

A New Look At the Transmitted Virus and Its Source In the Genital Tract

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QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.



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Premise:

An analysis of viral *env* sequences can be informative concerning the transmission event by revealing features of the selective pressures at work at the time of the genetic bottleneck and during the early establishment of a productive infection.

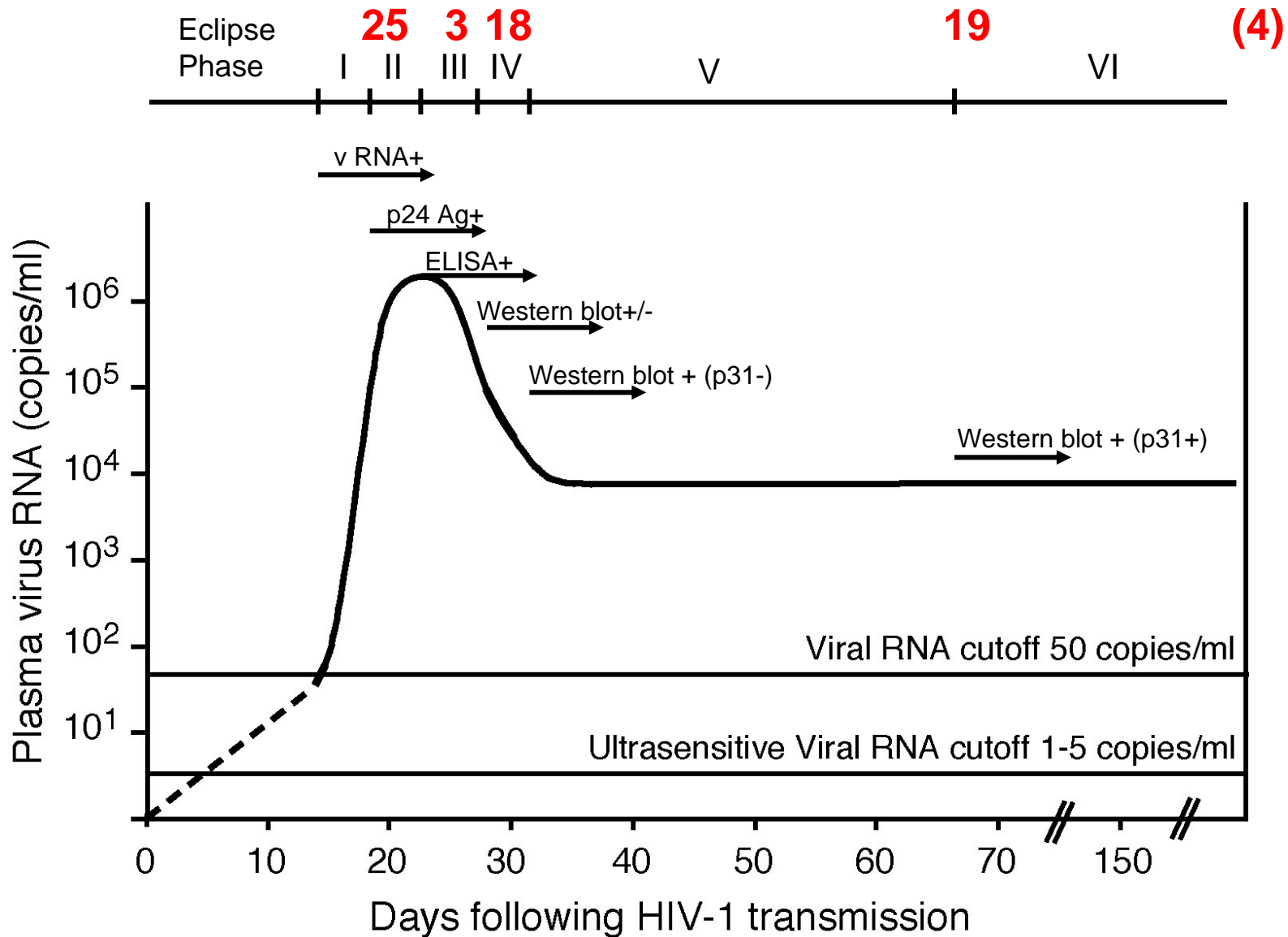
Specific Questions

1. What Are the Characteristics of the *env* Gene In People Acutely Infected With Subtype C HIV-1?
2. Can We Really Identify the Transmitted Virus?
3. What Are the Characteristics of the HIV-1 Population Found In Semen?
4. Why Are So Many Viruses Transmitted?

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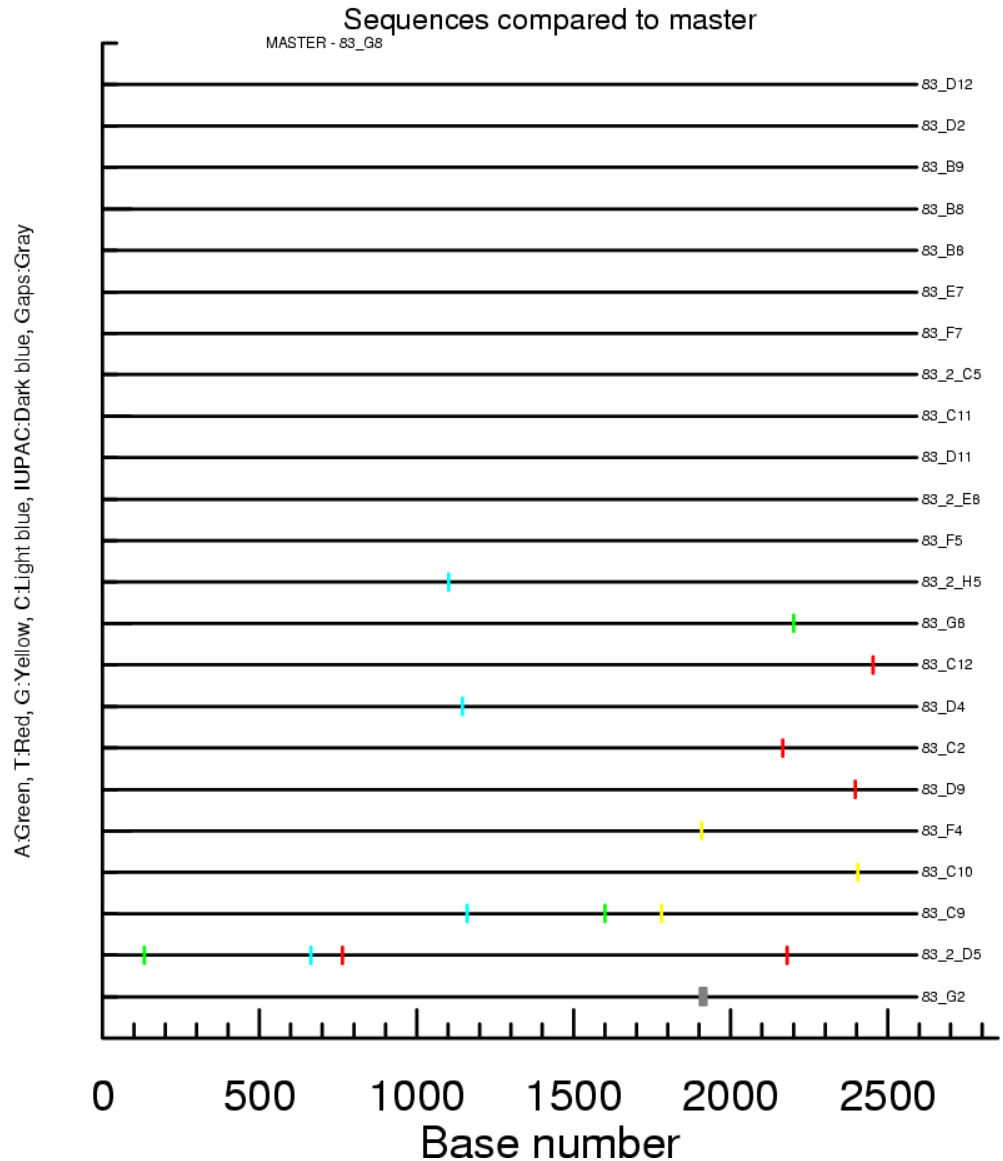
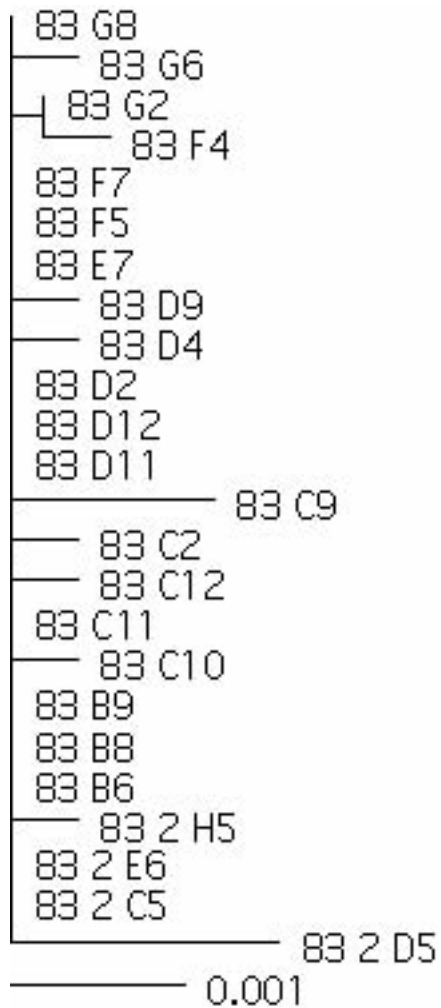
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Laboratory Staging of Primary HIV-1 Infection

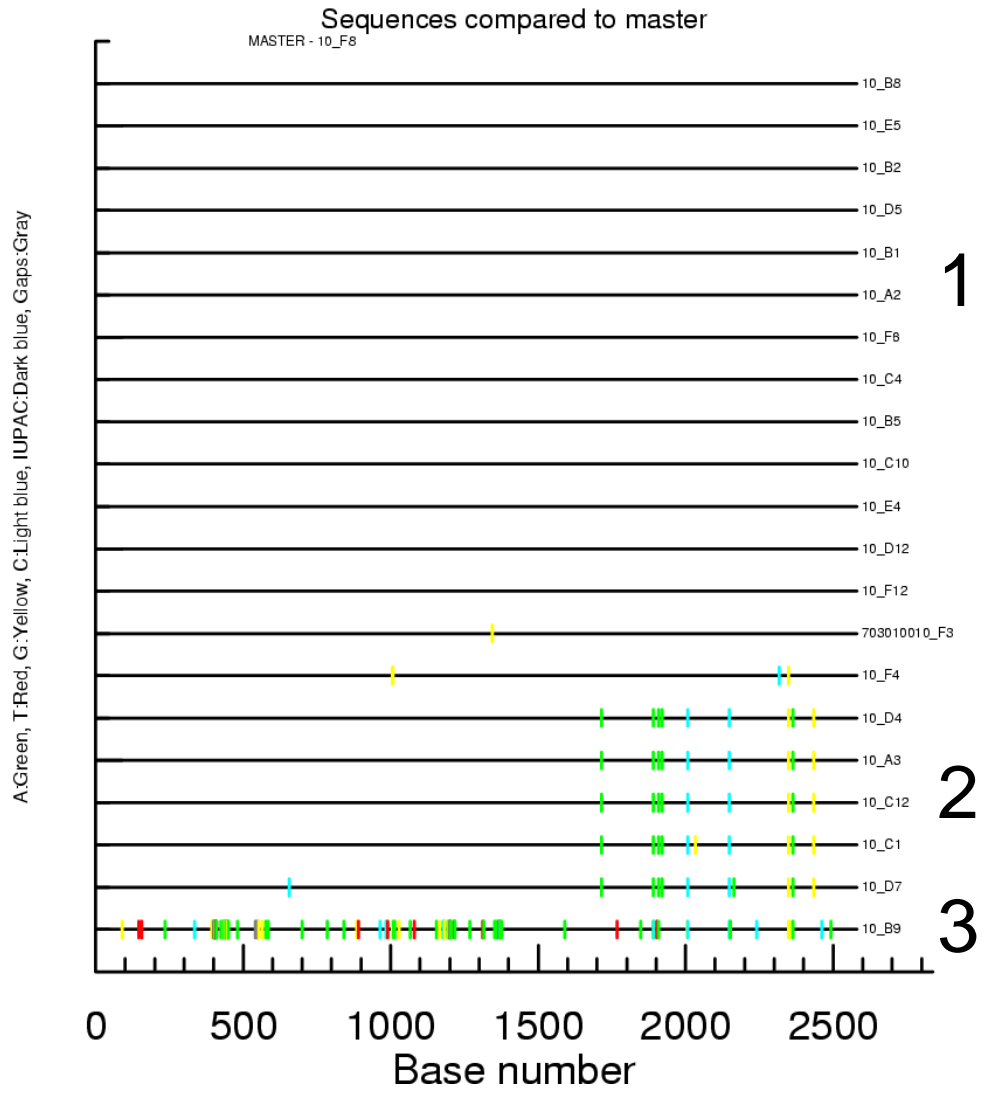
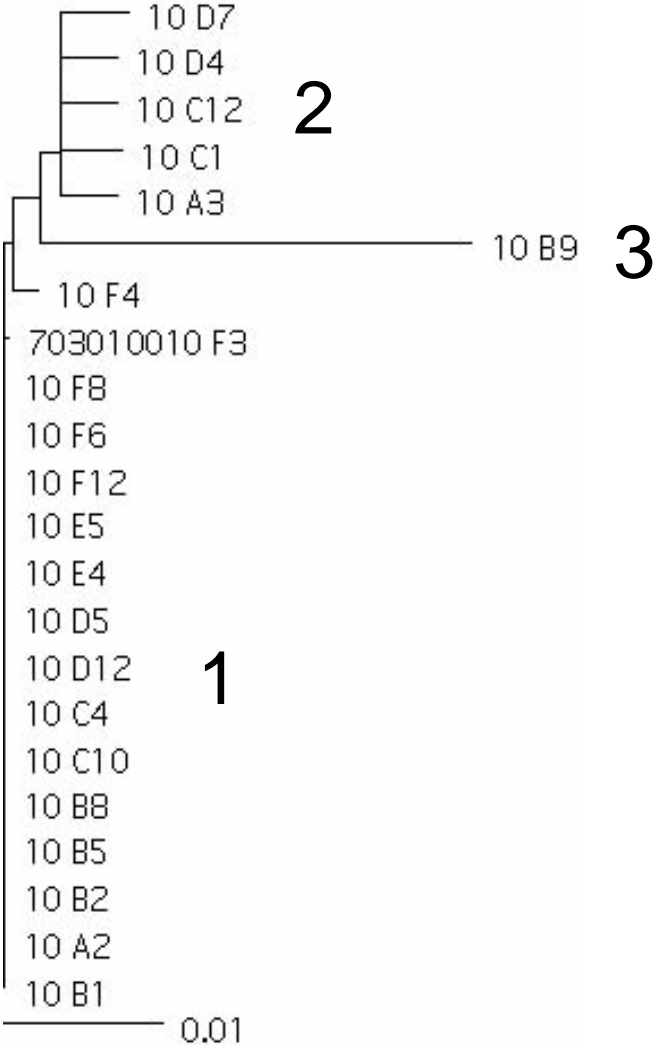


(Fiebig, AIDS 2003) **Plus Chronic Controls**

704010083--Infection With A Single Variant



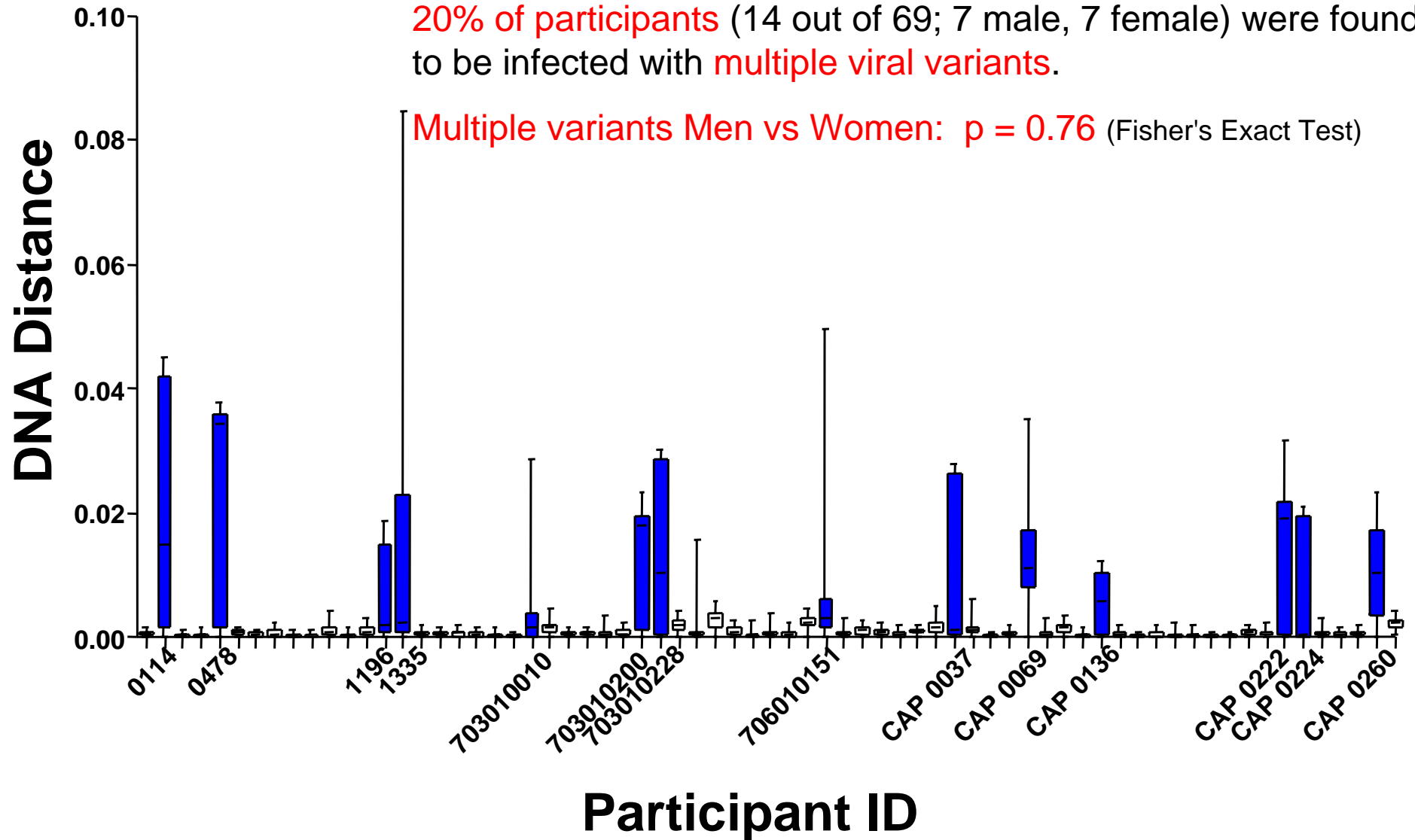
703010010--Infection With 3 Variants



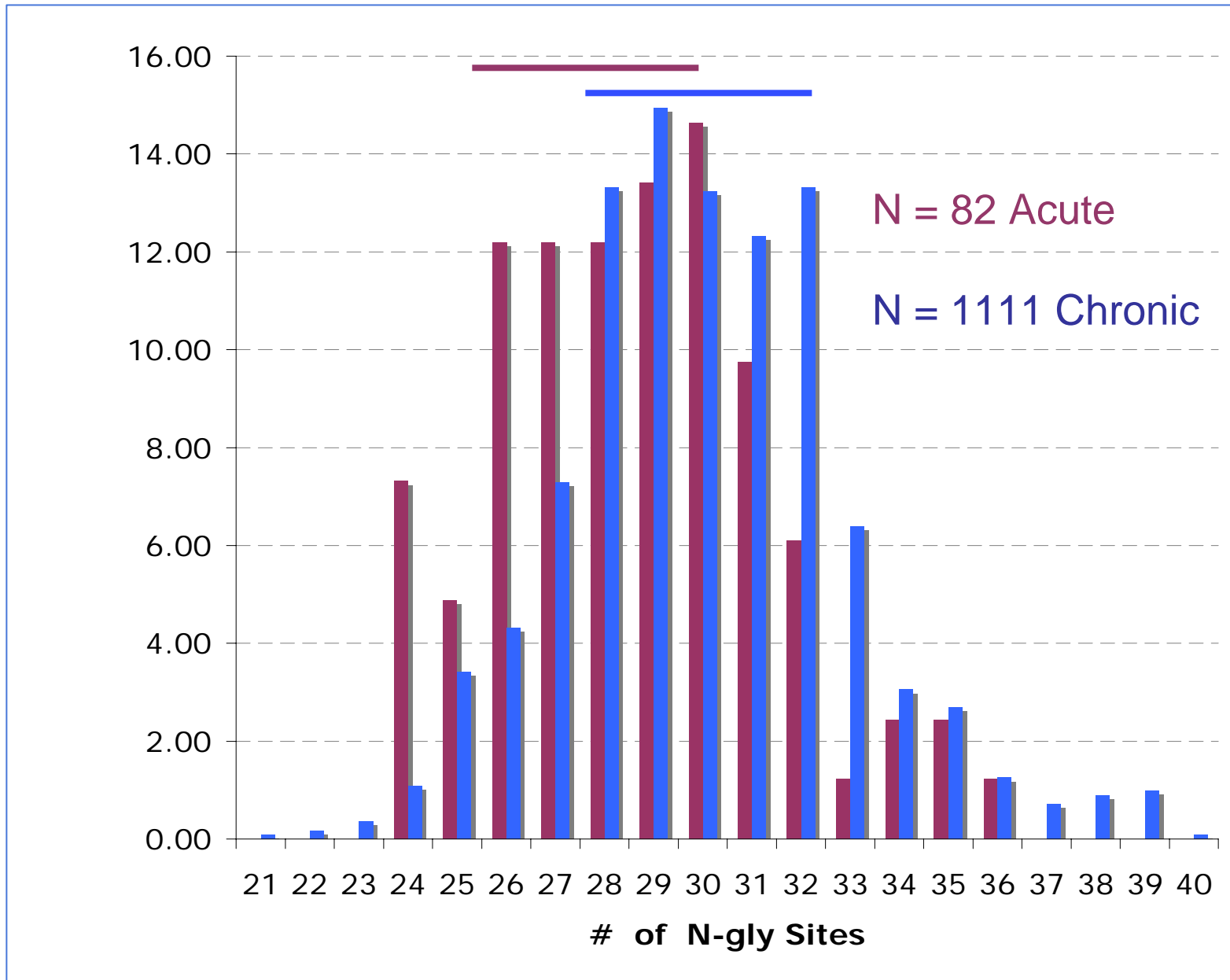
Complexity of the Subtype C Transmitted Virus

20% of participants (14 out of 69; 7 male, 7 female) were found to be infected with multiple viral variants.

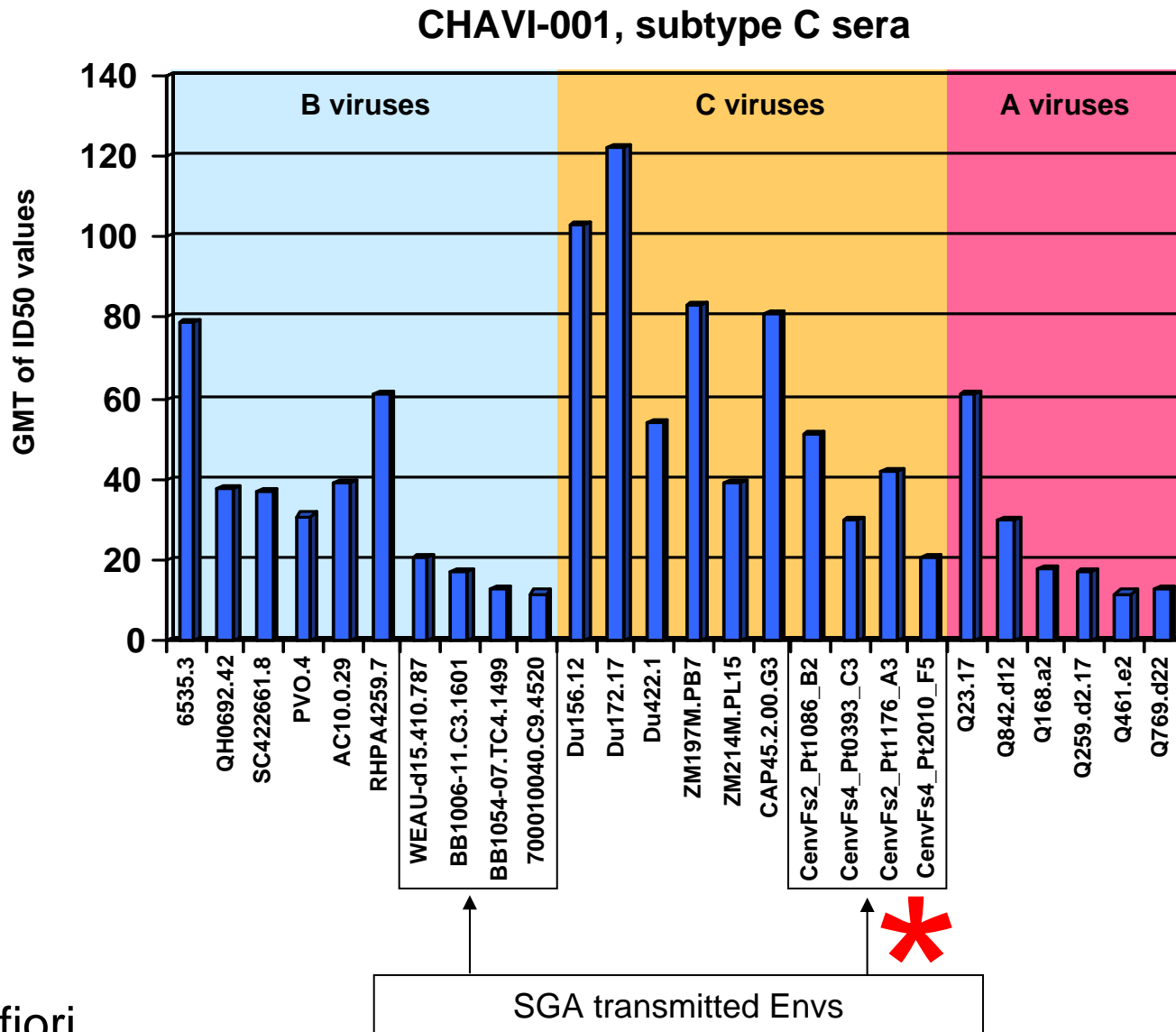
Multiple variants Men vs Women: $p = 0.76$ (Fisher's Exact Test)



Glycosylation Sites Are Under-Represented In Acute Subtype C



First Look: Transmitted Subtype C Env Proteins Are Not More Sensitive To Neutralization



What Are the Characteristics of the Transmitted *env* Gene In People Acutely Infected With Subtype C HIV-1?

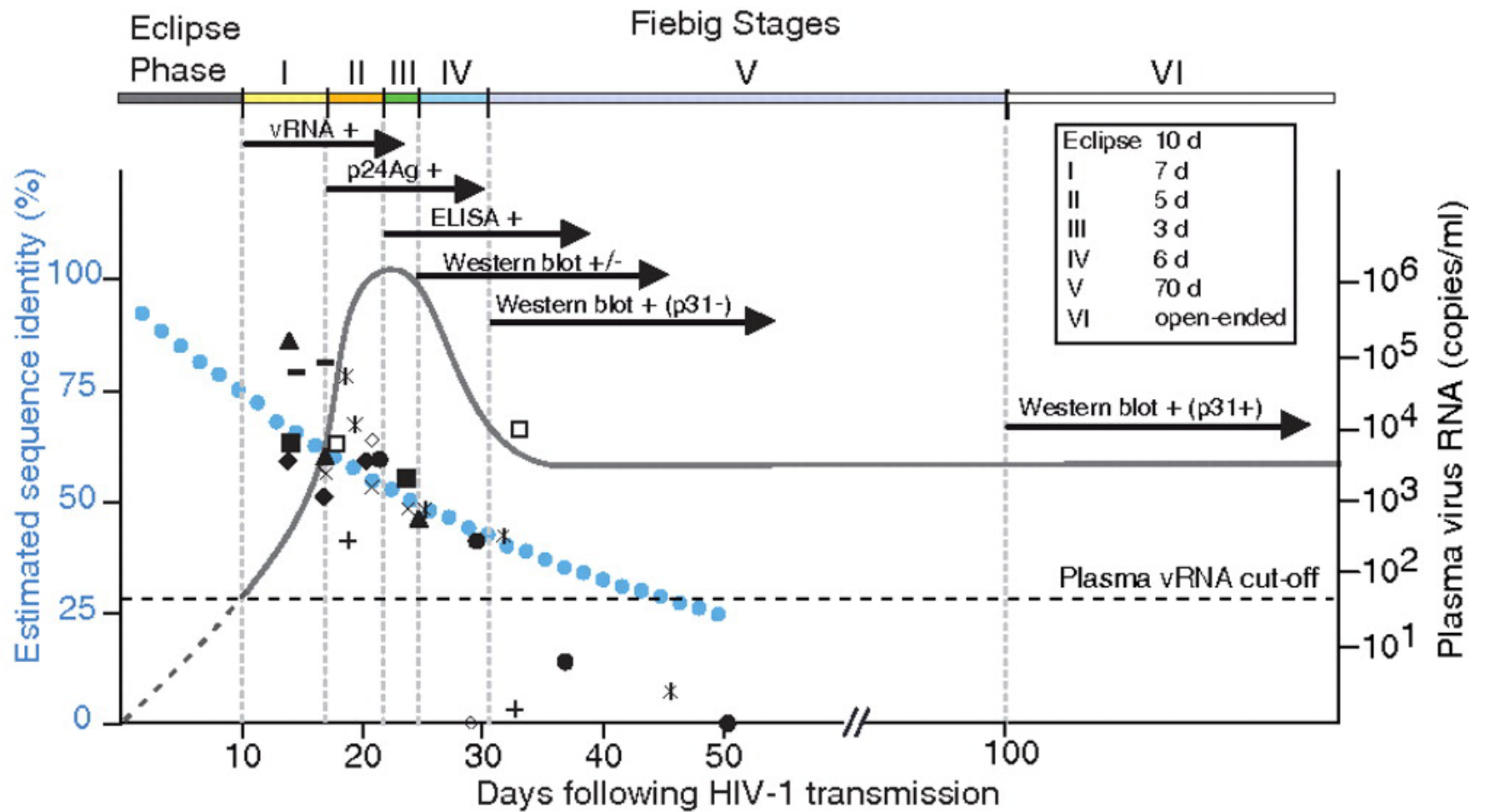
Evidence for fewer glycosylation sites in subtype C *env* genes from acutes vs chronics.

No difference between men vs women in the number of variants transmitted, BUT 20% of transmissions events involve the transmission of multiple variants.

Specific Questions

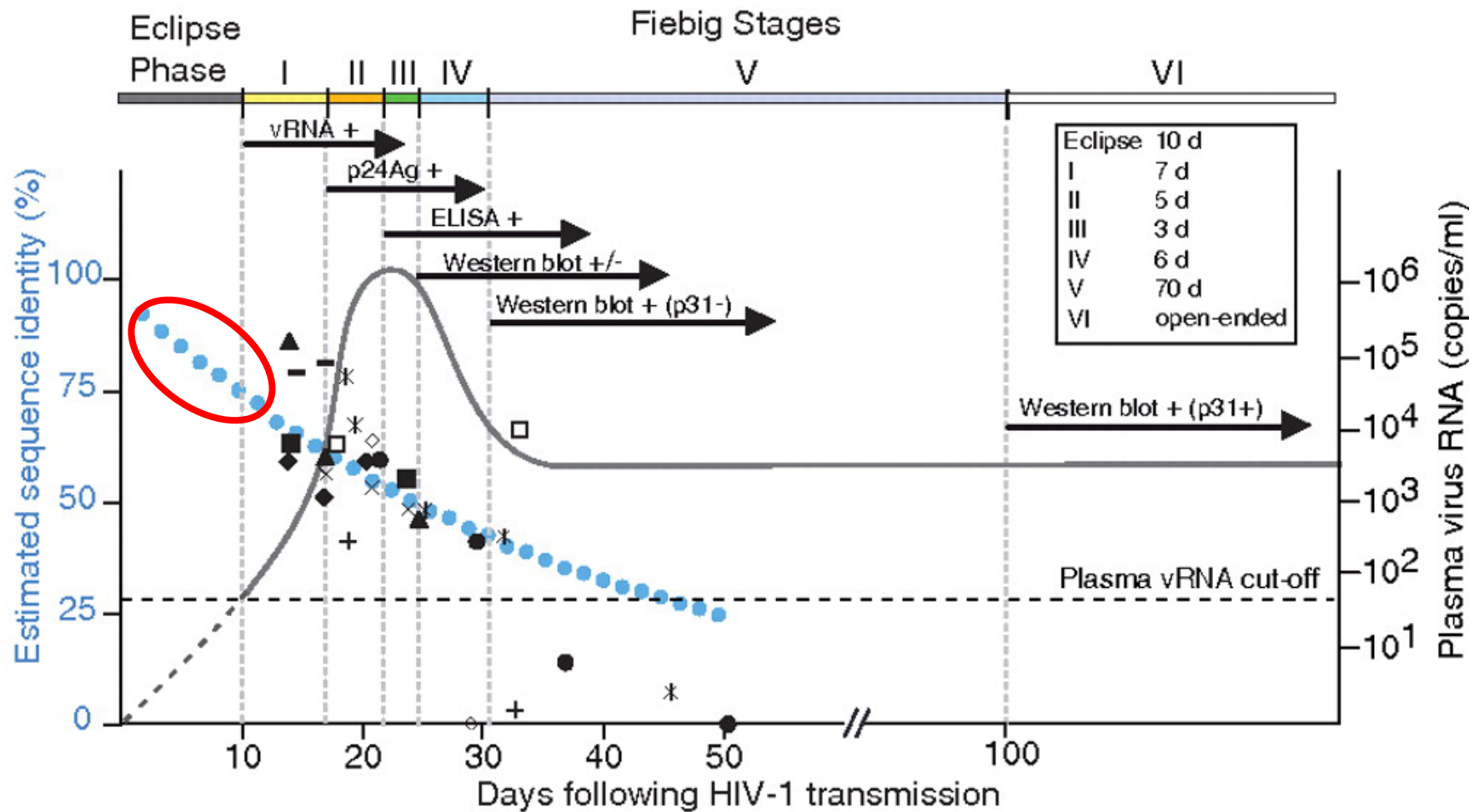
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Early Sequence Diversity Approximates Neutral Evolution



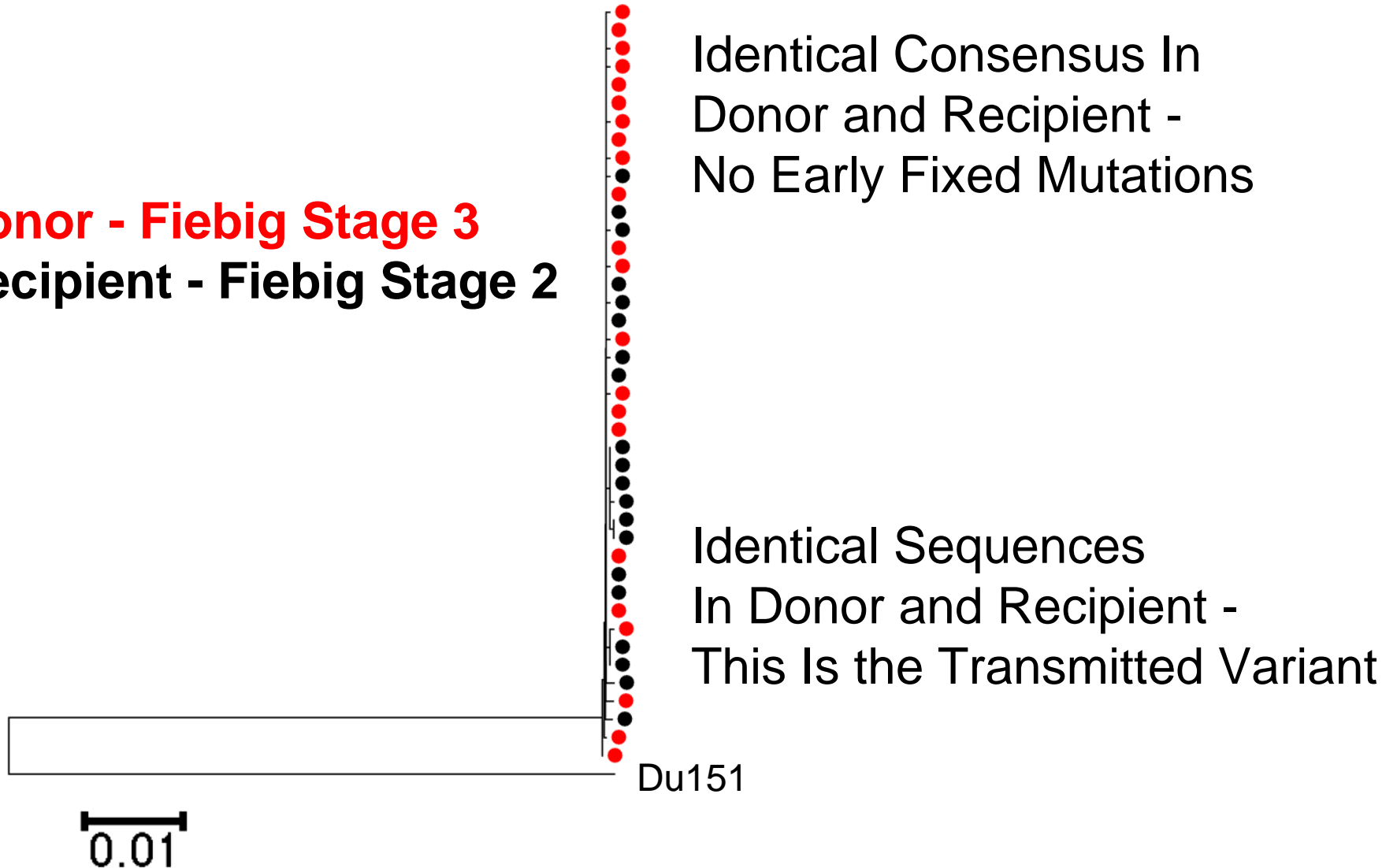
Keele et al., 2008

Are We Really Inferring the Transmitted Sequence? Is There Unseen Evolution?



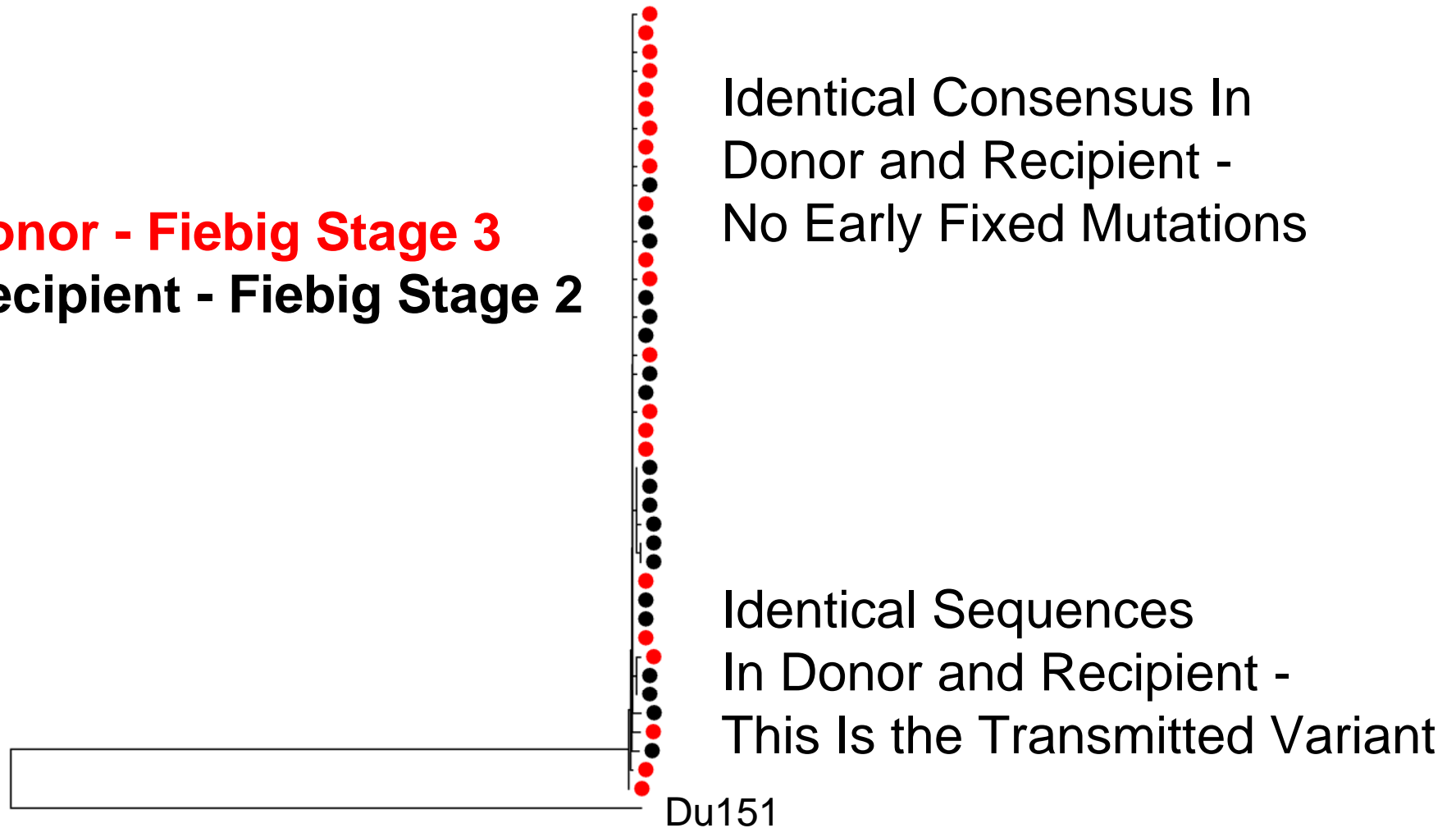
Acute-To-Acute: No Unseen Evolution

- Donor - Fiebig Stage 3
- Recipient - Fiebig Stage 2



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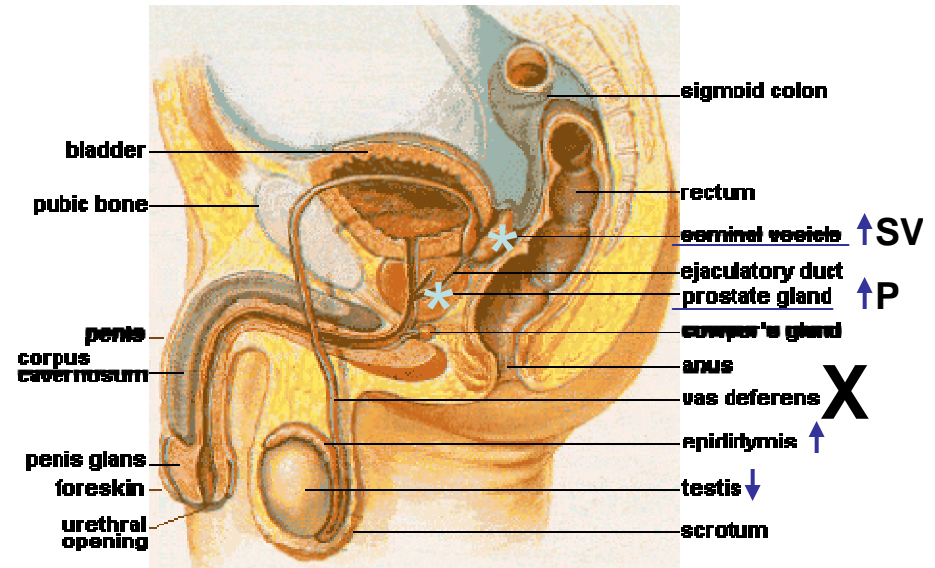
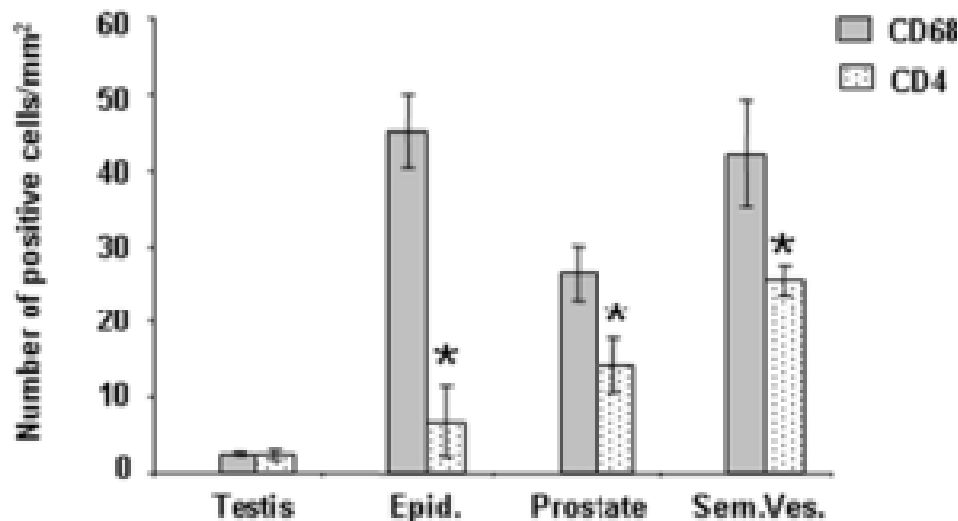
If there is selective pressure associated with transmission, it must occur in the donor or at the moment of transmission, not during outgrowth in the recipient.

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What Are The Characteristics of the HIV-1 Population Found In Donor Semen?

Target cells in seminal tract.



Macrophages and CD4+ Cells

Le Tortorec et al., PLoS One 2008

90% of semen volume comes from the seminal vesicle and the prostate.

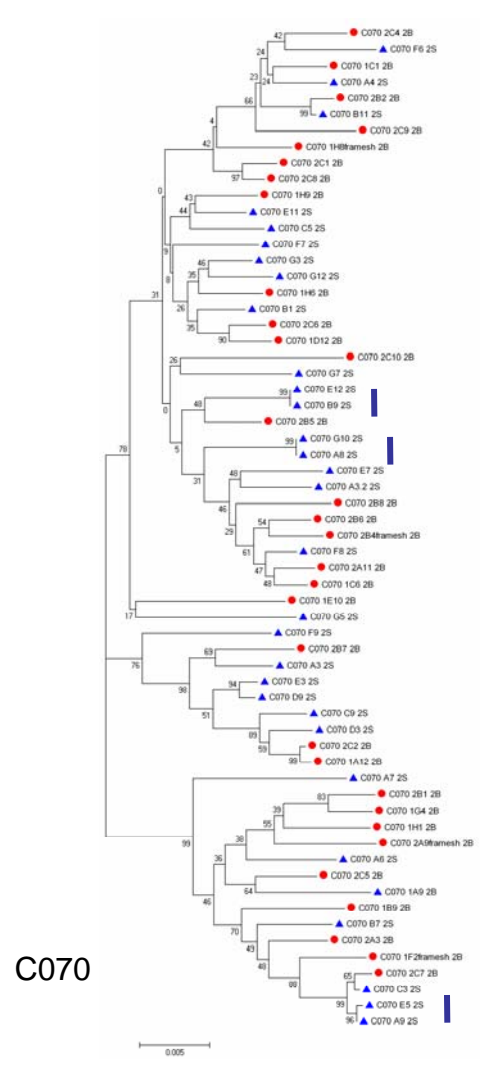
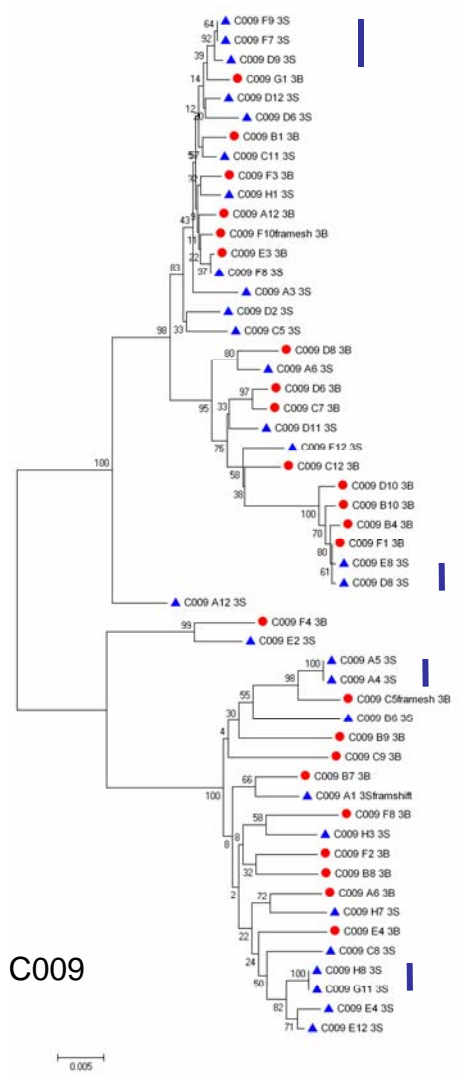
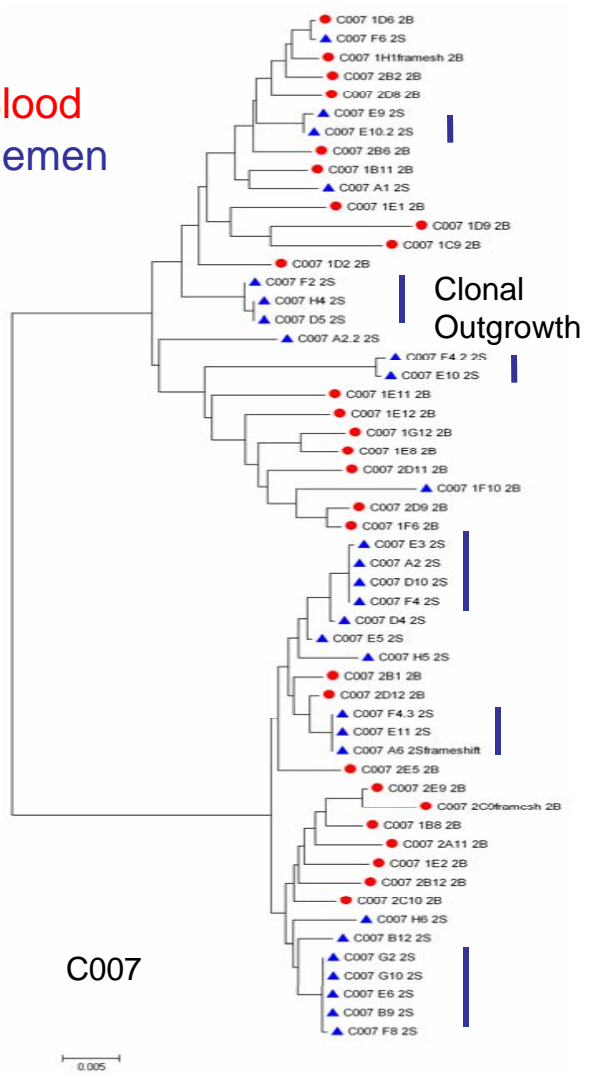
Vasectomy does not reduce viral RNA in semen.

What is the source of HIV-1 in semen?

Look at viral RNA in blood and semen (prostate, and/or SV).

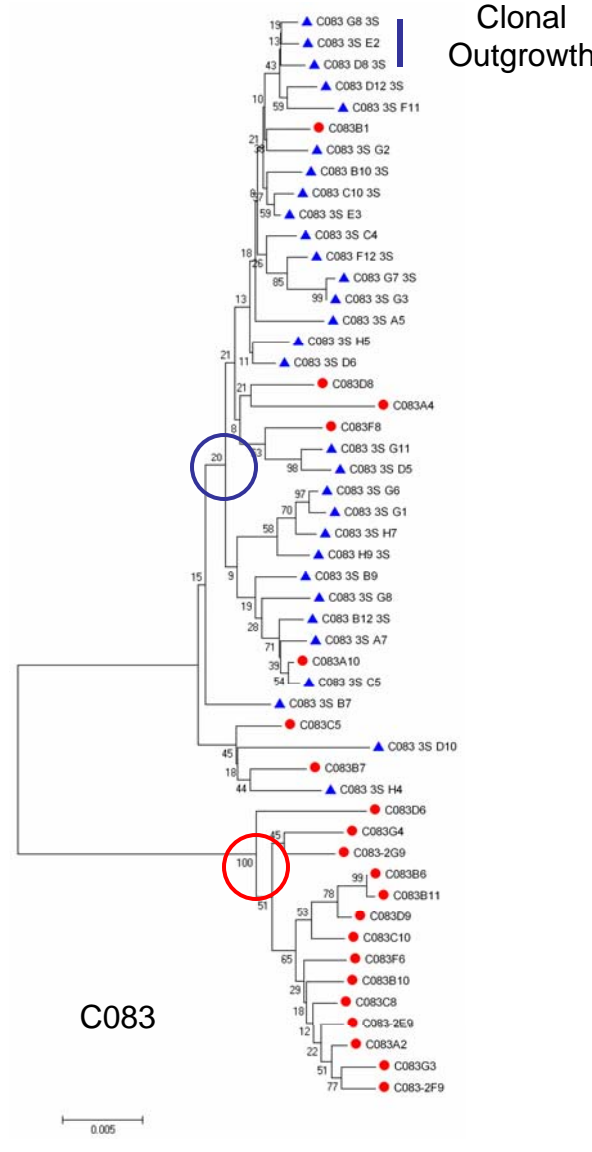
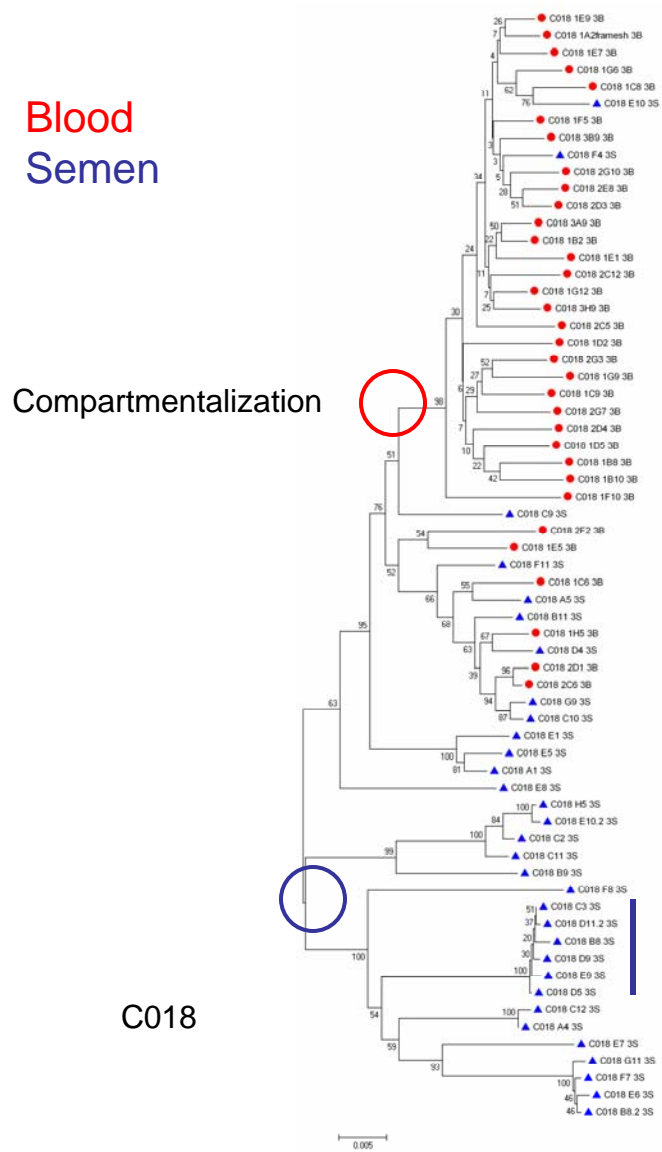
Blood and Semen Sequences Are Equilibrated But With Clonal Outgrowth In the Semen

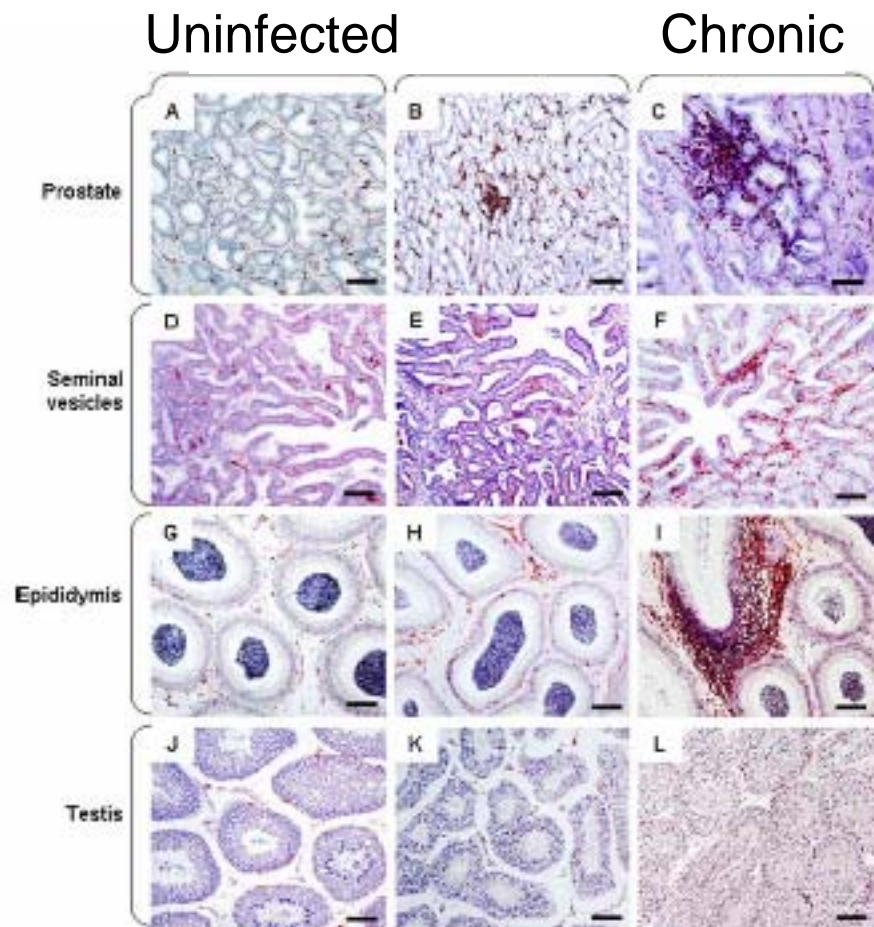
Blood
Semen



Blood and Semen Are Compartmentalized And With Clonal Outgrowth In Semen

Blood
Semen

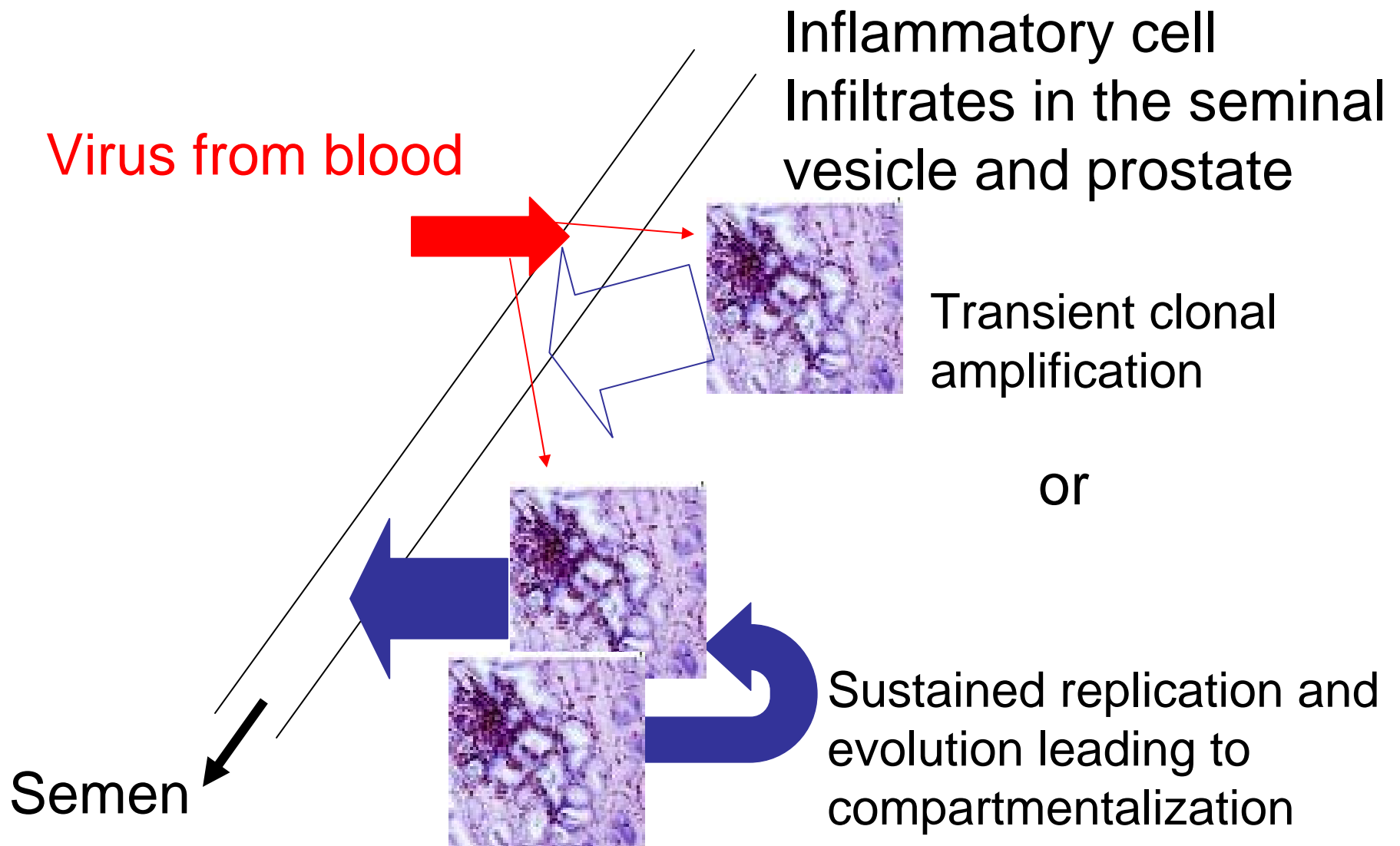




HLA-DR

Infiltrates of activated T cells may provide sites for the clonal outgrowth of virus (short term) or sustained replication which would result in **compartmentalization**.

Model For the Origin of HIV-1 In Seminal Plasma



Increasing immunodeficiency results in a transition from clonal amplification to compartmentalization.

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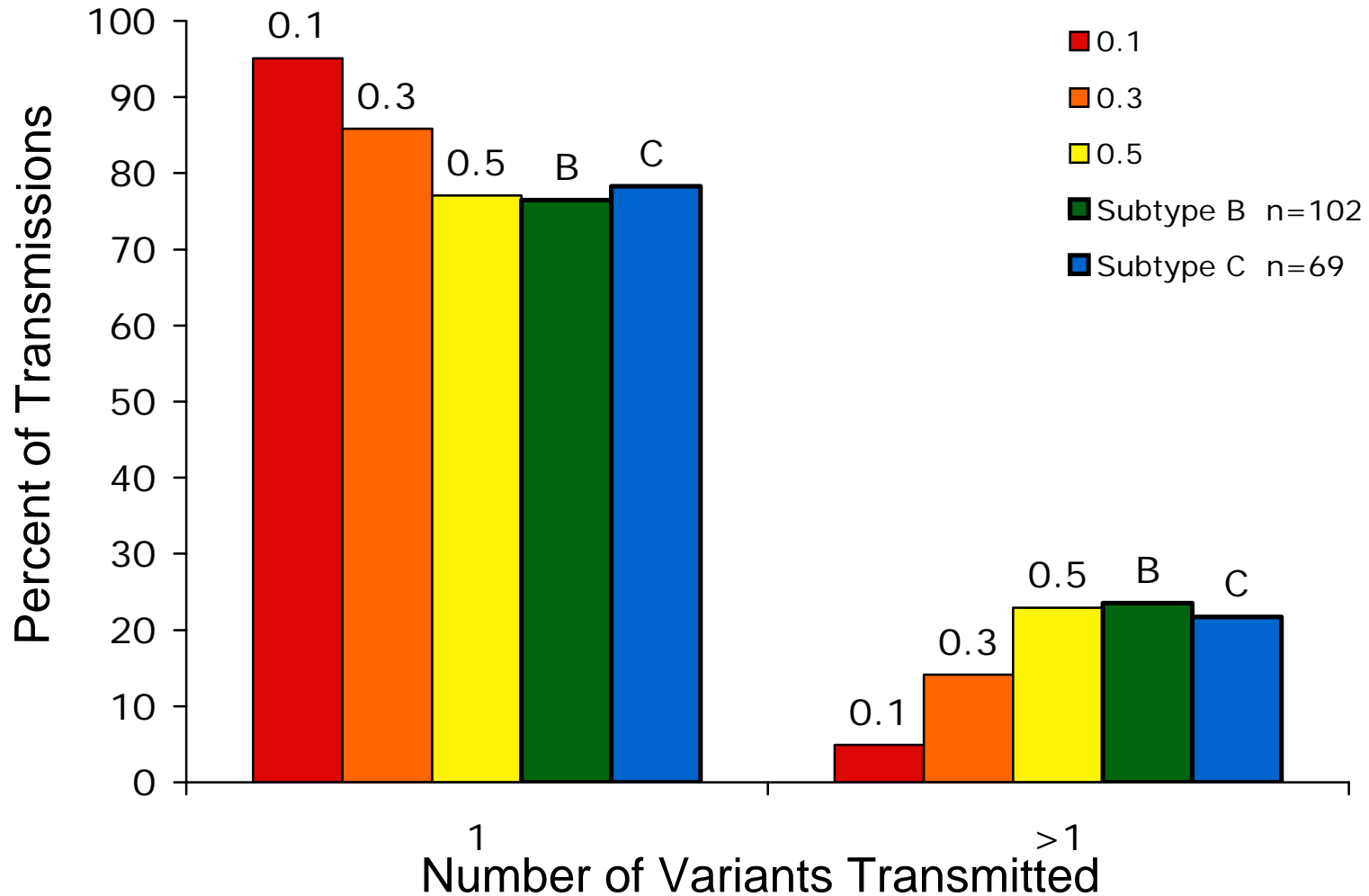
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20% of transmissions involve multiple variants

People infected with multiple variants progress more rapidly - additional diversity through recombination?

The Poisson Distribution Does Not Model The Transmission of Multiple Variants



The transmission of multiple variants cannot be the result of independent events at low probability.

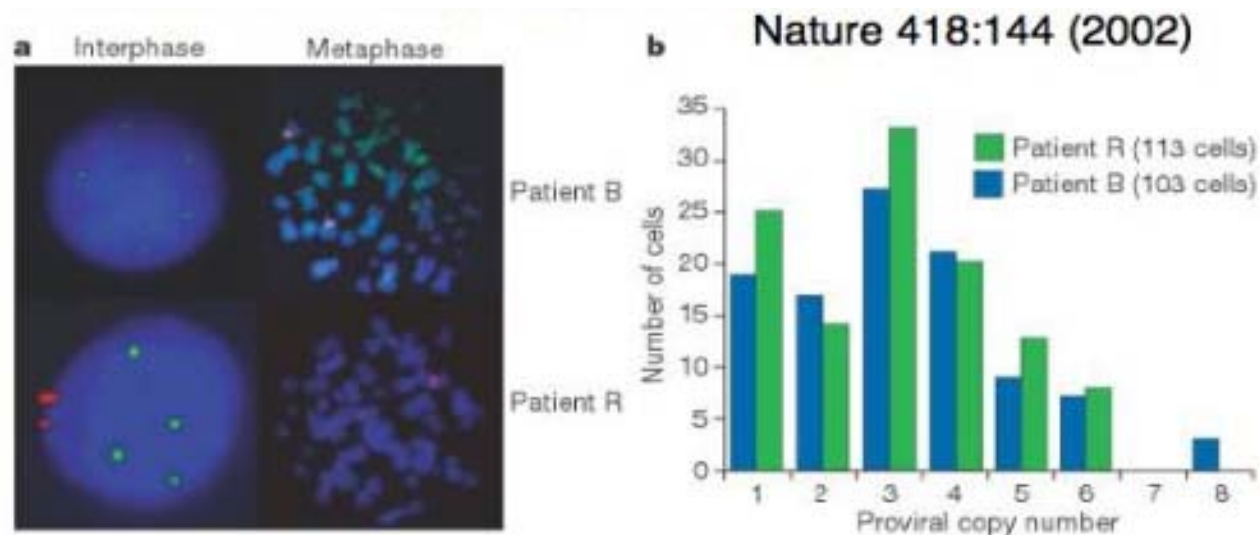
An Unexplained Anomaly: Transmission of Multiple Variants With Low Probability

1. Two (or more) rates. A low rate with the transmission of single variants and a transiently high rate (100 times higher) to account for multiple variants. **STD, trauma to the epithelium**

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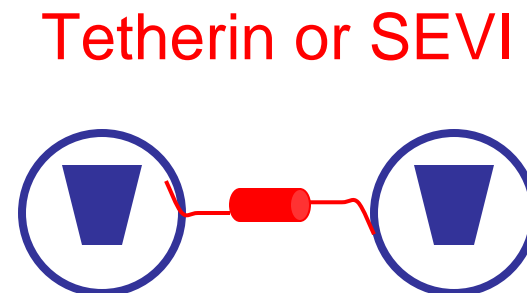
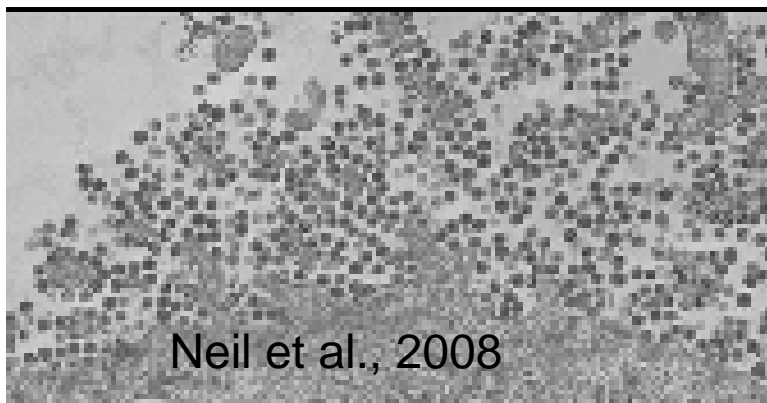
1. Two (or more) rates. A low rate with the transmission of single variants and a transiently high rate of 0.8 probability to account for multiple variants. STD, trauma to the epithelium
2. Transmission of multiple variants may be linked.

A. Low frequency transmission of a dually infected cell.



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The transmission of multiple variants occurs by an unknown mechanism and may impact both disease progression and vaccine efficacy due to increased early viral diversity.

A woman with blonde hair, wearing a purple patterned headband and a black backpack, is looking towards a large, layered red rock formation. The formation features a prominent, pointed peak in the center. The sky is clear and blue. The text "Thank You" is overlaid in white on the rock formation.

Thank You