Phenotypic Characterization of Transmitted/Founder Virus in HIV-1 Transmission Pairs

Poster # 218

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Background

In 60-90% of mucosal HIV-1 transmissions a single transmitted/founder (T/F) virus from a genetically diverse virus population of the transmitter infects the recipient. Whether HIV-1 transmission is a stochastic process or the T/F viruses have beneficial features facilitating transmission and infection is controversially discussed. Here, we compared the phenotypes of viruses isolated from matched transmission pairs in order to resolve if properties exist that favor transmission.

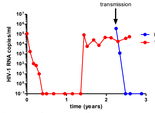
Methods

Identification of transmission pairs:

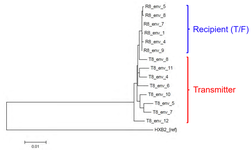
Patients enrolled in the Swiss HIV Cohort Study (SHCS) and the Zurich Primary HIV-1 Infection Study (ZPHI) were screened by:

1) Phylogenetic analyses of *pol* sequences from ~25'000 genotypic resistance tests from ~11'500 patients (genetic distance <1.5% between potential transmitter and recipient; at least one individual with primary HIV-1 infection)

2) Longitudinal clinical data of identified transmission pairs (viral load, therapy, risk group, gender, geography)



3) Phylogenetic analyses of *env* sequences generated by single-genome amplification of samples closest to the time point of transmission of identified transmission pairs



→ 9 transmission pairs identified

→ Primary virus isolates and *env*-pseudoviruses of samples closest to the time point of transmission were generated and characterized in respect to:

Virus isolates:
- **Replication capacity in PBMCs and monocyte-derived macrophages (MDMs)**
- **IFN-α sensitivity in PBMCs**

***env*-pseudoviruses:**
- **Sensitivity to entry inhibitors and neutralizing antibodies**
- **Entry kinetics**
- **Neutralisation by plasma of transmitter**

Results

Patient and virus characteristics of 9 transmission pairs

Transmitter	Recipient	Transmission mode[a]	Virus tropism		Interval (days)[b]		Viral load[c]		CD4 count[d]	
			Transmitter	Recipient	Transmitter	Recipient	Transmitter	Recipient	Transmitter	Recipient
T1	R1	MSM	R5	R5	95	32	153000	2325000	287	273
T2	R2	HET	R5	R5	49	42	18300	412857	416	625
T3	R3	MSM	R5X4	R5	215	129	34600	14400	115	656
T4	R4	HET	R5	R5	63	49	257532	428000	623	170
T5	R5	HET	R5	R5	57	43	9813	66000	681	346
T6	R6	MSM	R5	R5	33	61	2830	5970000	595	362
T7	R7	MSM	R5	R5	3	56	2260	56300	664	564
T8	R8	MSM	R5	R5	-20	26	43200	373000	422	430
T9	R9	MSM	R5	R5	72	71	1550	27800	516	429

a) MSM: men who have sex with men; HET: heterosexual. b) Interval from the estimated date of infection of recipient to the day of sample collection. c) HIV-1 RNA copies/ml of plasma.
d) CD4+ T cells/µl of blood.

No significant difference in replication capacity in PBMCs and MDMs between transmitter and recipient (T/F) viruses

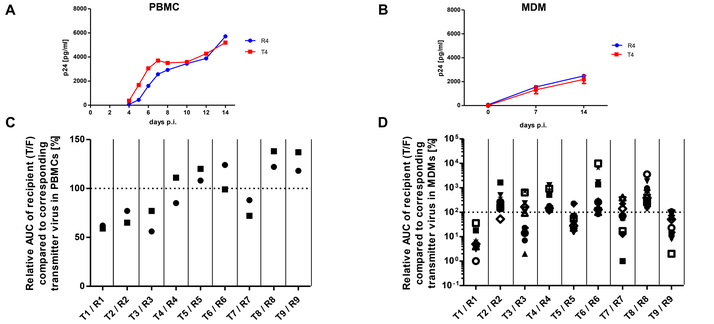


Figure 1. Replication capacity (RC) of transmitter and recipient (T/F) virus isolates in PBMCs and MDMs. (A) and (B) Representative growth curves of transmitter and recipient (T/F) virus isolates in PBMCs and MDMs. **(C) and (D)** Replication capacity (measured as area under the curve (AUC), day 4-14 for PBMCs and day 1-14 for MDMs) of recipient (T/F) viruses expressed relative to its corresponding transmitter isolate. Shown are independent experiments with cells from 2x3 (PBMC pools) and 12 (MDMs) different donors (indicated by different symbols). Growth capacity between transmitter and recipient (T/F) viruses was not statistically different (Wilcoxon matched-pairs signed rank test).

No indication of higher IFN-α resistance of recipient (T/F) viruses in transmission pairs

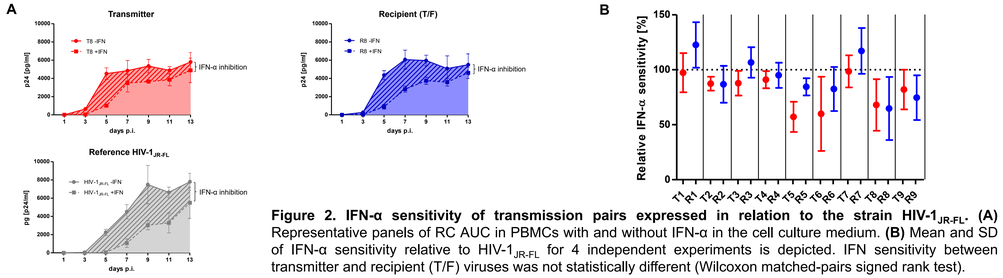


Figure 2. IFN-α sensitivity of transmission pairs expressed in relation to the strain HIV-1_{JR-FL}. (A) Representative panels of RC AUC in PBMCs with and without IFN-α in the cell culture medium. **(B)** Mean and SD of IFN-α sensitivity relative to HIV-1_{JR-FL} for 4 independent experiments is depicted. IFN sensitivity between transmitter and recipient (T/F) viruses was not statistically different (Wilcoxon matched-pairs signed rank test).

Comparable sensitivity to entry inhibitors / nAbs of transmitter and recipient (T/F) *env*-pseudoviruses

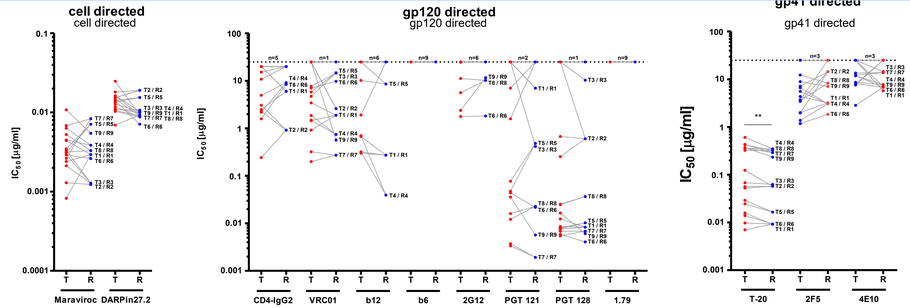


Figure 3. Sensitivity of *env*-pseudoviruses to entry inhibition in TZM-bl assay. Sensitivity of transmitter and recipient (T/F) pairs differed but recipients (T/F) proved not to have a significantly lower or higher sensitivity to any inhibitor (Wilcoxon matched-pairs signed rank test) with the exception of T-20 to which recipient (T/F) viruses were slightly more sensitive (p=0.0039). Depending on the diversity of *env*, between 1 to 3 *env*-pseudoviruses were generated per transmitter.

Transmitter and recipient (T/F) *env*-pseudoviruses show comparable entry kinetics

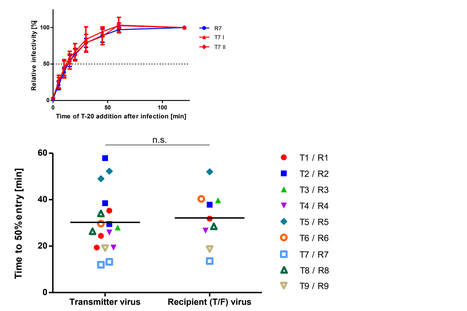


Figure 4. Entry kinetics of transmitter and recipient (T/F) *env*-pseudoviruses. (A) Entry kinetics for one representative transmission pair. **(B)** Time to attain 50% entry into TZM-bl cells. Data are means from three independent experiments. No significant difference was observed (Wilcoxon matched-pairs signed rank test).

Transmitter and recipient (T/F) viruses are resistant to plasma nAbs of transmitter circulating at transmission

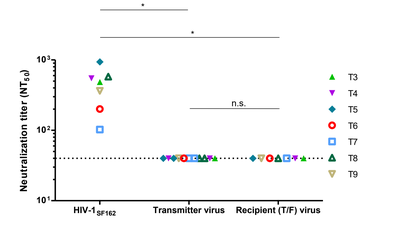


Figure 5. Neutralization assay of transmitters' plasma derived from closest time point to transmission against transmitter and recipient (T/F) *env*-pseudoviruses. Transmitter plasma was tested for neutralization against autologous, recipient (T/F) and HIV-1_{SF162} control virus. Statistical significance was tested with a Wilcoxon matched-pairs signed rank test. Note that 2 transmission pairs were not included as plasma from the time point of transmission was not available.

Conclusion

- **According to the investigated parameters no significant phenotypic pattern could be attributed to T/F viruses**
- **Recipient (T/F) viruses are neutralization resistant to plasma from transmitters from time point of transmission**
- **Our data strongly suggest that the transmitted virus shares the main phenotypic properties of the dominant strains circulating in the transmitter**

Acknowledgements

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