Reconciling the Founder Variant Multiplicity of HIV-1 with the rate of CD4+ T Cell Decline

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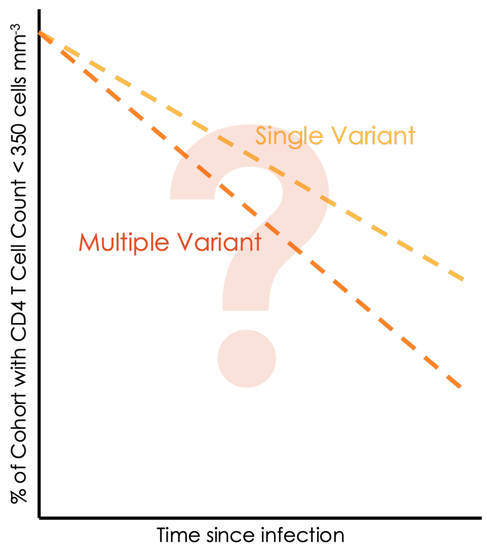
Introduction

- Without effective therapy, almost all people living with HIV will progress to AIDS. The rate of disease progression is determined by characteristics of the infecting virus such as replicative capacity or immunogenicity; and characteristics of the person such as age and Human Leukocyte Antigen phenotype.[1–4]
- The role of HIV-1 transmission on disease progression, however, is less well characterised.
- 75% of HIV-1 infections are initiated by a single genetic variant. In the remaining quarter of transmissions, the genetic bottleneck is mitigated, and infections are initiated by multiple variants.[5,6]
- **These infections initiated by multiple variants have previously been associated with higher viral load and a faster CD4+ T-cell decline…**[7-11]
- … but a mechanistic understanding that underpins this effect remains elusive



Aims

- To consolidate the existing observational evidence for an association between infections initiated by multiple variants and faster CD4+ decline.
- To construct a multi-model framework to reconcile the founder multiplicity of HIV-1 with CD4+ T-Cell decline, leveraging statistical and mathematical models of three well-characterised empirical relationships

Observational Evidence

Paper	N	Riskgroup	P (MV)	Viral Load		CD4+ T Cell	
Sagar 2003 [7]	156	HSX (MF)	0.57	VL at diagnosis, up to 96 months	*	% below 350 cells mm^{-3}	*
Abrahams 2009 [8]	69	HSX (MF)	0.22	SPVL (12 months)	ns	CD4+ (12 months)	ns
Janes 2015 [9]	100	HSX	0.32	VL at diagnosis, 3, 12, 24 months	**	CD4+ (12 months)	*
	63	MSM	0.25		***		ns
Chaillon 2016 [10]	26	MSM	0.53	VL at diagnosis	*	-	-
Macharia 2020 [11]	38	MSM	0.39	SPVL	ns	% below 350 cells mm^{-3}	***

Table 1: Cohort characteristics and key results from studies that have analysed the association between CD4+ T cell decline and multiple variant HIV infections. ns $P > 0.05$; * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$. HSX = heterosexual; MSM = men-who-have-sex-with-men

- We identified **six cohort studies** that have characterised associations between founder variant multiplicity, SpVL and CD4+ decline, of which:
  - **Four** cohort studies found that infection initiated by multiple variants was associated with higher SpVL.
  - **Two** further demonstrated link to lower CD4+ counts or faster CD4+ T Cell decline.
- Inferring a general conclusion from these data is challenging due to two main sources of heterogeneity:
  1. The studies analysed different measures and implemented different statistical methods.
  2. Uncertainty also arises from the proportion of multiple variant infections within a cohort:
     a. The probability of multiple variant infection varies significantly across risk groups, which may confound the association with CD4 decline.
     b. Early studies may have overestimated the proportion of infections initiated by multiple variants due to methodological limitations

References

1. Mellors et al., Science 1996; 2. Bartha et al., Trends in Immunology 2008; 3. Rosenberg PS et al., AIDS 1994; 4. Fellay et al., PLoS genetics 2009; 5. Keele et al., PNAS 2008; 6. Baxter et al., The Lancet Microbe 2023; 7. Sagar et al., J Virology 2003; 8. Abrahams et al., Science Translational Medicine 2019; 9. Janes et al., Nat Med 2015; 10. Chaillon et al., Virus Evolution 2016; 11. Macharia et al., PLoS pathogens 2020; 12. Hollingsworth et al., PLoS pathogens 2010; 13. Regoes et al., PLoS Biology 2014; 14. Thompson et al., Virus Evolution 2019.

Model Framework

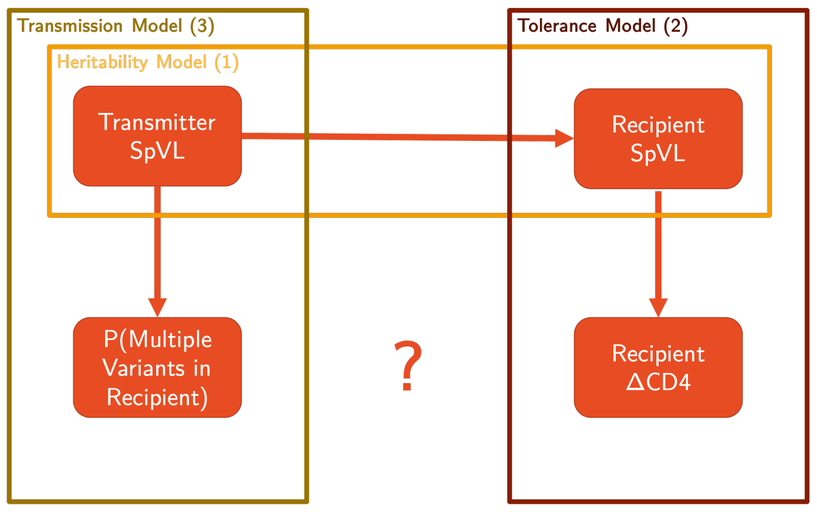


Fig.1 Directed graph of the model framework

- Our model framework leverages three well characterised relationships surrounding HIV-1 transmission and disease progression:
  1. **Heritability:** The proportion of variation in log10 SpVL, V, explained by genetic variation of the transmitted virus for individual, i, of pair, j:[12]
  $$V_{ij} = \overline{V_i} + \text{sex}_{ij} + \text{age}_{ij} + \text{riskgroup}_{ij}$$
  2. **Tolerance:** The rate of CD4+ T cell decline explained by SpVL and host characteristics:[13]
  $$\Delta CD4_{ij} = (sex_{ij} + age_{ij}) \times V_{ij}^2$$
  3. **Transmission:** A probabilistic model that predicts the probability of multiple variant infection for a given transmitter SpVL, v, averaged over the course of infection: [14]
  $$P(n\ particles) = f\binom{v}{n} p^n (1-p)^{v-n}$$
  $$P(N\ variants) = \sum_{n=N}^{v} \frac{P(N\ variants | n\ particles)}{P(n\ particles)}$$
  To reconcile the low acquisition probability with the relatively high probability of multiple variants, we assume transmission only occurs in a subset, 'f', of exposures. Each viral particle has probability, p, of transmission.
- We simulate an idealised transmitter population and combine model predictions to infer an association between the the probability of multiple variants and the rate of CD4 T cell decline.

Results

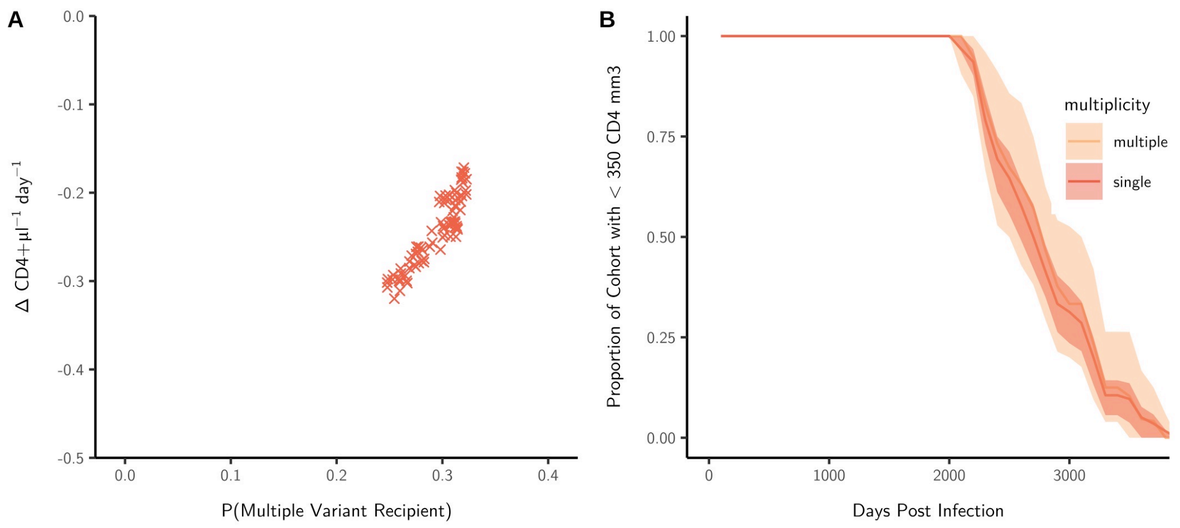


Figure 2: a) the daily rate of CD4 decline slows as the probability that a recipient's infection was initiated by multiple variants increases b) simulated survival curves highlight the substantial variation in the population-level outcome of multiple variant infection.

- When accounting for empirical relationships, in particular the contribution of the transmitted genotype to the recipient SpVL, we expect a **higher probability that infection is initiated by multiple variants to correlate with a slower rate of CD4 T cell decline** (Fig 2a).
- Assuming a fixed initial CD4 count, bootstrapped survival curves reveal **significant variation in the trajectories of multiple variant infection relative to single variant infection** (Fig 2b).

Conclusions

- Accounting for empirical relationships, we would expect **the rate of CD4 decline to decrease as P(Multiple Variants) increases.**
- Our model does not consider non-SpVL mediated effects, raising the possibility of a load-independent mechanism.
- Our framework reveals **substantial residual heterogeneity** associated with the disease progression of multiple variant infection.