A 29-year-old man with recently diagnosed HIV infection and a CD4 cell count of 225/mm³ began treatment with atazanavir (300 mg), ritonavir (100 mg), emtricitabine (200 mg), and tenofovir (300 mg) daily. For 18 months, he was treatment adherent and his plasma HIV RNA level was below the limit of detection. He then began a relationship with a new partner, who introduced him to methamphetamines. His medication adherence became erratic, and he missed appointments in clinic. Eventually, he was hospitalized for rehabilitation, and he resumed taking his medications on schedule. Following his discharge, he was found to have a plasma HIV RNA level of 11,400 copies/ml. Genotypic resistance testing revealed only an M184V mutation associated with emtricitabine resistance. A decision regarding his next treatment regimen needs to be made.

Current therapy
The clinical dilemma posed by this patient is commonly encountered by clinicians treating HIV-infected patients. This patient has clearly failed his treatment regimen, but genotypic resistance tests have failed to provide much guidance in choosing the next regimen.

Protease inhibitors (PI) represent valuable tools in the armamentarium of clinicians treating HIV-infected persons. Clinical trials in both treatment-naive and treatment-experienced subjects have demonstrated outstanding PI activity, and regimens containing PI may be recommended for use across these different patient populations (1). Indeed, two of the four recommended regimens for the initial treatment of HIV infections include PI (atazanavir and darunavir) (1).

Knowledge gap
Challenges for the PI class have included the need for pharmacologic boosting with some members of the class, especially if patients are more heavily treatment experienced and most notably if they are PI experienced (1). Numerous studies of patients who fail PI have not identified mutations in the protease gene associated with resistance (2–5). In a systematic review of first-line antiretroviral therapy, per mutations in the protease gene and guide the choice of subsequent PIs. However, in patients with a wild-type protease gene, clinicians will remain uncertain about the optimal choice of a PI for the next regimen. The second explanation involves the unique pharmacologic and pharmacodynamic properties of PI with high potency and relatively short half-lives, resulting in brief periods within the mutant selection window. Finally, the newly described env mutations may compromise PI activity. A fourth mechanism involving mutations at proteolytic cleavage sites has also been associated with PI resistance in a limited number of patients (8).

Recommendations
What are the implications for HIV clinical care? Until larger studies are completed assessing the frequency of env mutations, clinicians are likely to follow a simple paradigm. On the detection of virologic failure, reinforcing adherence to medications will result in resuppression of some patients. If resuppression does not occur, conventional genotypic resistance testing may identify mutations in the protease gene and guide the choice of subsequent PIs. However, in patients with a wild-type protease gene, clinicians will remain uncertain about the optimal choice of a PI for the next regimen. They will make an educated guess on the PI choice and will need to closely follow their patients on the new treatment regimen.

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