

HIV-1 Tropism, Disease Progression, and Clinical Management

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(See the article by Shepherd et al., on pages 1104–12.)

It has been 15 years since HIV-1 tropism was recognized as a prognostic marker for CD4⁺ T cell depletion and progression to AIDS [1]. The original studies were performed by testing HIV-1 strains for syncytia induction in MT-2 cell culture. These cell-based assays had a sensitivity of detection of 5% and predicted disease progression. They were, however, slow and labor-intensive and thus did not lend themselves to clinical use. The discovery of HIV-1 coreceptors in 1996 demonstrated that syncytia formation in MT-2 cells was usually induced by HIV-1 strains that used the CXCR4 (i.e., X4) coreceptor (hereafter, “X4 strains”) [2]. Early studies of coreceptor use (i.e., tropism) confirmed that HIV-1 strains that used X4 were as-

sociated with increased CD4⁺ T cell depletion and more rapid disease progression [3–7]. Basic studies demonstrated likely mechanisms by which X4 strains exhibited increased cytopathicity that accelerated CD4⁺ T cell loss and disease progression [8–10].

Several recent articles examined HIV-1 tropism in cohorts of infected individuals, some of whom were treated with combination antiretroviral therapy (cART) [11–15]. These studies determined viral coreceptor use by use of various methods, including sequence analysis of the V3 region of the HIV-1 envelope [11, 12], a heteroduplex tracking assay [13], and a cell-based phenotypic assay [14, 15]. All of these articles agreed that detection of HIV-1 strains that use the X4 coreceptor, usually mixed in the swarm of viral variants that use the CCR5 (i.e., R5) coreceptor, correlated with more rapid HIV-1 disease progression. Their findings also raised the question of whether tropism testing may aid in clinical management.

cART has led to a great reduction in rates of illness and death. A small proportion of patients, however, experience disease progression and virologic failure despite use of cART, triggering debate regarding when to start and when to switch cART [16–23]. New biomarkers may be helpful in identifying patients at high risk of disease progression and, therefore, likely to benefit from initiation or change of

cART. Nevertheless, determination of HIV-1 tropism has not yet been considered together with CD4⁺ T cell count and total viral load as a marker to be used for patient management.

The article by Shepherd et al. [24] in this issue of the *Journal* evaluated the Multicenter AIDS Cohort Study (MACS) cohort to address some remaining questions in the fields of HIV-1 tropism, pathogenesis, and disease progression. The MACS is a longitudinal US study of the natural history of HIV-1 infection in men who have sex with men. It includes >400 participants who seroconverted before 1995 and, therefore, is well suited to investigate HIV-1 disease progression in untreated men. In particular, the investigators addressed the following clinically relevant issues: the specific timing of X4 virus emergence in relation to the onset of total T cell decline and AIDS, the correlation between emergence of X4 strains and a subsequent increased rate of HIV-1 disease progression, and whether determination of the CD4⁺ T cell count can be an accurate screen for detection of X4 viruses.

The study examined the emergence of X4 strains in 67 seroconverters (of whom 58 had not initiated cART) over time, with an average of 10 serial samples per donor obtained 6 months apart. The participants displayed a wide range of rates of progression to AIDS, defined as development of a CD4⁺ T cell count of <200 cells/ μ L

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and/or an AIDS-defining illness. The samples were analyzed by use of the Trofile assay (Monogram Biosciences), a cell-based test that can detect the presence of X4 strains if they make up at least 5%–10% of the total viral swarm.

The study found that 52% of these men had X4 viral strains at ≥ 1 time point. The viral populations in each X4 virus–positive specimen used both CXCR4 and CCR5. Twenty-three percent of the men who had X4 viruses detected, however, exhibited ≥ 1 reversion to a population of CCR5-using viruses. These results may be due to variability in the Trofile assay, as has been reported [25]. As seen in previous studies, the detection of X4 strains was significantly correlated with more rapid progression to an AIDS-defining illness or a CD4⁺ T cell count of < 200 cells/ μ L, although some men developed AIDS without detectable levels of X4 strains.

There were also some noteworthy new findings. The median time between emergence of X4 virus to progression to AIDS or a CD4⁺ T cell count of < 200 cells/ μ L was 13.2 months among men who had X4 virus emergence before AIDS onset. Not only did X4 virus appear well before late stage disease, it also appeared a median of 0.83 years before the CD3⁺ inflection point, a marker that is closely associated with impending cellular immunologic decline [26].

Interestingly, in this study the CD4⁺ T cell count was not associated with subsequent detection of X4 viruses. Among men who had a detectable level of X4 virus before onset of an AIDS-defining illness, the median CD4⁺ T cell count when X4 virus was first detected was 475 cells/ μ L. Similar findings were previously reported [1, 12], although other studies found an association of X4 viruses with low CD4⁺ T cell counts [11, 14, 27]. The detection of X4 strains in men with relatively high CD4⁺ T cell counts in the present study may reflect the strength of the study's longitudinal design, compared with that of other study designs that involved cross-sectional data.

Surprisingly, in the present study neither CD4⁺ T cell count nor viral load was associated with the likelihood of having a detectable level of X4 virus at the next visit, 6 months later. The common detection of X4 strains at high CD4⁺ T cell counts indicates that many patients may develop X4 strains before they meet criteria (based on CD4⁺ cell count and viral load) for initiation of antiretroviral therapy that are outlined in current guidelines. Therefore, because X4 strains and their associated increased risk for more rapid disease progression cannot be reliably predicted by the CD4⁺ T cell count or viral load, a tropism assay is required for their detection.

This study contributes significantly to our understanding of the role of X4 viral strains in pathogenesis and disease progression. X4 strains appear to emerge well before AIDS onset and, therefore, are likely to be etiologically linked to CD4⁺ T cell decline and progression to AIDS. A recent quantitative study of tropism supported these findings and found that detection of X4 strains and the X4-specific viral load strongly predicted clinical disease progression independent of and in addition to CD4⁺ T cell counts or total viral load [13].

These recent studies of HIV-1 tropism and clinical disease progression have important clinical implications. As Shepherd et al. [24] point out, their findings and those of others suggest that it may be prudent to initiate cART as soon as X4 viruses are detected, because the emergence of X4 strains reflects an increased risk of HIV-1 disease progression. The criteria for starting cART have been discussed recently in light of new studies and improved drugs [22, 23]. Accumulating evidence strongly suggests that detection and, when available, quantification of X4 strains should be considered as potential new biomarkers to guide clinical management throughout HIV-1 infection. By revealing the presence of X4 strains, these biomarkers offer the potential to improve individualized therapy. HIV-1 tropism testing is currently used in the selection and monitoring of

coreceptor-blocking agents. It is now time to design studies to define the role of tropism testing and X4 viral load in determining when to start and when to switch antiretroviral therapy.

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