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Partner Characteristics Predicting HIV-1 Set Point in Sexually Acquired HIV-1 Among African Seroconverters

Jairam R. Lingappa,1,2,3 Katherine K. Thomas,3 James P. Hughes,4 Jared M. Baeten,1,2,5 Anna Wald,2,5,7 Carey Farquhar,1,5,8 Guy de Bruyn,9 Kenneth H. Fife,9 Mary S. Campbell,2 Saidi Kapiga,10 James I. Mullins,2,6,11 and Connie Celum,1,2,5 for the Partners in Prevention HSV/HIV Transmission Study Team

Abstract

Plasma HIV-1 RNA set point is an important predictor of HIV-1 disease progression. We hypothesized that inoculum size and HIV-1 exposure prior to HIV-1 transmission may modulate set point. We evaluated predictors of set point among 141 African HIV-1 seroconverters and their HIV-1-infected study partners. We compared characteristics of seroconverters and their HIV-1-infected partners and HIV-1 set point. Data were from a clinical trial of genital HSV-2 suppression with acyclovir to reduce HIV-1 transmission in HIV-1 serodiscordant couples with HIV-1 transmission linkage assigned through virus sequencing. Our analysis includes data from all transmissions including those with transmission linkage to the HIV-1-infected “source partner” and those that were not linked to their HIV-1-infected study partner. In multivariable analysis, higher plasma HIV-1 in source partners was associated with higher seroconverter set point (+0.44 log10 copies/ml per log10 source partner plasma HIV-1, p<0.001). In addition, bacterial vaginosis (BV) among female source partners near the time of infection was associated with higher set point in their male seroconverters (+0.49 log10 p=0.04). Source partner characteristics associated with lower set point included male circumcision (−0.63 log10 p=0.03) and assignment to acyclovir (−0.44 log10 p=0.02). The proportion of variation in set point explained by plasma HIV-1 RNA of the source partner, after controlling for other factors, was 0.06. Source partner plasma HIV-1 level is the most significant predictor of seroconverter set point, possibly reflecting characteristics of the transmitted virus. Acyclovir use, BV among women source partners, and circumcision among male source partners may alter the set point by affecting transmitted virus inoculum in the source partners’ genital compartment.

Introduction

Increased plasma HIV-1 set point (i.e., the steady-state concentration of virus in plasma established after acute infection) is strongly associated with increased risk of HIV-1 disease progression and transmission,1–3 making factors that predict set point of interest for understanding the pathogenesis of HIV-1 infection. Studies of newly HIV-1-infected individuals have shown that during the process of early HIV-1 infection, a balance between cytotoxic T lymphocyte host responses and virus escape contributes to determining HIV-1 set point,4 and that, in this context, specific host genetic characteristics (e.g., alleles in the HLA and KIR loci) also influence set point.5–10 Studies evaluating HIV-1-infected source partners in diverse epidemiologic contexts have found that plasma HIV-1 RNA levels of source partners11–14 and genetic characteristics of their transmitted viruses15 are associated with HIV-1 set point in their seroconverter partners. Collectively, these findings have been interpreted as demonstrating that fixed genetic characteristics of the host and transmitted virus define set point in the newly infected partner.16 However, in stable HIV serodiscordant couples,

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