To the Editor—Thackray and Field [1] raise 4 points that they believe explain why our recent study [2] failed to document the virologic superiority of famciclovir over valacyclovir that they described in several reports and numerous abstracts.

First, the route of infection did differ, as we acknowledged in our Discussion section [2]. They argue, however, that infection of the cornea (as opposed to the ear pinna in their model system) would favor direct uptake of virus into the axons, eliminating the opportunity a drug started 24 h later might have to limit viral amplification in the ganglia. We believe that any such aspect of our model system is overstated. In our studies, virus titers in tissues continued to rise for some days after the start of treatment (figure 3 in [2]). Thus, there remained ample opportunity for viral replication to be affected by the drugs. Nonetheless, we failed to observe any differential benefit of famciclovir. Moreover, Thackray and colleagues [3–5] reported experiments in which they delayed treatment even further and still observed superiority of famciclovir.

Second, Thackray and Field [1] are concerned about the virus inoculum that we used, because it was associated with universal mortality in the absence of treatment. It is true that no positive controls remained with which to compare the effects of treatment on latency and reactivation; however, untreated animals survived long enough for us to observe that famciclovir and valacyclovir were equivalent in virologic outcome measures of the acute infection.

Third, with regard to a rebound of virus titers, we disagree that there is a “variance with the results published” [1]. It has been our experience that the time points chosen are more than sufficient to track the spread of herpes simplex virus (HSV) from the eye to the trigeminal ganglia and into the brain. With the chosen time points, we saw the spread of virus through these tissues. Moreover, we detected no differences in the effect of either drug during the testing period. Obviously, for a true rebound to occur, the initial infection first must be cleared. Clearance was beginning to occur by the final time point, post-infection day 11. In an immunosuppression model, Field et al. [3] tested ear and brain samples on intermittent days and still detected a rebound of virus titers.

Fourth, we claimed equivalence of both drugs in “terminating ganglionic infection” [2], by which we meant the presence of infectious virus in the tissue. Despite their claim to the contrary, Thackray and Field [4, 5] reported that famciclovir was superior in reducing the amount of both infectious and latent virus in ganglia and in “preventing the establishment of latency” (Discussion in [4]; Introduction and Discussion in [5]).

We agree that each animal model has its own advantages and disadvantages. We believe, from our own data, that famciclovir and valacyclovir are equivalent for the acute treatment of HSV infections and will continue to believe so until a well-designed clinical trial proves otherwise.

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References


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The Journal of Infectious Diseases 2000;181:1518

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0022-1899/2000/181014-0046$02.00

Questions about Results Reported with Potent Antiretroviral Therapy for Human Immunodeficiency Virus Type 1 Infection

To the Editor—Zaunders et al. [1] report the clearance rates of plasma human immunodeficiency virus (HIV) type 1 RNA and peripheral blood HIV-1 DNA levels, the phenotypic profiles of CD4 and CD8 lymphocytes, and anti–HIV-1 antibody levels in patients treated for 52 weeks with antiretroviral therapy (combination of zidovudine, lamivudine, and indinovir). Therapy was begun during primary HIV-1 infection (PHI). Results were compared with results for HIV-1–uninfected subjects, un-
treated patients with PHI, and patients with established HIV-1 infection. The data reported raise several questions.

First, by week 8 a similar decrease in peripheral blood HIV DNA levels was observed in both treated and untreated patients. What was the reason for the decrease in untreated patients, and why was there no difference in the decreases in the 2 groups?

Second, reverse-transcriptase inhibitors prevent reverse transcription (RT) of HIV RNA into HIV DNA, whereas protease inhibitors render newly produced virions noninfectious. Furthermore, according to the most recent model of HIV-1 pathogenesis reported by Ho et al. [2] and Wei et al. [3], productively infected lymphocytes have a half-life of $\approx$1.6 days. However, Zaunders et al. [1] found continued expression of viral antigens. In this case, one would expect the HIV DNA to increase or at least to remain stable in the untreated patients with PHI and to decrease rapidly in treated patients. What is the explanation for their findings that treatment “had little direct effect on HIV-1 DNA burden” [1, p. 326] and that “no significant difference in the number of copies per microgram of PBMC [peripheral blood mononuclear cells] DNA was observed between treated and untreated PHI patients at baseline or at weeks 8, 24, or 52” [1, p. 322]?

Third, the antiretroviral drugs used by Zaunders et al. affect neither transcription of proviral DNA nor translation of HIV RNA into proteins (i.e., expression of viral RNA and proteins). In other words, they decrease HIV RNA indirectly by decreasing HIV-1 DNA viral burden. How then did treatment lead to a decline of HIV RNA from 6.0 log$_{10}$ copies/mL at baseline to 0 copies/mL after week 36 while having “little” effect on HIV-1 DNA burden?

Fourth, when discussing their findings with regard to the phenotypic profiles of the CD8 lymphocytes, Zaunders et al. wrote, “The persistence of HIV-1 DNA together with increased CD8 T lymphocyte turnover and activation indicate continued expression of viral antigens [1, p. 320].” How is it possible to have continuous expression of HIV proteins in the absence of HIV RNA?

Fifth, if there was continuous expression of viral antigens, why did only 2 patients treated with highly active antiretroviral therapy (HAART) develop “typical antibody responses to HIV-1, as determined by serial Western blots” [1, p. 325]? Was there, at any stage of the study, a difference between the Western blot profiles of HAART-treated and -untreated patients with PHI?

Sixth, given that the aim of the study was to compare treatment between patients with PHI and “HIV-1-uninfected subjects, untreated PHI patients, and patients with established HIV-1 infection, [1, p. 320]” why, with the exception of the lymphocyte profiles, were no data presented on the HIV-1-uninfected subjects and the patients with established HIV-1 infection?

Finally, for the measurement of the HIV RNA, Zaunders et al. [1] used the Roche Amplicor quantitative RT polymerase chain reaction (PCR) kit. However, according to the manufacturer, “the Amplicor HIV-1 Monitor test is not intended to be used as a screening test for HIV or as a diagnostic test to confirm the presence of HIV infection” (Roche Diagnostic Systems, [Branchburg, NJ], 06/96, 13-08088-001). Researchers at the University of Massachusetts School of Medicine found that “plasma viral load tests were neither developed nor evaluated for the diagnosis of HIV infection…. Their performance in patients who are not infected with HIV is unknown,” and their use leads to “misdiagnosis of HIV infection” [4, p. 37]. One British virologist noted, “Those laboratories which undertake HIV screening and confirmation assays understand fully the technical problems associated with PCR and other amplification assays and it is precisely for those reasons that PCR is NOT used as a confirmatory assay (as discussions with any competent virologist would have informed them)” [5, p. 38]. Thus, if it is possible that Zaunders et al. did not detect HIV RNA, could this explain the lack of correlation between HIV DNA and HIV RNA?

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The Journal of Infectious Diseases 2000;181:1518–19
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Reply

To the Editor—Our results [1] showed that, although there was a 4–5 log decrease in plasma human immunodeficiency virus