HIV Transmission – Lessons from Heterosexual Couples in Africa

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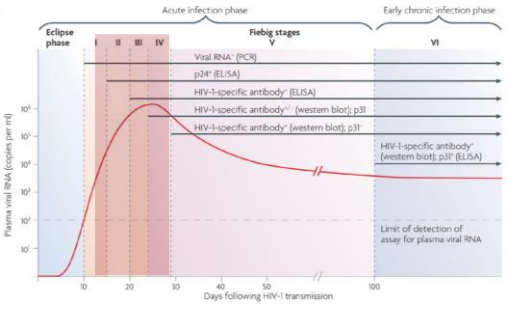
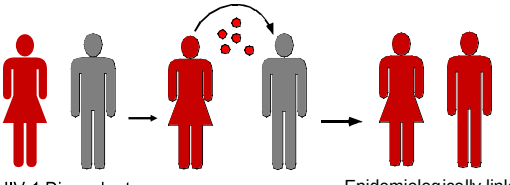
HIV-1 transmission risks vary by route of infection

- Heterosexual – vaginal intercourse
  - Male to Female – 1 in 200 - 1 in 2000
  - Female to Male – 1 in 700 – 1 in 3000
- MSM
  - Intrarectal – 1 in 20 – 1 in 300
- Mother to Child
  - Intra-partum/breast milk – 1 in 5 -1 in 10
  - Intra-uterine – 1 in 10 – 1 in 20
- IDU
  - Intravenous – 95 in 100 - 1 in 150

Studies of transmission in humans are generally limited to an early viremic phase



HIV-1 transmission in discordant couples: allows analysis of both 'donor' and 'recipient' viruses



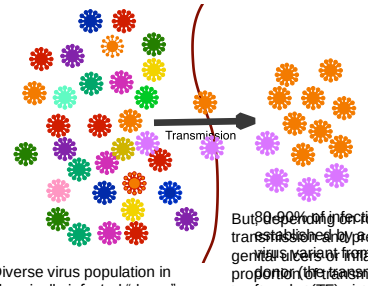
HIV-1 Discordant Couple

Despite a >2/3 reduction in transmission through counseling and condom provision

Epidemiologically linked transmission pair

75-80% of transmissions

Transmission of HIV-1 is associated with a genetic bottleneck



Diverse virus population in chronically infected "donor"

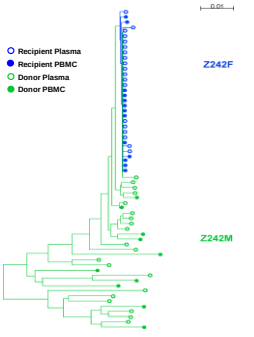
But depending on route of transmission and prevalence of genital ulcers of inflammation, a proportion of transmissions involve multiple variants from the same partner

99.99% of infections are established by a single virus variant from the donor (the transmitted founder (TF) virus)

Wolinsky 1992; Wolfs 1992; Abu-Raddad 2009; Derdeyn 2004; Keele 2008

Phylogenetic Analysis of the Transmission Bottleneck

- In this linked transmission pair the recipient virus is homogeneous and originates from a single branch of the donor phylogenetic tree - thus a single genetic variant has established infection. (Derdeyn 2004, Haaland 2009).
- Employing modeling and phylogenetic analysis of the single genome amplified sequences of viruses isolated very early from >100 acutely infected individuals to impute the TF virus, showed that ~80% of infections were the result of a single virus variant. (Keele 2008).

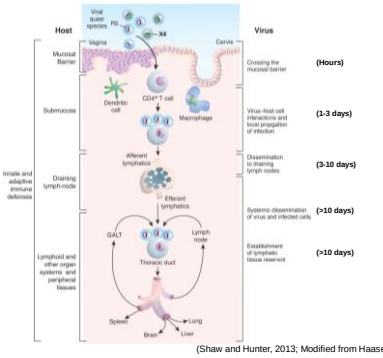


HIV-1 transmission has both stochastic and selective components

The role of chance:

- The transmitted variant must:
  - be located within the genital tract
  - interact with the genital or rectal mucosa
  - cross the epithelial barrier and infect a susceptible target cell
  - have a sufficient number of secondary target cells for infection to spread and establish a localized and then systemic infection

Current concept of HIV-1 infection of the female genital tract

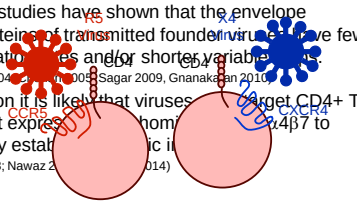


(Shaw and Hunter, 2013; Modified from Haase, 2010)

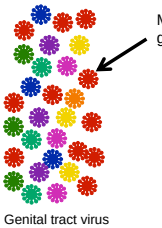
HIV-1 transmission has both stochastic and selective components

A role for selection:

- A majority (>95%) of infections are initiated by viruses that use CCR5 as a co-receptor
  (Connor 1997; Scarlatti 1997; Long 2002; Keele 2008)
- Several studies have shown that the envelope glycoproteins of transmitted founder viruses have fewer glycosylation sites and/or shorter variable loops
  (Derdeyn 2004; [illegible] 2005; Sagar 2009, Gnanakaran 2010)
- In addition it is likely that viruses [illegible] target CD4+ T cells that express [illegible] homing receptor α4β7 to efficiently establish [illegible] infection
  (Arthos 2008; Nawaz 2011; [illegible] 2014)



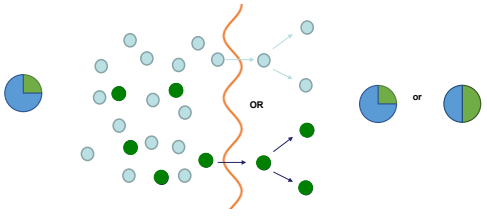
Evidence for selection during transmission



- Although in most individuals the genetic makeup of the genital tract HIV-1 is reflective of that in the blood, enrichment of genital tract-specific populations is observed.
- Despite the presence of these enriched genital tract populations of virus the transmitted founder virus represents a minor variant from the genital and blood virus populations.

Anderson 2010; Boeras 2011

Probabilistic model for transmission

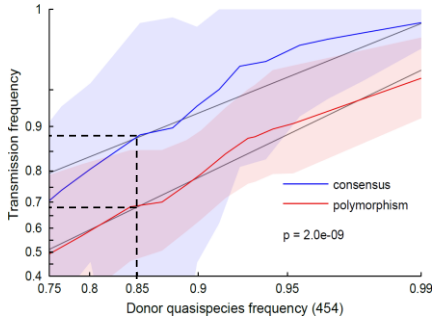


Given two variants, with some relative frequency, is the transmission probability a function only of relative frequency or also of relative transmissibility?

Analysis for selection during transmission

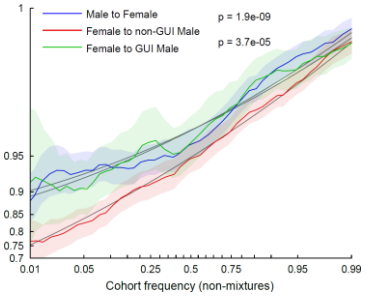
- Determine the most common (consensus) amino acids at each position of Gag, Pol, and Nef proteins for viruses from a Zambian cohort of 375 persons.
- Perform 454 whole genome sequencing of 5 transmission pairs.
- Analyze the frequency of each amino acid at each position in donor and recipient viruses.
- Calculate transmission frequency of each consensus amino acid and each non-consensus amino acid (polymorphism).

Non-consensus amino acids are selected against during transmission

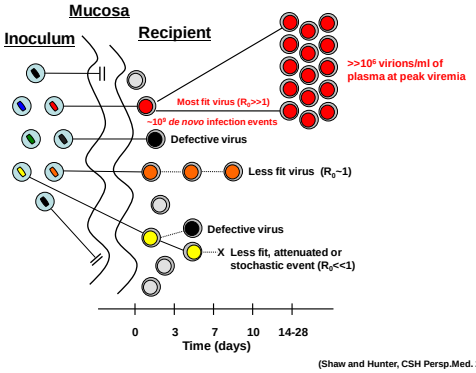


Impact of gender and genital ulcers/inflammation on selection bias

- Stronger selection bias during transmission to men
- Men are infected with viruses with fewer non-consensus mutations - more likely to be fitter viruses
- BUT men with genital ulcers or inflammation have a lower barrier to infection and a selection bias similar to women

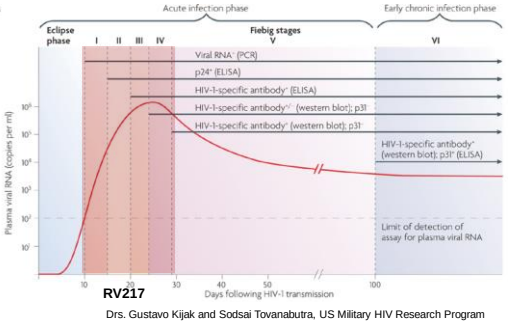


HIV-1 transmission involves competition between viruses



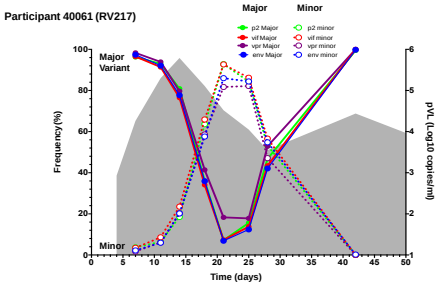
(Shaw and Hunter, CSH Persp.Med. 2012)

Viruses during the earliest stages of infection reveal competition during dual infections



Drs. Gustavo Kijak and Sodsai Tovanabutra, US Military HIV Research Program

Viral dynamics early in multiple variant infections



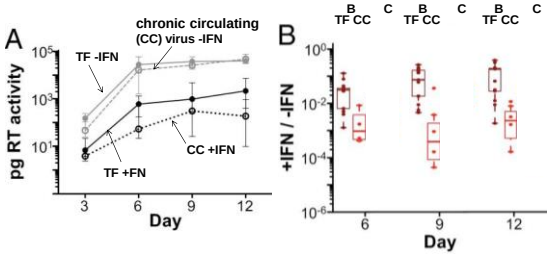
Drs. Gustavo Kijak and Sodsai Tovanabutra, US Military HIV Research Program – in preparation

Can we translate this evidence for selection into identifiable biological traits?

Such traits could provide clues for targeted interventions.

- Recent studies (Parrish 2013) comparing transmitted founder virus infectious molecular clones (IMCs) to IMCs from chronically infected individuals, showed that for subtype B viruses:
  - TF viruses replicated better (2x) in CD4+ T cells
  - TF viruses were more resistant to the antiviral effects of IFNα

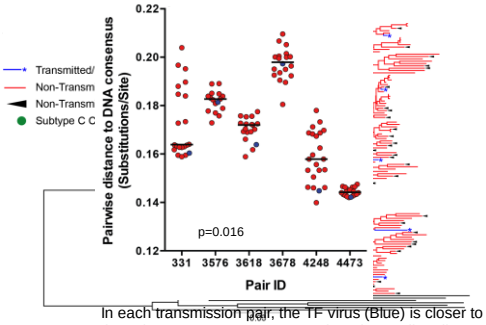
Interferon resistance of transmitted founder (TF) viruses



Impact of IFNα was not significant for subtype C viruses, primarily because the chronic circulating (CC) viruses were more resistant

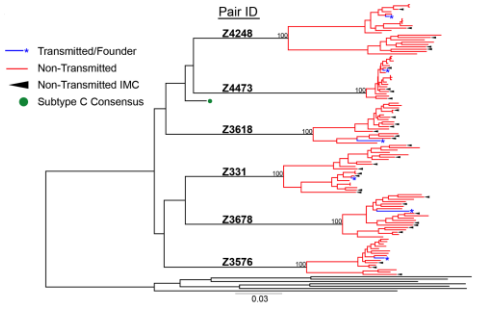
Parrish 2013; Fenton May 2013

Analysis of 6 subtype C transmission pairs



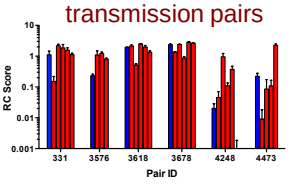
In each transmission pair, the TF virus (Blue) is closer to the cohort consensus sequence than the median distance for NT viruses (Red) confirming the selection bias observed with Gag, Pol and Nef sequences.

IMC generation from 6 subtype C transmission pairs



Deymier et al. Virology 2014 - Particle infectivity of HIV-1 full-length genome infectious molecular clones in a subtype C heterosexual transmission pair following high fidelity amplification and unbiased cloning

Replication and IFNα resistance in subtype C transmission pairs



Transmitted founder (IMC-derived) viruses (Blue) do not exhibit preferential replication versus NT viruses (Red) in activated CD4 cells *in vitro*

Subtype C transmitted founder viruses (Blue) do not consistently exhibit higher resistance to interferon than NT viruses (Red)

HIV Transmission

- Is characterized by a severe genetic bottleneck that can be modulated by genital inflammation and ulceration
- Involves a selection for viruses from the transmitting partner quasispecies with greater transmission fitness
- Selects for less glycosylated, CCR5 using viruses, which likely take advantage of the α4β7 homing marker to target infected cells to the gut lymphoid tissue
- In some cases selects for viruses with higher resistance to interferon, but this is not apparent in subtype C transmission pairs
- May be better modeled in future studies using tissue explants and humanized mice. An expanding panel of authentic viruses from transmission pairs and acute infections are now available to explore these possibilities

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