Quantifying Uncertainty in HIV Transmission Risk from Persons with Low-Level Viremia

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BACKGROUND

In 2023 the World Health Organization released a policy stating that "*"People living with HIV who have a **suppressed but detectable [low-level viremia, 200 – 1000 copies/mL]** viral load and are taking medication as prescribed have **almost zero or negligible** risk of **transmitting HIV** to their sexual partner(s)."* Our goal was to **quantify transmission risk** (and uncertainty) associated with **low level viremia** and its **implications** in settings with infrequent VL monitoring.

EXISTING EVIDENCE

Among 323 transmission events, only **2 transmission events** were associated with a VL **<1,000 copies/mL** (Broyles et al., The Lancet, 2023).

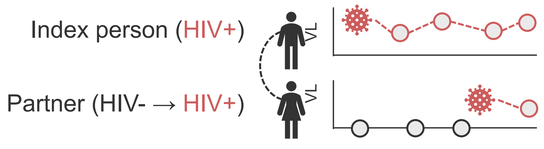
However, among studies with index partners on treatment:

- **HPTN052**: **1/8** linked infections had index **VL <1,000 copies/mL** (Cohen et al., NEJM, 2016)
- **Partners PREP**: **1/3** linked infections had index **VL <1,000 copies/mL** (Mujugira et al., JAIDS, 2016)

METHODS: DATA

We utilized epidemiological and virological data from >15,000 participants with HIV in the population-based **Rakai Community Cohort Study (1995-2022).**

TRANSMISSION COHORT: We utilized longitudinal HIV testing and viral load monitoring from monogamous cohabitating serodiscordant (HIV+/HIV-) couples. We estimated the relationship between index **viral load** and **rate of transmission** using a mechanistic model of viral transmission.



VIRAL LOAD COHORT: Paired viral load measurements from 91 people living with HIV on treatment were used to quantify stability of **low-level viremia** and simulate viral-load trajectories over 12-months of follow-up.

We estimate **2.9 transmissions** per 100 person-years at a viral load of **1,000 copies/mL** and **1.3 transmissions** per 100 person-years from individuals with **low-level viremia** after accounting for viral rebound

METHODS: TRANSMISSION MODEL

Probability of transmission per sexual act:

$$P(\text{transmission} \mid \text{index VL}, \text{sexual act}) = \rho_{\text{prod.}}(1 - \rho_{\text{est.}})^{c}$$

$\rho_{\text{prod.}}$: prob. act allows transmission; $\rho_{\text{est.}}$: per-virion prob. establishment; c: constant of proportionality

Probability of transmission during partnership

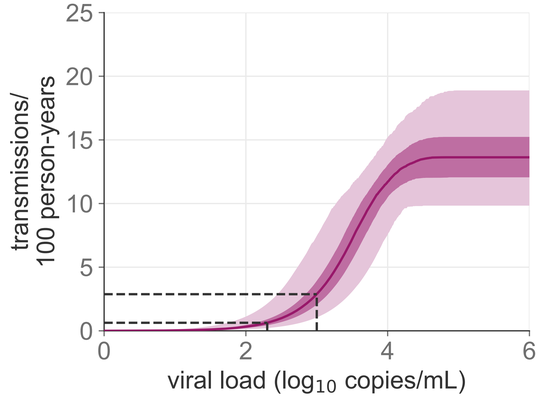
$$P(\text{transmission} \mid \text{partnership}) = 1 - (1 - P(\text{transmission} \mid \text{sexual act}))^{\#\text{frequency of acts}}$$

Probability of seroconversion During partnership

$$P(\text{HIV+} \mid \text{partnership duration}) = 1 - (1 - P(\text{transmission} \mid \text{partnership}))e^{-\text{extra-couple transmission rate} \times \text{partnership duration}}$$

RESULTS

We fit this model to 93 seroconversions among 940 couple-years of follow-up from 415 monogamous serodiscordant couples. We focused on pre-treatment index partners as their viral loads are more stable and informative of the relationship between viral load and transmission rate.



We estimate **2.9 (95% CI 1.1-7.5) transmissions** per 100 person-years at a viral load of **1,000 copies/mL**

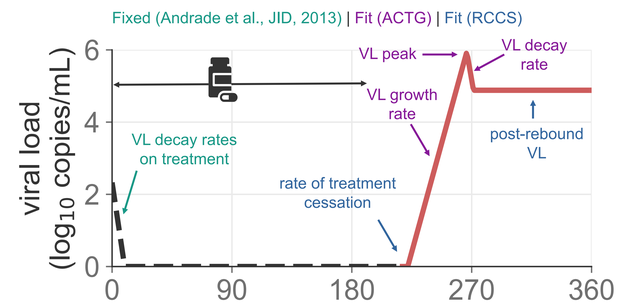
We estimate **0.6 (95% CI 0.2-2.1) transmissions** per 100 person-years at a viral load of **200 copies/mL**

RESULTS (CONTINUED)

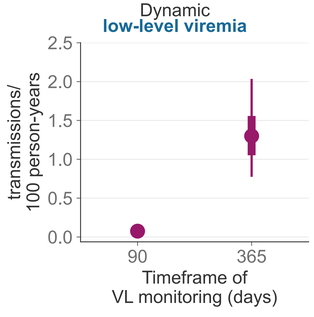
Among people self-reporting ART use, **low-level viremia** is **highly unstable**. 28% with **LLV** rebound within 16-28 months.

Initial (copies/mL)	Follow-up (16-28 months) (copies/mL) <200	200-1,000	>1,000	Total
<200	4,416 (97%)	48 (1%)	88 (2%)	**4,552**
200-1,000	55 (58%)	13 (14%)	27 (28%)	**95**
>1,000	134 (41%)	19 (6%)	174(53%)	**327**
Total	**4,605**	**80**	**289**	**4,974**

We simulated **viral load dynamics** during 12 months of follow-up after initial **LLV**



days



We estimate **1.3 (95% CI 0.8-2.0) transmissions** per 100 person-years from the average individual with **low-level viremia** accounting for **viral rebound**.

This risk could be reduced by 94% [93%-96%] with **90-day monitoring** vs. annually

CONCLUSIONS

Mathematical models can **quantify uncertainty** in biological processes using available evidence, supporting **data-driven policy.** Our results suggest **transmission** from individuals with **low-level viremia** is **reduced** compared to higher VL**, but non-zero.**

ACKNOWLEDGEMENTS

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NIH CDC Rakai Health Sciences Program Center for AIDS Research