Title

Bayesian methods provide a posterior probability by day for possible dates of HIV acquisition which is useful in clinical trials

Journal

JOURNAL OF THE INTERNATIONAL AIDS SOCIETY, 27

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Publication Date

2024-10-01

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

Abstract Supplement

Abstracts from HIVR4P 2024, the 5th HIV Research for Prevention Conference, 6 - 10 October

Lima, Peru & Virtual

HIVR4P 2024

Volume 27, Supplement 5, October 2024

WILEY

Background: Women aged 15–24 years old carry a disproportionate burden of the new HIV infections diagnosed in Southern Africa. While the causes of this HIV gender-and-age are unclear, one key hypothesis argues that age-disparate relationships with older men drive infection in younger women.
Methods: We conducted whole-genome sequencing of HIV in a large phylogenetic study to model the transmission of the virus between demographic groups in the rural setting of KwaZulu-Natal, South Africa, utilizing data from the Vukuzazi cohort. Samples with HIV viral loads >50 copies/ml were submitted for whole-genome sequencing. Adequate sequences were arranged into genomic clusters using a maximum likelihood phylogeny. Potential transmission pairs within clusters were analysed alongside the age and sex data of participants. The distribution of pairings between different age and sex groups was compared to a model in which pairs were drawn from the HIV-positive population by chance.
Results: The Vukuzazi cohort enrolled 18,025 participants, 6069 of whom were HIV positive, and 1232 of whom had viral loads over 50 copies/ml; sequencing of these samples yielded 1097 adequate genomes. Phylogenetic analysis produced 89 clusters containing a total of 205 individuals, and 73 possible linkages between men and women. Only 32 of these 89 potential transmission links (36%) were between men in an older age group than the women. When compared to a model population in which pairings between men and women in different age groups occur randomly within the sample, the number of pairs in all age-sex combinations was within the 95% confidence interval if pairs were drawn randomly.
Conclusions: Our data does not support the assertion that the gender gap in HIV prevalence is driven by older men pairing with younger women. This dogma has been used to influence public health messaging over the last two decades, based on previous research, and may be less true than initially thought. Current work suggests that there likely is a contribution of age-disparity in transmission, though with significantly smaller age gaps than initially suggested.

OA0807LB

Bayesian methods provide a posterior probability by day for possible dates of HIV acquisition which is useful in clinical trials

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Background: Precisely identifying the time of acquisition is important to evaluate correlates and protective thresholds in HIV prevention clinical trials. However, estimating acquisition timing is often challenging due to relatively sparse visit schedules and variable biomarker detection during early HIV acquisition. To address these challenges, statistical methods were developed to better estimate the time of acquisition from control cohorts (FRESH/RV217) for application to prevention trials such as the AMP trials.
Methods: Timing estimation methods utilized either diagnostic test markers or sequence diversity from HIV-1 GP (gag/Δpol) and REN (rev/vpu/env/Δnef) regions. For AMP, we used Bayesian methods to combine these estimators and thus obtain higher precision and accuracy. The resulting Bayesian estimator outputs posterior probability distributions, from which we generated point estimates and credible intervals (CI) for the timing estimates, as well as the date of diagnosable acquisition (DDA), with the goal of comparing them to the gold standard data from the accurately timed acute acquisition FRESH and RV217 studies. The "gold standard" estimator for DDA was computed as the mid-point between a participant's true last negative and first positive diagnostic tests, which is accurate and very precise (4 days, range 2–7 days) due to the frequent sampling in these studies.
Results: Overall, the 95% credible interval (CI) was smaller for the combined estimator (median width 6 days, IQR 4–21.5 days) than for the diagnostic estimator alone (median width 15 days, IQR 11–23 days). The overall coverage of the COB was lower for the combined than the diagnostic estimator (0.515 vs. 0.835, respectively) although the CI is more accurate for combined. The differences between the estimators were especially notable in antibody-negative samples (median 95% CI width [IQR] 3 days [3–5 days] vs. 12 days [7–14 days]) for combined and diagnostic, respectively.
Conclusions: Accurate timing estimators help evaluate the effectiveness of preventive measures and understanding the time of HIV acquisition can help tailor intervention doses, in bNab studies such as the AMP and future trials. Acute infection data, as described here for the RV217 and FRESH cohorts, also provide valuable insights into viral dynamics associated with the acquisition and establishment of infection.