# Ambiguous nucleotide calls from population-based sequencing of HIV-1 are a marker for viral diversity and the age of infection

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Background. The time passed since the infection of a human immunodeficiency virus (HIV)-infected individual (the age of infection) is an important but often only poorly known quantity. We assessed whether the fraction of ambiguous nucleotides obtained from bulk sequencing as done for genotypic resistance testing can serve as a proxy of this parameter. Methods. We correlated the age of infection and the fraction of ambiguous nucleotides in partial pol sequences of HIV-1 sampled before initiation of antiretroviral therapy (ART). Three groups of Swiss HIV Cohort Study participants were analyzed, for whom the age of infection was estimated on the basis of Bayesian back calculation (n = 3,307), seroconversion (n = 366), or diagnoses of primary HIV infection (n = 130). In addition, we studied 124 patients for whom longitudinal genotypic resistance testing was performed while they were still ART-naive. Results. We found that the fraction of ambiguous nucleotides increased with the age of infection with a rate of .2% per year within the first 8 years but thereafter with a decreasing rate. We show that this pattern is consistent with population-genetic models for realistic parameters. Finally, we show that, in this highly representative population, a fraction of ambiguous nucleotides of >.5% provides strong evidence against a recent infection event < 1 year prior to sampling (negative predictive value, 98.7%). Conclusions. These findings show that the fraction of ambiguous nucleotides is a useful marker for the age of infection.
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