HIV Antiretroviral Postexposure Prophylaxis: A Cautionary Note

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(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-
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.

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References


