Reply to Abbate et al

To The Editor—Abbate and colleagues [1] report similar findings to ours [2] in terms of the utility of deep sequencing for the determination of human immunodeficiency virus (HIV) tropism, lending further confidence to this approach. They note that the major advantage of our results is the evaluation of the ability of deep sequencing to predict actual virologic outcomes to CCR5-antagonist medication rather than its comparison with a nominal Trofile assay call.

Abbate and colleagues [1] rightfully express caution at extending our results (which were generated using HIV RNA from plasma) to the peripheral blood mononuclear cell (PBMC) compartment from which cell-associated HIV DNA may be amplified and tested. Specifically, they caution against using the same cutoff point of 2% non-R5 variants used for plasma samples in our study [2] to apply to PBMC samples, given that they and others have reported higher X4 prevalence, higher variability, and unclear clinical relevance for this compartment [3–5]. We believe that the need for clinical validation of the PBMC compartment is not exclusive to genotypic tropism testing, but also applies to phenotypic assays that start with cellular HIV DNA.

Our efforts to address genotypic tropism testing from PBMCs are ongoing and have only recently been presented at the latest Conference on Retroviruses and Opportunistic Infections [6]. In that study, we performed deep sequencing with HIV DNA amplified from baseline PBMCs, paired with HIV RNA from the matching plasma samples in 181 patients entering the maraviroc arms of the Maraviroc versus Optimized Therapy in Viremia Antiretroviral Treatment-Experienced Patients and A4001029 trials. Sequences were interpreted using geno2pheno, and the same optimized cutoff of 2% was used [7]. Although our results are preliminary, they indicate that deep sequencing could be performed from the PBMC compartment and was generally a comparable predictor of maraviroc response relative to other approaches in plasma samples. We did note, however, that the plasma compartment was marginally more predictive of response when the compartments gave differing tropism calls [6].

It should be noted that both of these studies have included a large number of patients with non-R5 Trofile results who nevertheless received a CCR5 antagonist [2, 6]. The patient population published in the Journal of Infectious Diseases is also the same population used to validate the original Trofile assay [8, 9]. The effect on our results of “prescreening” with Trofile was mitigated by the inclusion of maraviroc-treated patients with non-R5 HIV infection. Further efforts to minimize this effect have recently confirmed the utility of the deep sequencing approach [10]. Despite these strengths, we agree with Abbate and colleagues [1] that more research is needed both in genotypic and phenotypic approaches involving PBMCs to establish the maximal clinical utility of this compartment.

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References


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