HIV Transmission – Lessons from Heterosexual Couples in Africa

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

Transmission of HIV-1 is associated with a genetic bottleneck

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

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

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; Derdeyn 2008; Sagar 2009; Gnanakaran 2010)
- In addition, it is likely that viruses that use CCR5 as a co-receptor infect CD4+ T cells that express the gut homing marker α4β7 to efficiently establish systemic infection (Arthos 2008; Nawaz 2011; Siddappa 2014)

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

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

Viral dynamics early in multiple variant infections

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
Identification of FTM and MTF

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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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 to interferon than NT viruses (Red). Confirming the selection bias observed with Gag, Pol and Nef sequences.

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.

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).

IMC generation from 6 subtype C transmission pairs

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.

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.