HIV Coreceptor Use in Heavily Treatment-Experienced Patients: Does It Take Two to Tangle?

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(See the article by Wilkin et al. on pages 591–5)

Although great strides have been made in developing treatments for HIV infection, several fundamental questions about HIV pathogenesis remain unanswered. One of these involves the relationship between HIV cellular tropism (as determined by coreceptor use) and disease progression. Given the pending availability of antiretrovirals with coreceptor specific activity, studies that allow us to untangle the threads of this relationship are urgently needed. Some intriguing and relevant data on HIV coreceptor use in treatment-experienced patients are reported by Wilkins and colleagues in this issue of Clinical Infectious Diseases [1].

As early as 1988, a connection between the cellular tropism of HIV and disease progression had been reported [2, 3]. Over the next decade, the capacity of virus to cause syncytium formation on MT-2 cells was commonly used to assess this characteristic and was shown to be highly predictive of disease progression in the host [4–8]. With the discovery in 1996 of the chemokine coreceptors CCR5 and CXCR4, it became evident that the syncytium-inducing phenotype was a result of the expression of CXCR4 but not CCR5 on MT-2 cells [9, 10]. Thus, strains of virus capable of entry using CXCR4 as a coreceptor were generally associated with disease progression, whereas the exclusive use of CCR5 was found in strains from most patients with recent infection and was not independently associated with disease progression [3, 7, 11]. Nonetheless, in studies involving natural history cohorts, ~50% of patients experienced disease progression without evidence of CXCR4-using virus [7, 8, 11].

The introduction of HAART in 1996 dramatically impacted the course of disease in patients receiving antiretroviral therapy; however, issues of drug-related toxicities and drug resistance led to a continued need for antiretroviral drugs with novel targets. The first approved antiretroviral agent that targeted viral entry was enfuvirtide (T-20), a peptide inhibitor of membrane fusion that targets the viral envelope glycoprotein gp41. As of late 2006, several other entry inhibitors were under development, and at least 2 of these, maraviroc and vicriviroc, were in the late stages of clinical development. These compounds act through binding to the host CCR5 receptor and blocking engagement of the viral envelope glycoprotein gp120. The need for coreceptor-use testing during the clinical development of coreceptor-binding inhibitors led to the development by Monogram Biosciences of the coreceptor use assay Trofile. Trofile is a single-cycle assay that uses virus particles pseudotyped with full-length patient plasma virus envelopes. Virus entry is evaluated on U87 cell lines expressing CD4 and either the CCR5 or CXCR4 coreceptor, and tropism is defined on the basis of the ablation of a luciferase reporter signal by coreceptor-specific inhibitors. The assay reports whether virus populations use only CCR5 coreceptors (R5), use only CXCR4 coreceptors (X4), or are dual-tropic or mixed HIV-1 populations that use both CCR5 and CXCR4 coreceptors (D/M); the latter may include individual viruses capable of entry using either coreceptor, mixtures of R5 and X4 virus, or some combination thereof.

Recent studies using the Trofile assay seem to indicate a trend toward an increasing frequency of D/M or X4 virus with increasing treatment experience. For example, among treatment-naive patients, >80% of patients harbored R5 strains, <20% harbored D/M strains, and <1% harbored X4 strains [13]. In a study involving patients who were experiencing failure of a first-line treatment regimen [12], 22% had D/M or X4 strains, whereas in another study [14], patients with intermediate levels of treatment experience had a prevalence of D/M or X4 strains of ~33%. Although these increasing prevalence rates could reflect a simple associ-
ation between decreasing CD4+ cell counts and the emergence of D/M or X4 virus, some reports also suggest that treatment itself may favor the emergence of D/M or X4 strains in plasma or may fail to inhibit their emergence in cellular reservoirs [15, 16].

Until recently, coreceptor use data were lacking for heavily treatment-experienced patients with limited treatment options, which is the group with perhaps the most urgent need of novel antiretroviral agents. Here, Wilkins et al. [1] have reported on coreceptor use in a large group of such patients who were screened for the AIDS Clinical Trial Group A5211 vicriviroc protocol. Subjects had median HIV RNA levels >4.5 log10 copies/mL and CD4+ cell counts <60 cells/μL; this report thus presents data for only the second such heavily treatment-experienced population to date, following a report in 2006 regarding coreceptor use in the enfuvirtide phase III T-20 versus Optimized Regimen Only (TORO) studies [17]. As Wilkins et al. [1] point out, results from the A5211 and TORO cohorts were highly concordant. In particular, both studies found an overall prevalence of D/M or X4 strains of 50%, which is remarkably consistent with findings from patients experiencing disease progression in natural history cohorts.

One intriguing set of observations in close agreement between the A5211 and TORO studies related to patients harboring X4 strains. Although comprising only 2%–4% of the studies’ populations, this was, nonetheless, among the highest prevalence rates reported to date and allowed direct comparison with R5 or D/M strains. Those results were striking: first, although D/M strains were associated with lower CD4+ cell counts than those associated with R5 strains, X4 strains were not—in both cohorts, X4 strains were associated with CD4+ cell counts fully as high as those associated with R5 strains. X4 strains were also associated, in both studies, with significantly lower median baseline HIV RNA levels than those associated with either R5 or D/M strains. Their characteristics were, in fact, remarkably similar to those reported for the very few (<10) HIV-infected patients homozygous for the CCR5 Δ32 allele (and, thus, harboring functionally X4 strains) described in the literature [18]. These observations lend support to the notion, discussed in the article by Wilkins et al. [1], that strains with a syncytium-inducing phenotype would probably be overwhelmingly characterized as D/M, rather than as X4, by the Trofile assay. Taken together with the characteristics of X4 strains highlighted above, this may point to a tangle of assaults from both CCR5-using and CXCR4-using viral envelopes as the cause of disease progression associated with the syncytium-inducing/CXCR4 phenotype.

An interesting contrast to earlier reports is that little or no association was observed in the A5211 and TORO cohorts between higher viral load and the presence of D/M strains. One possible explanation is that, in earlier, more cross-sectional studies, higher viral loads may have acted as a surrogate marker for more advanced disease status and, thus, a greater likelihood of harboring D/M or X4 strains. However, assays like Trofile also appear to be more sensitive in detecting strains with moderate levels of CXCR4 use than the MT-2 assay or predictions made from V3 loop genotyping [19]; thus, the current assay may simply be detecting CXCR4 use earlier in the course of the infection. Importantly, the clinical relevance of such observations remains unclear. For example, a study of the large HAART Observational Medical Evaluation and Research cohort found that CXCR4 use predicted by V3 loop genotype (using the “11/25” rule) was independently predictive of an increased risk of nonaccidental death and poorer CD4+ cell count response during subsequent antiretroviral therapy, whereas CXCR4 use determined by the more sensitive Trofile assay was not [12, 20]. Additional studies with longer follow-up will be needed to address the clinical significance of the differences between assays.

The combined data from the A5211 and TORO studies provide intriguing insights into characteristics associated with D/M and X4 strains in the context of long-term antiretroviral therapy. They also raise important questions about the application of data on coreceptor use and disease pathogenicity obtained in earlier patient cohorts or using different assay systems to the development of novel treatment paradigms. In particular, they suggest that the presence of CCR5 use makes an important contribution to ongoing CD4+ cell depletion, even after the emergence of CXCR4 use. In that regard, it can be hoped that new studies of coreceptor use during antiretroviral treatment will help to address these questions and will aid in unraveling the tangled web of HIV disease pathogenesis.

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References


6. Karlsson A, Parsmyr K, Aperia K, Sandstrom E, Fenyo EM, Albert J. MT-2 cell tropism of human immunodeficiency virus type 1 isolates as a marker for response to treatment and...


