virus transmission between male sexual partners. *Am J Epidemiol* **1999**; 150:306–11.
  34. Ritola K, Pilcher CD, Fiscus SA, et al. Multiple V1/V2 *env* variants are frequently present during primary infection with human immunodeficiency virus type 1. *J Virol* **2004**; 78: 11208–18.
  35. Subbarao S, Otten R, Ramos A, et al. Chemoprophylaxis with oral tenofovir disoproxil fumarate (TDF) delays but does not prevent infection in rhesus macaques given repeated rectal challenges of SHIV [abstract 136LB]. In: Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections (Boston). **2005**.
  36. Palmer S, Kearney M, Maldarelli F, et al. Multiple, linked human immunodeficiency virus type 1 drug resistance mutations in treatment-experienced patients are missed by standard genotype analysis. *J Clin Microbiol* **2005**; 43: 406–13.
  37. Beltrami EM, Luo CC, de la Torre N, Cardo DM. Transmission of drug-resistant HIV after an occupational exposure despite postexposure prophylaxis with a combination drug regimen. *Infect Control Hosp Epidemiol* **2002**; 23:345–8.
  38. Perdue B, Mellors J, Quinn T, JM. HIV-1 transmission by a needle-stick injury despite rapid initiation of four-drug postexposure prophylaxis [abstract 210]. In: Program and abstracts of the 6th Conference on Retroviruses and Opportunistic Infections (Chicago). **1999**.
  39. Jochimsen EM. Failures of zidovudine post-exposure prophylaxis. *Am J Med* **1997**; 102: 52–5.