Poster Session # E10
Abstract Number 0392
26th Conference on Retroviruses and Opportunistic Infections
March 4 - 7, 2019
Seattle, WA

HIV Rebound in the Male Genital Tract after ART Interruption

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Background

- To cure HIV, we need a better understanding of the distribution of HIV reservoirs throughout the many compartments of the body outside of the blood.

Objective

To determine if HIV reservoirs in the male genital tract contribute to viral rebound after antiretroviral therapy (ART) interruption.

Cohort and Sampling

Population: Twelve people living with HIV (PLWH) who began ART during acute or early infection were enrolled in a randomized, double-blind, placebo-controlled clinical trial of HIV-MAG DNA vaccine prime, rVSVN4CT1gag booster vaccine (NCT01859325).

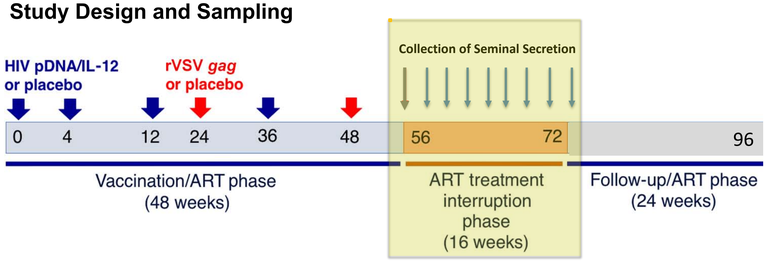
Population Characteristics

Characteristics N=12	
Age (years)	42 (24-54)
Gender: male	12 (100%)
Ethnicity: white	6 (50%)
Time from EDI to ART (days)	25 (3-73)
ART exposure (years)	3.5 (2-13)
CD4$^+$ T cell counts/µl (after rebound)	510 (390-1430)

Legend: EDI: estimated date of infection, ART: antiretroviral therapy, numbers show median (range) or % as indicated.

Sampling. Paired blood and semen were collected up to 9 longitudinal time points after ART interruption.

Study Design and Sampling



Data Generated and Bioinformatics

Sequencing. Deep sequencing of C2-V3 env, gag and pol (MiSeq Illlumina) was performed on longitudinally collected paired blood and semen samples. Reads were analyzed with purpose-built bioinformatics pipeline. Cleaned mapped reads were used to reconstruct HIV haplotypes. The number of haplotypes strictly included the number of distinct quasi-species or variants present in at least 1% or more in the viral population

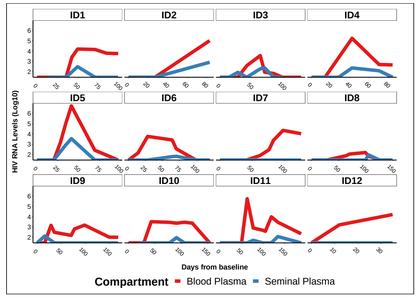
Viral diversity. Intra-patient genetic diversity in each compartment was evaluated for each subdomain/segment. The Shannon entropy index (S) was calculated using a formula that accounts for both the number of distinct reads and their proportional representation in the dataset.

Results

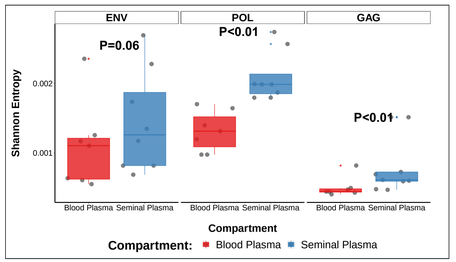
Vaccine had no effect on kinetics and magnitude of HIV RNA rebound in blood plasma (Sneller et al, STM 2017).

Compared to blood, HIV RNA rebound in semen occurred significantly later (median of 66 versus 42 days post ART interruption) and reached lower levels (164 versus 16,224 copies/ml).

Despite ART started during early infection, HIV diversity was higher in semen compared to blood in all three coding regions.



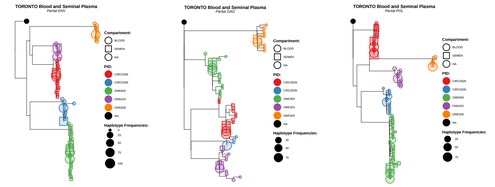
Legend. HIV RNA Rebound after ART interruption in blood (**red**) and seminal plasma (**blue**).
Participant ID1-4 were randomized to the placebo group. Participants ID5-12 were randomized in the vaccine group.



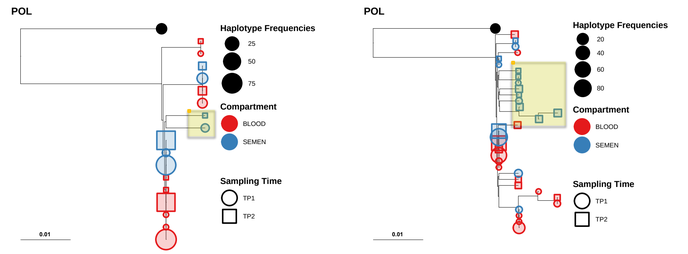
Legend. Viral diversity (Shannon entropy) was assessed after adjusting for haplotype frequency for all three regions in blood (**red**) and semen (**blue**).

Results

Paired sequence data were available for 5 participants.



Phylogenetic analysis confirmed the presence of compartment-specific monophyletic HIV RNA populations in at least one HIV region in 2 out of the 5 participants in longitudinal time-points.



Legend. **Approximate maximum likelihood phylogenetic reconstruction of sequences generated from longitudinally collected HIV-1 RNA Populations in blood and semen from 5 participants.** HIV haplotypes above a minimal frequency threshold of 0.01 were extracted from cleaned reads and were used to construct approximate maximum likelihood phylogenies using FastTree (Price et al., 2009).

Conclusions

- **Higher diversity in the genital compartment suggests distinct evolutionary dynamics.**
- **Unique viral populations are observed in seminal plasma**
- **Reservoirs in all anatomic compartments need to be actively targeted to achieve a complete functional cure.**

Acknowledgments. This work was supported by the Department of Veterans Affairs and grants from the National Institutes of Health: AI120008 (R01 Smith-P3 deep sequencing tech), AI131385 (P01 Smith-R3 Last GR, Early Treatment interruption), AI100665 (Smith-K24Training), MH097520 (Smith-Viral Aging), DA034976 (Smith-Avant Garde), DA041507 (Smith-SMRT Brain TaPHR), AI119422 (Smith-Perturb Immune Stimulation), AI028274 (Richman-CFAR), AI027384 (Richman/Gianella-BEAT Delaney), MH083512 (Heaton/HIRRC), MH107345 (Heaton/LetterMe-HAND-Age-related), AI108039 (Little-PIRC), AI104283 (Strain-R33), DA037811 (Patterson-Tijuana), AI68636 (ACTG-supplements), AI134295 (Gianella-Sex Hormones & Persistence), HD094646 (Gianella-Declining Sex Hormones), AI027763 (Gianella Supplement-CMV driven mechanisms).