More on the Treatment-Tropism Relationship: The Impact of Prior Antiretroviral Treatment on HIV Coreceptor Tropism among Subjects Entering AIDS Clinical Trials Group 175

To the Editor—CCR5 (R5) and CXCR4 (X4) are the major coreceptors that, along with CD4, mediate HIV entry in vivo [1, 2]. The R5 antagonists in development inhibit replication of R5-using HIV variants [3], but they have little activity on X4 or dual/mixed populations (R5X4) [4].

Detectable R5X4 and X4 are more prevalent among the treatment experienced, which suggests that treatment may select for X4 use. This has been observed in cross-sectional analyses of clinical trials and clinical cohorts [5, 6]. In untreated patients, an increase in X4 use is associated with CD4+ T cell count decline [7]; however, causality has been difficult to establish. The relationship between treatment and tropism has been confounded by differences in nadir CD4+ T cell counts between treated and untreated patients.

Hunt et al. [5] recently reported that patients with partial viral suppression receiving diverse combination therapies have >4-fold greater odds of harboring detectable X4-using virus than do treatment-naive subjects, independent of CD4+ T cell counts and CCR5Δ32 genotype. However, the higher prevalence of X4-using viruses in treated subjects may be explained by lower pretreatment nadir CD4+ T cell counts.

AIDS Clinical Trials Group (ACTG) 175 was a randomized, placebo-controlled study conducted in 1991 to assess the benefit of combination therapy versus monotherapy in preventing clinical progression to AIDS/death in patients with CD4+ T cell counts between 200–500 cells/mm³ [8]. A total of 2467 subjects were randomized to receive zidovudine (ZDV), didanosine (DDI), ZDV plus DDI, or ZDV plus zalcitabine. Quantitative HIV-1 RNA levels were obtained and peripheral blood mononuclear cell and MT2 cell cultures were done at selected sites. At the Stanford site, 74 subjects enrolled and had tropism determined by virus culture and MT2 cell assay at study entry; other data collected included treatment history, symptom history, age, CD4+ T cell count, baseline viral load, present or prior HIV-related symptoms, and proportion of CCR5Δ32 heterozygotes were not different between the 2 groups (table 1). ZDV exposure remained significantly associated with SI virus at baseline in a multivariate logistic regression model that controlled for the above variables, with an odds ratio of 8.01 (95% confidence interval, 1.62–39.7). Baseline CD4+ T cell count showed a trend toward association with tropism in the univariate analysis and was significant in the multivariate model, with an odds ratio of 1.01 (95% confidence interval, 1.00–1.01).

Our data are in agreement with those

### Table 1. Baseline cohort characteristics at study entry, categorized by detectable syncytia (SI) vs. no detectable SI (NSI), as determined by MT2 cell–based tropism assay.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SI (n = 16)</th>
<th>NSI (n = 58)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>38.5 (33.5–45.5)</td>
<td>35 (31–41)</td>
<td>.36</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA load, log10 copies/mL</td>
<td>4.18 (3.55–4.95)</td>
<td>4.26 (3.74–4.62)</td>
<td>.91</td>
</tr>
<tr>
<td>Baseline CD4+ T cell counts, cells/mm³</td>
<td>349 (283–425)</td>
<td>345 (270–422)</td>
<td>.92</td>
</tr>
<tr>
<td>Zidovudine experienced, proportion (%)</td>
<td>10/16 (63)</td>
<td>19/58 (33)</td>
<td>.044</td>
</tr>
<tr>
<td>Present or prior HIV-related symptoms, proportion (%)</td>
<td>0/16 (0)</td>
<td>8/58 (14)</td>
<td>.19</td>
</tr>
<tr>
<td>CCR5Δ32 heterozygotes, proportion (%)</td>
<td>2/15 (13.3)</td>
<td>13/53 (25)</td>
<td>.49</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median (interquartile range), unless otherwise indicated.

* P values are 2-sided and were determined by the Wilcoxon rank-sum test for nonparametric continuous variables and by Fisher’s exact test for categorical variables.
of Hunt et al. in that they indicate that treatment may enhance selection of X4-using virus, even with ZDV monotherapy. The frequencies of SI virus in the treatment-experienced group (34%) and the treatment-naive group (11%) were similar to those reported by Hunt, despite the different assays used to measure tropism. Although we did not have nadir CD4+ T cell count data in this cohort with prior ZDV monotherapy only, the subjects were likely at their nadir at the time of enrollment. Evidence for this is provided by the overall results of ACTG 175—subjects who were treatment naive and received ZDV monotherapy achieved a maximum CD4+ T cell count gain of 14 cells/mm3 at week 8 and had returned to baseline CD4+ T cell counts by week 20 [8]. Prior studies have shown that ZDV is preferentially phosphorylated in activated T cells that express high levels of R5 and has less activity in resting T cells [9]. An earlier study comparing ZDV monotherapy with DDI monotherapy showed that ZDV had better activity against NSI (R5-using only) than against SI (X4-using) biological clones, whereas DDI had better activity against SI clones [10]. This ZDV-specific effect could have contributed to our results, although specific treatments did not appear to have differential effects in Hunt et al.’s study. The other possibility, as Hunt et al. pointed out, is that treatment-mediated reductions in R5 expression and associated reduced immune activation may favor the selection of X4-using viruses [11]. Whatever the mechanism, antiretroviral therapy appears to select for an increase in X4-using viruses among patients who have persistent viremia. In defining the strategic use of R5 inhibitors, it may be important to focus on drug-naive patients, who are less likely to have developed X4-using viruses.

Nancy S. Shulman, Seble G. Kassaye,
Mark A. Winters, Elizabeth Johnston,
and David A. Katzenstein
Division of Infectious Diseases, Stanford University School of Medicine, Stanford, California

References

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Reprints or correspondence: Dr. Nancy S. Shulman, Div. of Infectious Diseases, Stanford University School of Medicine, 300 Pasteur Dr., S-169, Stanford, CA 94305 (nshulman@stanford.edu).

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Reply to Shulman et al.

To the Editor—In their correspondence, Shulman et al. [1] report that patients receiving zidovudine (AZT) monotherapy were much more likely to harbor CXCR4-using viruses than treatment-naive patients. The observed enrichment of CXCR4-using syncitia-inducing viruses appeared to be independent of CD4+ T cell count and confirms the findings of prior studies from early during the treatment era regarding the effect of AZT on co-receptor tropism [2]. These observations are also consistent with data from our group and others indicating that heavily pretreated patients receiving partially suppressive combination antiretroviral regimens are more likely to harbor CXCR4-using viruses than treatment-naive patients, independent of CD4+ T cell count [3–5]. It remains unclear why treated patients with drug-resistant viremia are enriched for CXCR4-using viruses. As outlined by Shulman et al., thymidine analogues such as AZT are unique among all antiretroviral drugs in that they require intracellular phosphorylation by an activation-dependent cellular kinase for activity. Because resting CD4+ T cells typically express low levels of both the activation-dependent kinase and the CCR5 coreceptor but high levels of CXCR4, AZT monotherapy may select for viruses that use CXCR4 for entry [2]. Although this could readily explain the observations of Shulman et al., it is