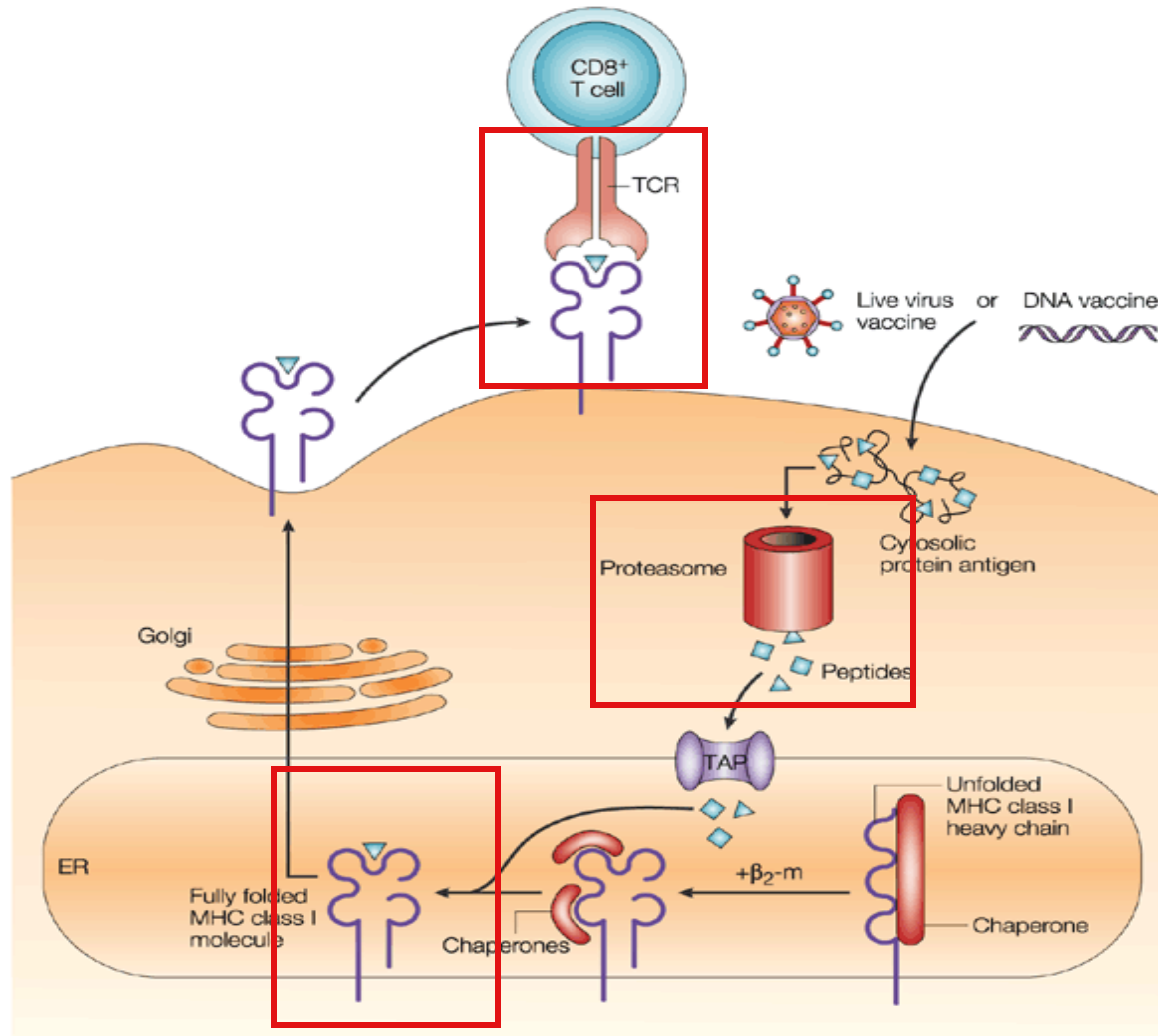


Dynamics of CTL Epitope Escape
and Reversion in an African Subtype
C Cohort

Malinda Schaefer
Emory Vaccine Center

Viral peptide presentation by HLA Class I molecules to CD8⁺ T cell



HIV CTL Immune Escape Follows a Predictable Mutational Pathway

- In response to an individual's HLA alleles, certain predictable escape mutations will arise during the course of HIV infection
 - 84% of HLA-B*57 individuals have a mutation at T242 in the epitope TW10 - Leslie et al. Nat Med, 2004. **10**(3): p. 282-9.
- Several groups using large cohorts have linked HLA alleles and specific amino acid polymorphisms in HIV-1

HIV-1 HLA Linked Amino Acid Polymorphisms

B*1401	PFRDYVDRFFKTLRAEQATQD
B*5801	FFKTLRAEQATQDVKNWMTDT
B*4403	KTLRAEQATQKVKNWMTDTLL
B*0801	LLVQNPDCKTILRALGPGA

Epitope

Polymorphism location

Rates of Epitope Escape and Reversion

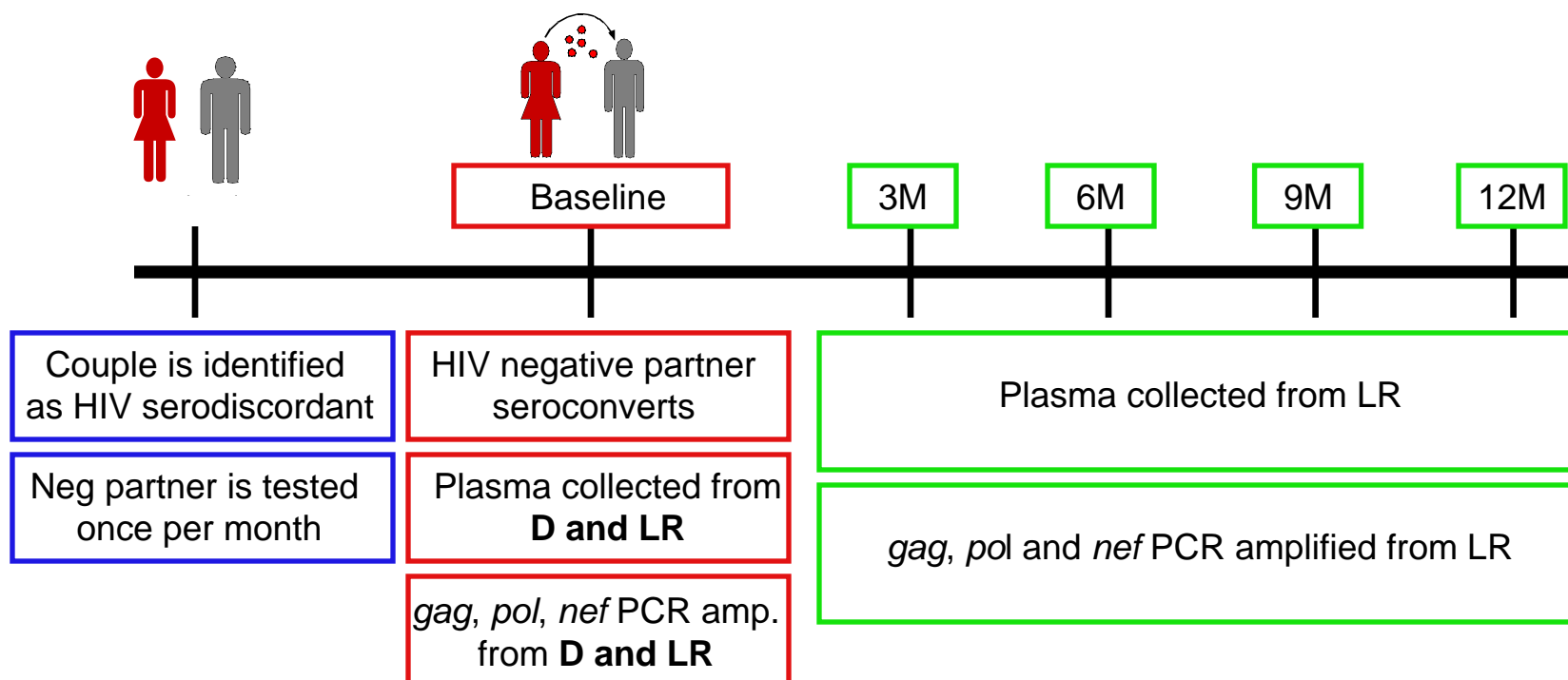
- Previously, an elegant 1 year longitudinal study of 98 acutely infected individuals was done to determine rates of epitope escape and reversion - Brumme et al. J Virol. 2008 Sep;82(18):9216-27
- However, because the transmitted viral sequence was unknown, assumptions were made regarding the presence of escape mutations at the baseline time point
 - Polymorphisms present at baseline in a person with the linked HLA allele were counted as a new escape mutation
- Additionally, because the transmitted viral sequence was unknown, the escape and reversion rates determined were not directly comparable
- To avoid these assumptions we examined epidemiologic linked transmission pairs

ZEHRP

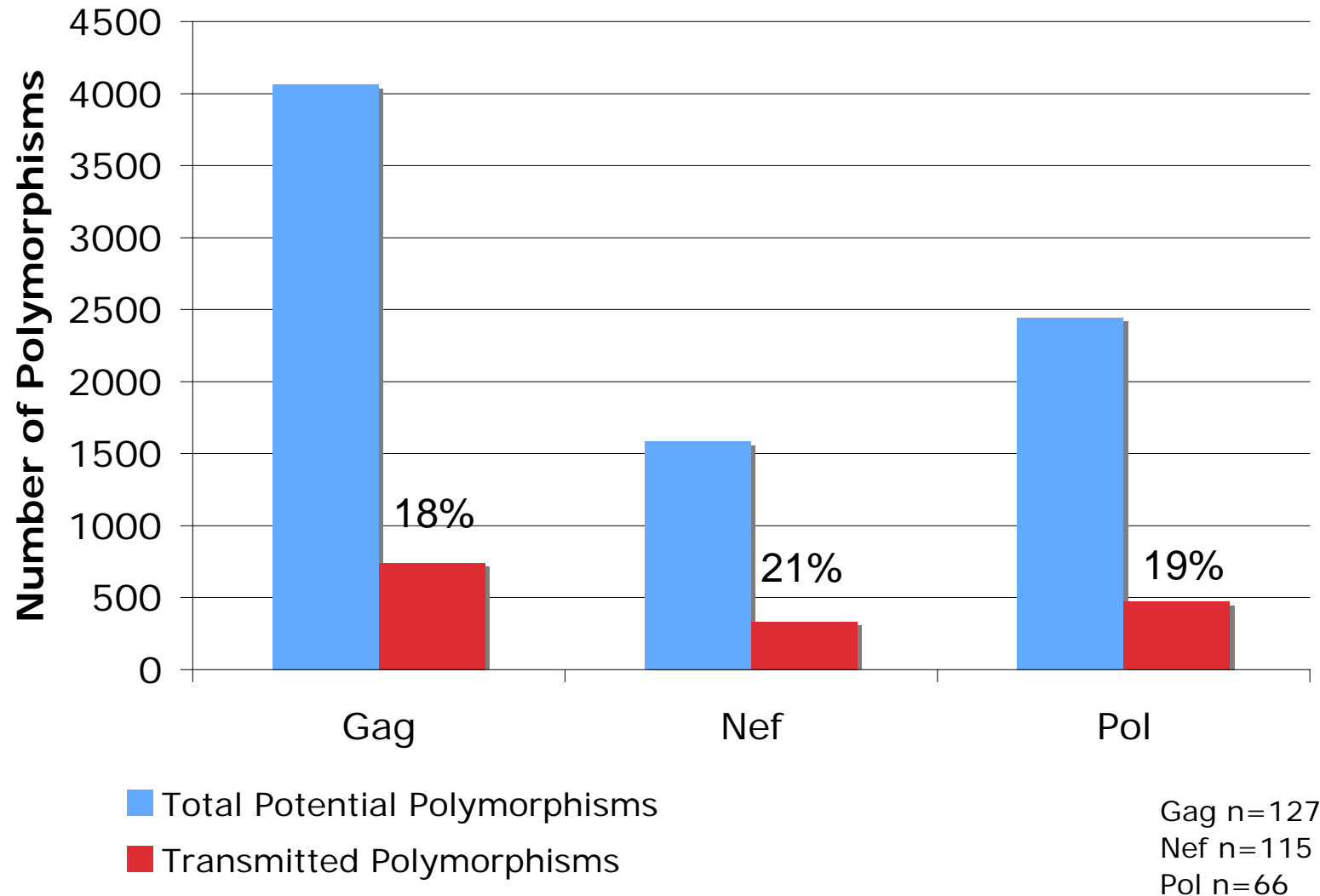
- Zambia-Emory HIV Research Project (ZEHRP)
- Established by Dr. Susan Allen in 1994 in Lusaka, Zambia to provide voluntary HIV testing, counseling, health care and follow-up to cohabiting couples
- If a couple is identified as serodiscordant, the couple is enrolled into the cohort and receives ongoing counseling and condom provision at 1 and 3 month intervals
- Transmission in the cohort has been observed in 8.5% of couples per year

Methods

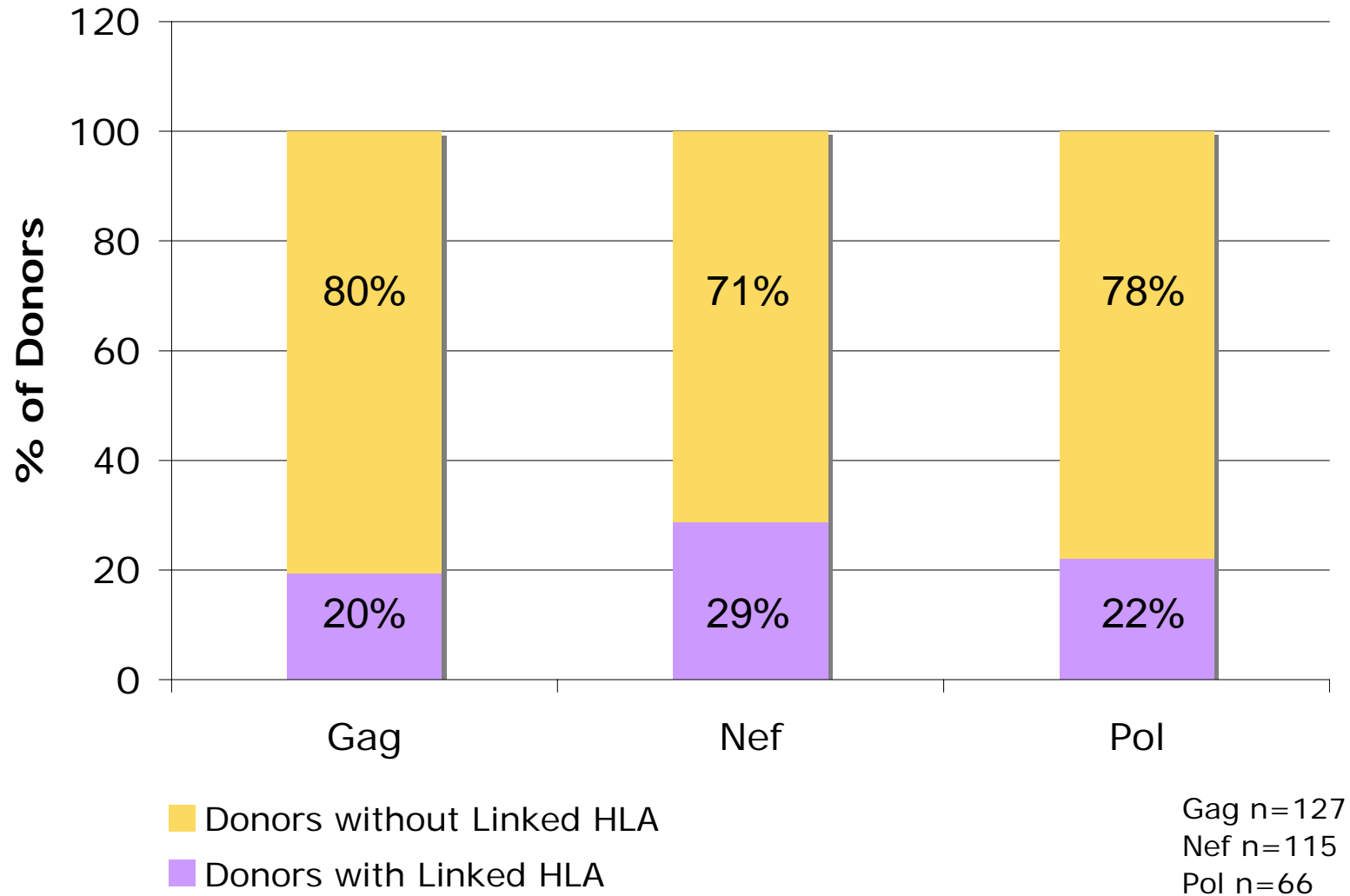
- Linked transmission pairs were identified from ZEHRP
 - gag*, *pol* and *nef* genes were PCR amplified from plasma virus
 - Population DNA sequencing was performed
 - Amino acid polymorphisms associated with known HIV epitopes were identified using previously published data
- Matthews et al. J Virol. 2008 Sep;82(17):8548-59



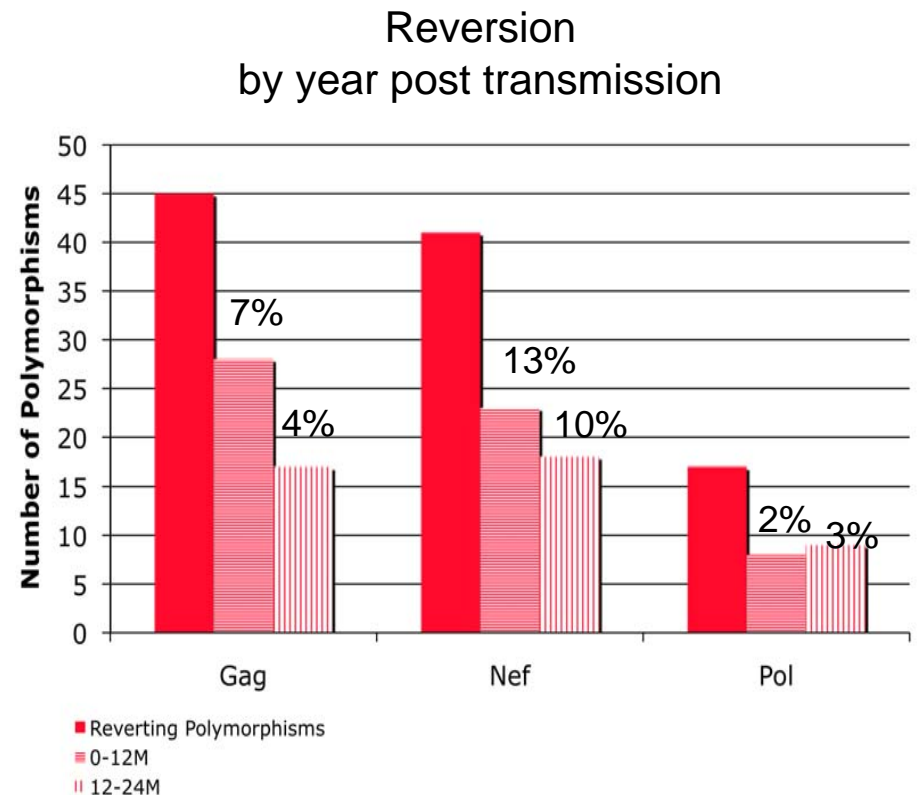
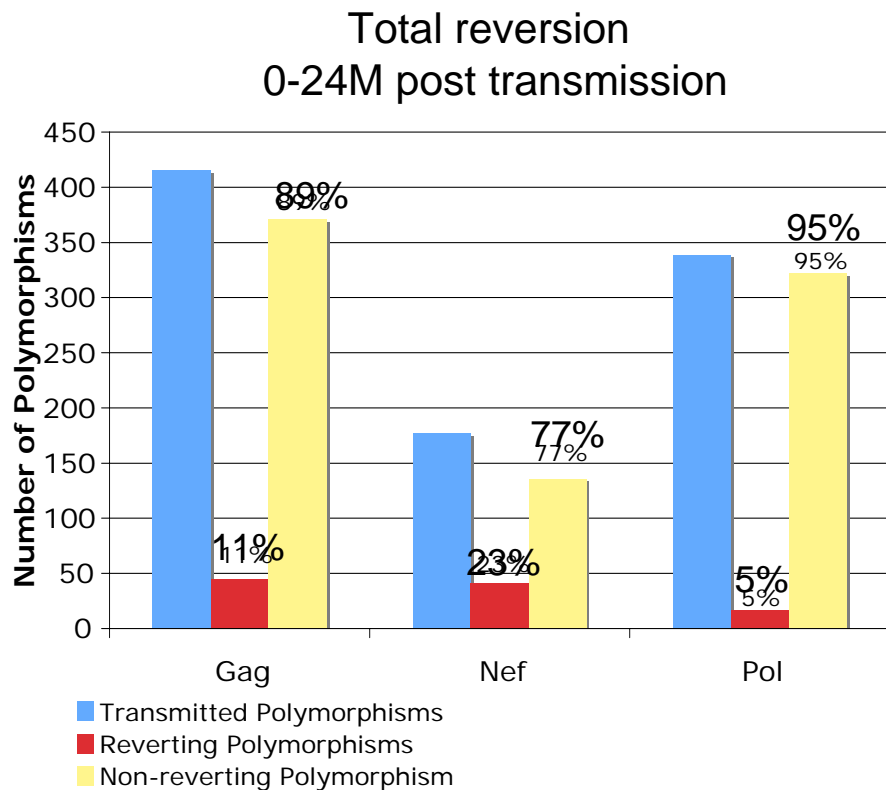
A large fraction of HLA-linked polymorphisms in Gag, Nef and Pol are transmitted from the Donor



The majority of transmitted polymorphisms are not selected by the donor HLA alleles



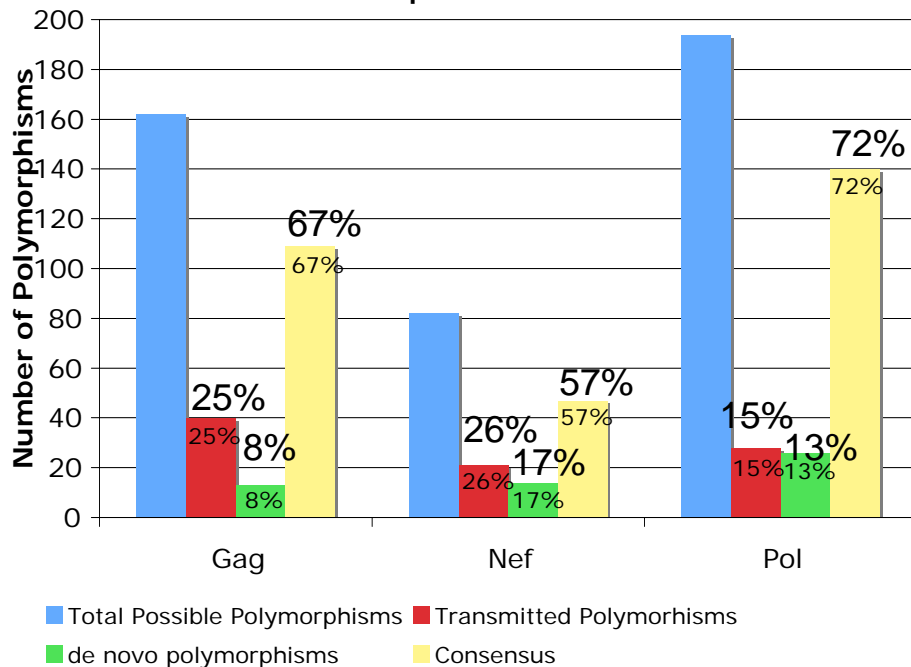
The majority of transmitted polymorphisms do not revert during the first two years post transmission



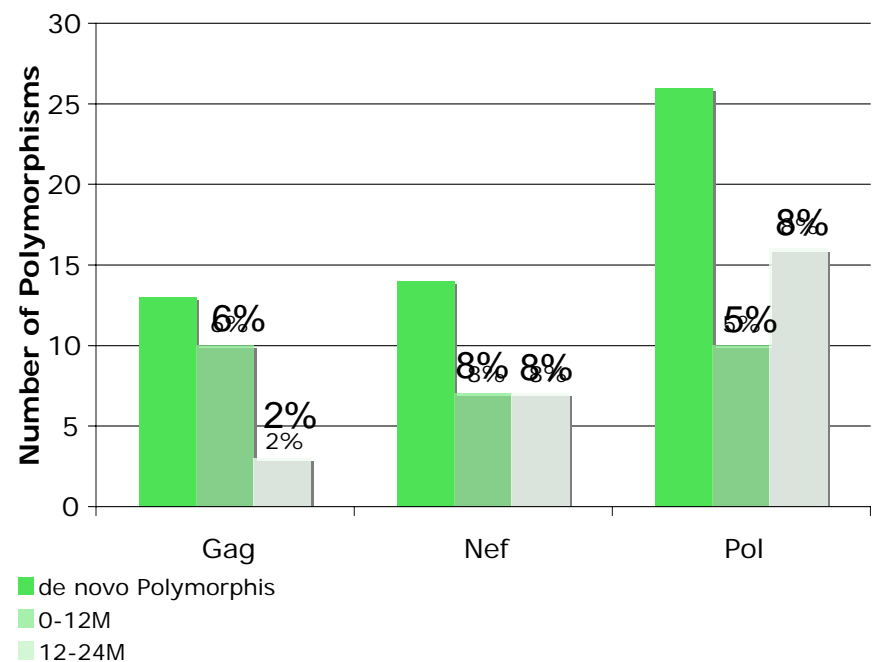
Gag n=63
 Nef n=60
 Pol n=52

Overall during the first 2 years of infection the majority of polymorphisms attributable to the recipient's HLA were transmitted from the donor

Total de novo polymorphisms
0-24M post transmission



de novo polymorphisms
by year post transmission



Gag n=63
 Nef n=60
 Pol n=52

Summary

- Polymorphisms in Gag, Nef and Pol are transmitted more frequently than previously recognized
- The majority of transmitted polymorphisms were not linked with the donor HLA and are unlikely to have been selected in the donor
- Only a small percentage of transmitted polymorphisms reverted to consensus during the first two years of infection
- Transmitted Nef polymorphisms revert more quickly than Gag and Pol polymorphisms
- A minority of polymorphisms present at 1 year post transmission represent new polymorphisms
- Thus, transmission pairs are critical for an accurate assessment of HLA linked viral evolution in a newly infected individual

Acknowledgements

Emory University

Eric Hunter, Ph.D.

Cindy Derdeyn, Ph.D.

Dan Claiborne

Andy Godoshian

Jessica Prince

Hunter and Derdeyn

Lab Members

Emory/ZEHRP cohorts

The Staff and Participants

Susan Allen, M.D., MPH

Elwyn Chomba, M.D.

Lawrence Mwananyanda, M.D.

Joseph Mulenga, M.D.

Amanda Tichacek, MPH

Nicole Luisi, MPH

University of Alabama- Birmingham

Paul Goepfert, M.D.

Richard Kaslow, M.D, MPH

James Tang, D.V.M, Ph.D.

Funding:

International AIDS Vaccine Initiative

US Centers for Disease Control

US National Institutes of Health Grants MH-66767; AI-51321; AI-064060; AI-084409

Fogarty AIDS International Training in Research Program FIC 2D43 TW001042

Virology Core of the Emory Center for AIDS Research P30 AI050409

Highlighter plots allow a visual representation of fixed nucleotide changes

