

flucytosine and fluconazole, but repeatedly relapsed despite fluconazole maintenance therapy initially dosed as recommended [2,3] and subsequently intensified. At the time of relapse, the patient showed no clinical evidence of non-compliance, maldigestion or malabsorption; no drugs potentially affecting triazole pharmacokinetics were taken. The occurrence of *C. neoformans* strains less susceptible to fluconazole after primary and secondary azole antifungal prophylaxis has been reported previously [4,5]. In line with the present observation, this report may well explain the relapses of cryptococcal disease. Interestingly, the loss of azole susceptibility of *C. neoformans*, which developed during fluconazole maintenance therapy, apparently affects various azole compounds differentially, as susceptibility to voriconazole *in vitro* was consistently found even after clinical failure. Therefore, the relapse observed during voriconazole maintenance therapy was probably caused by insufficient bioavailability of this particular compound within the CSF with the present dosing regimen.

In summary, this report demonstrates that: (i) *C. neoformans* resistance to triazoles (fluconazole, itraconazole) may emerge during fluconazole maintenance therapy; (ii) fluconazole/itraconazole-resistant strains remain sensitive to voriconazole *in vitro*; (iii) despite its preserved *in-vitro* activity, voriconazole may not be potent enough to prevent cryptococcal meningitis relapse with

the standard dose used; and (iv) after the development of azole resistance, intravenous amphotericin B maintenance therapy remains an option for the long-term control of cryptococcal meningitis in AIDS patients.

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References

1. Powderly WG. **Cryptococcal meningitis and AIDS.** *Clin Infect Dis* 1993, **17**:837–842.
2. Powderly WG. **Recent advances in the management of cryptococcal meningitis in patients with AIDS.** *Clin Infect Dis* 1996, **22** (Suppl. 2):119–123.
3. Manfredi R, Chiodo F. **Role of fluconazole in the management of AIDS-related cryptococcosis, according to daily dosing.** *Chemotherapy* 1998, **44**:206–214.
4. Berg J, Clancy CJ, Nguyen MH. **The hidden danger of primary fluconazole prophylaxis for patients with AIDS.** *Clin Infect Dis* 1998, **26**:186–187.
5. Brandt ME, Pfaller MA, Hajjeh RA, *et al.* **Molecular subtypes and antifungal susceptibilities of serial *Cryptococcus neoformans* isolates in human immunodeficiency virus-associated cryptococcosis.** *J Infect Dis* 1996, **174**:812–820.

Another reality check: the direct costs of providing post-exposure prophylaxis in a population-based programme

Low-Beer *et al.* [1] and Pinkerton *et al.* [2] put forth data suggesting that providing post-exposure prophylaxis (PEP) in situations of sexual exposure to HIV would be unaffordable. In response, Merchant [3] postulated that the application of clear eligibility criteria and other guidelines would in fact allow for an affordable non-accidental PEP programme to exist. We have undertaken to investigate this further by calculating the expected costs of our population-based accidental exposure PEP programme, and comparing them with what this programme has actually cost.

In March 1999, the British Columbia Center for Excellence in HIV/AIDS produced its Guidelines for Accidental Exposure to HIV Infection [4]. This programme allows individuals who have sustained a potential accidental exposure to HIV occupationally, in the community, or through sexual assault to access antiretroviral agents at no cost to the individual. In an exposure assessed as high risk, three-drug antiretroviral therapy is prescribed. If the risk is considered to be moderate, two-drug antiretroviral therapy is prescribed.

Our analysis was restricted to individuals accidentally

exposed who received a 5 day starter kit between April 1999 and November 2000, and who did and did not go on to receive the 23 day follow-up. Data were collected through the dispensation of accidental exposure kits and their prescription forms. In addition, in August 1999, a self-administered questionnaire was distributed by the pharmacy to the individuals who had at that time received the 23 day follow-up. This survey collected data on details regarding the exposure (including the location and source risk) and other related issues. Pharmaceutical and dispensing costs were obtained from the hospital pharmacy. Exposure details were obtained from the self-administered surveys, and then used as a sub-sample in a decision-tree analysis (see Fig. 1) to determine the expected and observed adherence to the accidental exposure guidelines, as well as the observed and expected drug dispensation costs based on exposure characteristics.

During the study period, the pharmaceutical and dispensing costs of the programme were Can\$538 098. The total expected costs based on what should have been dispensed according to guidelines during this same period were Can\$239 283, approximately Can\$298 000

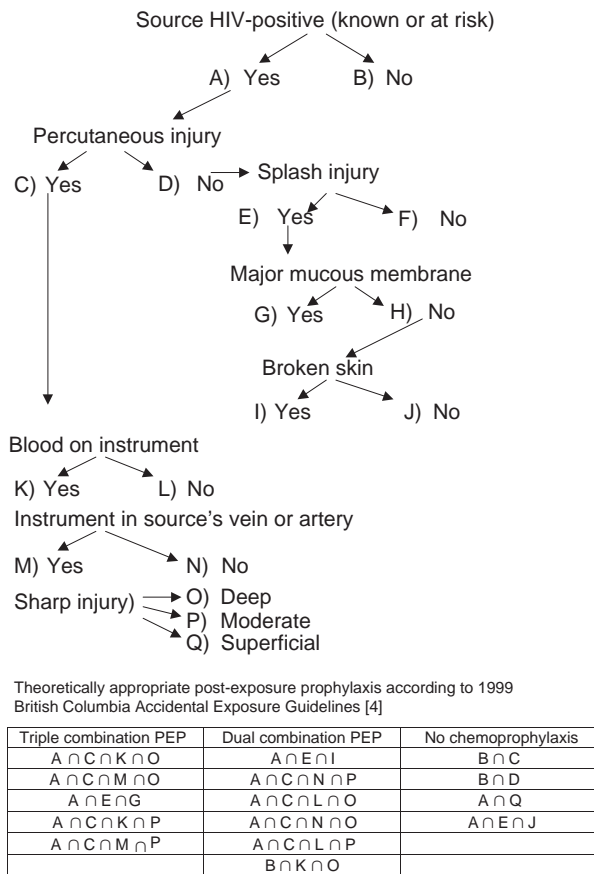


Fig. 1. Post-exposure prophylaxis decision-tree analysis.

less than what it actually did cost. There were zero seroconversions after accidental exposure reported during this period among individuals known to have taken post-exposure prophylaxis.

Within our sub-sample (n = 104), data indicate that whereas 39 (38%) individuals received three-drug therapy, only nine (9%) should have, resulting in 30% of individuals receiving three-drug therapy who should not have. Similarly, 65 (62%) individuals received two-drug PEP, although only 33 (32%) should have. A total of 54 (52%) individuals received PEP who, according to the guidelines, should not have received any chemoprophylaxis whatsoever. More specifically, approximately 19% of individuals who received three drugs should have received two, and 6% of individuals who received three-drug therapy should not have received any chemoprophylaxis at all. Less than 1% of individuals who received two-drug therapy should actually have received three drugs.

Merchant [3] raised two other issues that we were able to address. First, he suggested that the cost of post-exposure prophylaxis may be reduced because patients will not, for a variety of reasons, complete the full

course of antiretroviral therapy. Our data indicated that only approximately 30% of individuals continued with the 23 day follow-up treatment. However, once the prescription was filled, the cost to the programme was accrued regardless of whether or not the patient completed the prescription. Therefore, the actual costs of PEP programmes must take account of prescriptions filled, not necessarily consumed.

The second and more ethically complex question that Merchant [3] raised regarded the cost-effectiveness of PEP based on preventing new HIV infections. The number of seroconversions expected during the period of our study could be calculated on the basis of published data of seroconversion probabilities [5,6]. On the basis of these probabilities (high-risk source plus percutaneous injury 0.003; low-risk source plus percutaneous injury 0.0000015; high-risk source plus mucocutaneous injury 0.001; low-risk source plus mucocutaneous injury 0.0000005), we estimated that in the absence of our PEP programme, 0.71 seroconversions would have occurred among all 2064 individuals who did receive PEP. In essence, our programme spent over half a million Canadian dollars preventing almost one new seroconversion.

In summary, our data suggest that this population-based, post-accidental exposure prophylaxis programme, despite the presence of clear guidelines, is costing a substantial amount of money. Although the number of potential sexual exposures can be debated, it is certainly going to be a higher number than accidental exposures, and the discussions have not yet even raised the topic of injection drug users. Our analysis suggests that even in the presence of clear criteria, a sexual exposure PEP programme would be prohibitively expensive, and could even have negative ramifications on both the prevention of new infections and the care of those already infected.

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References

1. Low-Beer S, Weber AE, Bartholomew K, et al. A reality check: the cost of making post-exposure prophylaxis available to gay

- and bisexual men at high sexual risk. [Correspondence] *AIDS* 2000, **14**:325–326.
2. Pinkerton SD, Holgrave DR, Kahn JG. **Is post-exposure prophylaxis affordable?** [Correspondence] *AIDS* 2000, **14**:325.
 3. Merchant RC. **Post-exposure prophylaxis affordability: a clearer reality.** [Correspondence] *AIDS* 2001, **15**:541–542.
 4. McLeod WA, O'Shaughnessy MV. *Management of accidental exposure to HIV.* British Columbia, Canada: British Columbia Centre for Excellence in HIV/AIDS; March 1999.
 5. Katz MH, Gerberding JL. **Post exposure treatment of people exposed to the human immunodeficiency virus through sexual contact or injection drug use.** *N Engl J Med* 1997, **336**:1098–1100.
 6. Royce RA, Sena A, Cates Jr W, Cohen MS. **Sexual transmission of HIV.** *N Engl J Med* 1997, **336**:1072–1078.