Estimation of HIV-1 Transmission During Recent Infection in Switzerland

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Take home messages:



- **We found high fraction of transmission during recent HIV infection in Switzerland**
- **Among chronic phase transmitters, substantial fraction of the transmission events occurred after the transmitter has interrupted ART**
- **"Treatment-as-prevention" needs to be accompanied by early diagnosis, treatment continuity, adherence and retention in care interventions**

Why this study was done?

- The fraction of transmissions which occur during recent HIV infection is essential for the success of Treatment-as-Prevention as an HIV "Endgame" strategy.
- Previous studies have shown discrepant estimations of the fraction of transmissions attributable to recent infection, ranging from less than 10% to 70–80%.
- Unfortunately, high proportion of HIV transmissions during recent infection may compromise the effectiveness of "Treatment-as-prevention" mainly because many recently infected patients are yet unaware of their HIV positive status and thus remain untreated.

What methods were used?

- Seroconversion dates were estimated based on a hierarchical algorithm, which relied on participation in the Zurich Primary Infection Study (ZPHI), CD4 counts, dates of HIV positive/negative tests, clinical symptoms and ambiguous nucleotides in the viral sequence.
- A Phylogenetic tree was constructed with 19,604 Swiss sequences and 90,994 non-Swiss background sequences.
- Swiss transmission pairs were identified using 104 combinations of genetic distance (1%-2.5%) and bootstrap (50%-100%) thresholds, to examine the effect of those criteria.
- Pairs were classified as recent or chronic transmission based on the maximal time interval between estimated seroconversion dates (Figure 1). Transmission during recent infection was defined as transmission during 12 months since seroconversion. Additional analysis was performed for a definition of 6 months since seroconversion.
- Logistic regression with adjustment for clinical and demographic characteristics was used to identify risk factors associated with having transmitted during recent or chronic infection.

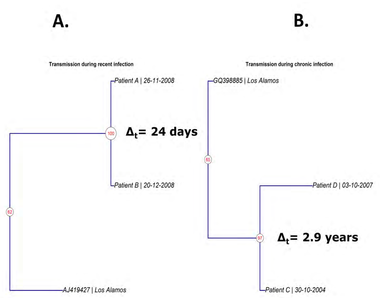


Figure 1. Example of potential transmission events during recent (panel A) and chronic (panel B) HIV infection as represented on the phylogeny. The tips of the tree represent HIV sequences from different patients, SHCS patients are designated by A-D letters. The numbers at the tree nodes represent the bootstrap percent (red) for each node. Δ_t represents the time interval between the seroconversion dates of the pair members. The cophenetic genetic distance within pair A-B and C-D is 0.1% and 0.6%, respectively.

What was found?

- Seroconversion dates could be estimated for 4,079 patients on the phylogeny, which comprised between 64 (distance 1%, bootstrap 100%) to 342 transmission pairs (distance 2.5%, bootstrap 50%), Figure 2.
- 43.1% (range 41%-58%) of the transmissions in our study occurred during the first year of infection while 32% (range 28%-45%) occurred during the first six months six seroconversion.
- Stricter phylogenetic definition of transmission pairs was associated with higher recent transmission fraction, Figure 3. For all four distance thresholds examined the fraction of transmission during recent infections increased sharply for higher bootstrap values (>90%) indicating that high bootstrap thresholds preferentially bias the selection toward recently infected transmission pairs.

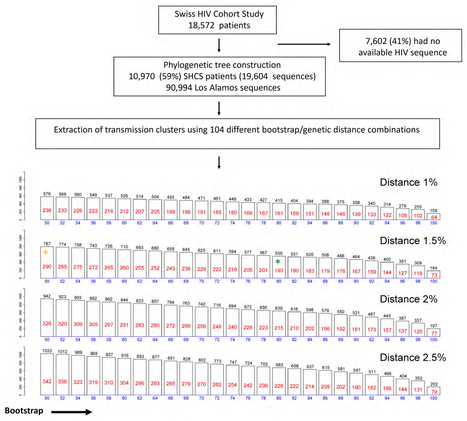


Figure 2. Outline of the study. Each bar represents a different combination of bootstrap/genetic distance thresholds. Black numbers on top of the bars represent the number of transmission pairs which correspond to the specific combination. Red numbers represent the number of transmission pairs with available seroconversion dates for both members. Blue numbers at the x-axis represent ascending bootstrap thresholds. The green star designates the dataset which was used for the main logistic regression analysis and the yellow star the dataset which was used for the sensitivity analyses.

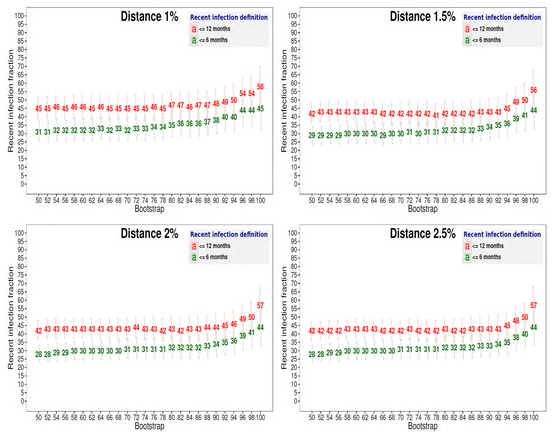


Figure 3. SHCS based estimation of transmission during recent HIV infection. Red numbers represent the fraction of transmissions during recent infection, according to a definition of recent infection as twelve months since seroconversion. Green numbers represent recent transmission fraction for a definition of six months since seroconversion. Vertical lines represent 95% confidence intervals for proportion.

- Chronic phase viral load area under the curve (AUC) adjusted-OR 3.76 (95% C.I 1.74-8.09) and time-to-ART-start adjusted-OR 1.37/year (95% C.I 1.07-1.76) were associated with chronic-phase transmission as opposed to recent transmission, Table 1.
- For 17/112 (15%) chronic phase transmitters: (i) The date of ART initiation preceded the infection time-window of the recipient (Figure 4) (ii) There was a documented treatment interruption during the infection window (iii) There was a viral load test >400 copies/mL. Hence these individuals most likely transmitted HIV during treatment interruption.

	Crude OR (95% C.I)	P-value	Adjusted OR (95% C.I)	P-value
Age at infection	0.96 (0.93-0.99)	0.016	0.97 (0.92-1.01)	0.115
Sex				
Male (Ref.)				
Female	1.19 (0.52-2.71)	0.678	3.53 (0.69-18.01)	0.129
Risk group				
Men who have sex with men (Ref.)				
Heterosexuals	1.16 (0.57-2.37)	0.687	0.51 (0.11-2.46)	0.404
Injection drug users	1.78 (0.63-4.99)	0.274	0.46 (0.05-4.21)	0.494
Subtype				
Non-B (Ref.)				
B	1.54 (0.75-3.18)	0.244	1.31 (0.42-4.06)	0.641
√CD4 counts [a]	1.03 (0.98-1.08)	0.21	0.95 (0.88-1.02)	0.13
Transmission year	0.98 (0.92-1.05)	0.537	1.12 (0.99-1.26)	0.065
Time to ART (years)	1.61 (1.31-1.97)	<0.0001	1.37 (1.07-1.76)	0.013
Chronic RNA VL AUC	3.26 (1.97-5.39)	<0.0001	3.76 (1.74-8.09)	0.001

[a] Earliest treatment naïve measurement after enrollment

Table 1. Logistic regression analysis for being recent (<=1 year since seroconversion, coded as 0) versus chronic (>1 year since seroconversion, coded as 1) phylogenetically linked HIV transmitter. N=150 transmitters (complete cases), Bootstrap 80%, genetic distance 1.5%. Abbreviations: C.I, confidence interval; OR, odds ratio; ART, antiretroviral therapy; VL AUC, viral load area under the curve.

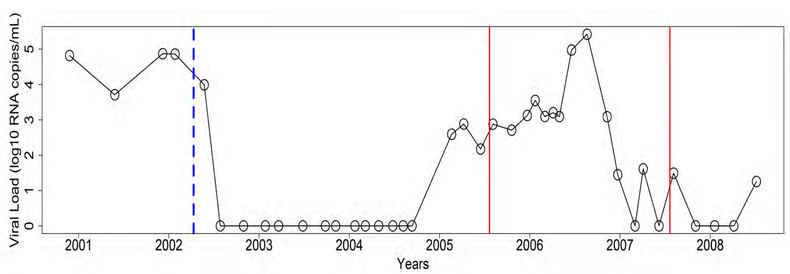


Figure 4. Example of potential post-ART transmission in which the antiretroviral therapy (dashed blue line) was started before the lower bond of the recipient`s infection window (red vertical lines, last negative HIV test date -90 days and the first positive test date), hence in this scenario there is a high degree of certainty that the transmission occurred after ART was initiated by the transmitter. The black lines depict the viral load measurements of a hypothetical transmitter.