SYSTEMIC INFLAMMATION, GUT DYSBIOSIS AND GUT MICROBIOME IMPACT HIV MIGRATION DYNAMICS

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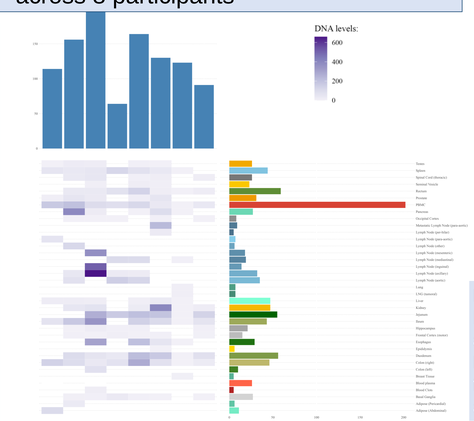
BACKGROUND

HIV persists in the human body, including the gastrointestinal (GI) tract where the virus causes cellular damage, microbial translocation and inflammation. The GI tract also acts as a source of rebounding virus upon cessation of ART. In this study, we investigate HIV dynamics between tissue reservoirs and evaluate biomarkers, viral reservoir characteristics, and microbiome composition associated with viral dynamics in **8 participants** of the Last Gift cohort.

METHODS

- Bayesian discrete trait analyses (DTA) were conducted using HIV DNA single genome full env sequencing data across **33 tissues** (10-25/participant) including 7 GI tissues (Figure 1). These models were used to infer HIV dynamics (number of estimated migration events) between sampled tissues.
- A panel of 44 cytokines were measured perimortem in blood plasma (ELISA and Luminex assays). Microbiome was characterized in GI tissue (bacterial 16S-rDNA sequencing).
- Bayesian hierarchical models were used to interrogate the association between viral migration between tissues and (1) HIV reservoir characteristics (size measured by digital droplet (dd)PCR, diversity, and genetic distance), (2) microbiome composition, and (3) soluble biomarkers.
- The models included predictors of the source and recipient tissues, whether the tissues are within the same biological system, and host- and tissue- level effects.

Figure 1. Quantification and sequencing of HIV reservoir across 8 participants



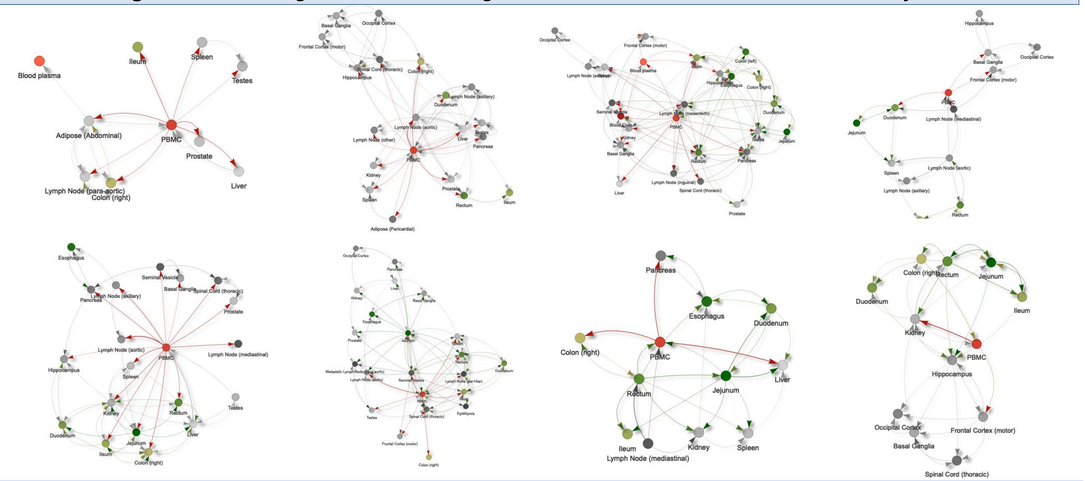
Legend: HIV full envelope single genome sequencing was performed, and HIV DNA levels were measured via ddPCR in 8 Last Gift participants across 33 unique tissues (10-25 per participant). Heatmap shows HIV DNA levels in sampled tissues. Vertical and horizontal bars show the number of single genome HIV sequences obtained for each participant (vertical) and tissue (horizontal).

HIV reservoir dynamics **are** driven by local *inflammation* and *gut dysbiosis*

RESULTS

- *Population characteristics.* Primarily male (7 of 8) and White/Caucasian (7 of 8). Two participants stopped ART at 53 and 70 days prior to death (LG01 and LG04).
- *Inflammatory markers.* The DTA showed that viral migration within, from or toward GI tissues (Figure 2) was associated with higher levels of markers of inflammation and homeostasis (e.g. IL-22, RANTES) and lower blood levels of ICAM1, a regulator of cellular responses in inflammation (Figure 3).
- *Viral characteristics.* The DTA showed strong associations between lower genetic distance between viral populations at anatomical sites and increased viral migration between those sites. Among GI tissues, viral diversity in source and recipient tissues was also positively associated with viral migration.
- *Gut microbiome*. A positive association between viral migration and the abundance of Fusobacteria (marker of inflammation) in the source tissue, and Actinobacteria in the recipient tissue. More viral migration from tissues with lower Firmicutes/Bacteroides ratio (marker of gut dysbiosis).

Figure 2. Viral migration within the gastrointestinal tract and across the body



Legend: *Global host HIV dynamics of FL HIV env sequences from 8 participants.* Tissues (nodes) are colored according to the sampling location with gastrointestinal tissues in shades of green, blood samples in red and other tissues in shades of grey. Edges are colored according to the tissue sources. Results from Bayesian discrete diffusion models performed with BEAST. Only migration events with Bayes Factors ≥ 3 are considered. We showed viral migration between GI tissues (green lines between green dots) but also migration from GI tissue toward other systems (green lines toward green or red dots) or from PBMC (red) or other tissues (grey) toward the GI (red and grey lines).

CONCLUSIONS

- This study further supports the impact of HIV reservoir composition on viral dynamics.
- We showed that systemic inflammation and microbial gut environment also impacted HIV dynamics.
- Our approach provides a robust way to evaluate host and tissue level markers associated with directional HIV dispersal within host.

ADDITIONAL KEY INFORMATION

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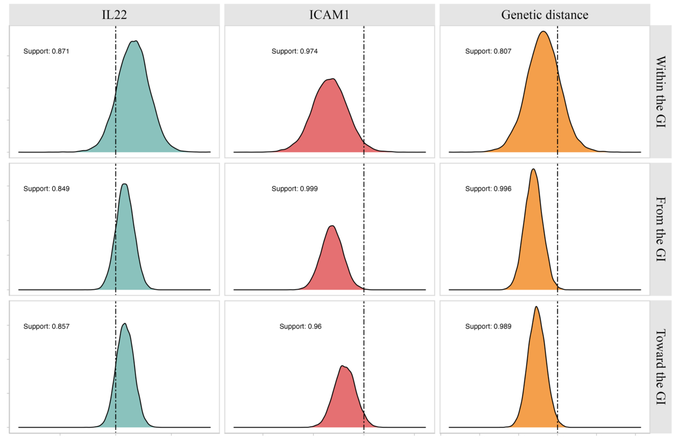
For more on the Last Gift Study: http://lastgift.ucsd.edu/

Figure 3. Viral dynamics is associated with local inflammation and HIV reservoir composition



Legend: *Posterior distribution of the estimates for three selected biomarkers (predictors) associated with viral movement (outcome) obtained from a Bayesian hierarchical model (BHM). The* model was developed to assess the association between viral movement and host and tissue level predictors. Predictors included 44 cytokines measured in blood plasma close to the time of death, virological measures of gastrointestinal (GI) tissue reservoirs including HIV DNA level (ddPCR), viral diversity and genetic distance between tissue (inferred from single genome sequencing data) and GI microbiome (16S-rDNA-pyrosequencing). Here we show a positive association between IL-22 levels and viral movement within the GI, and from/toward the GI (green). There was also a negative association between level of ICAM1 (red) and genetic distance between tissue (orange) and viral movement. The support represents the probability that estimates are greater or less (depending on the assumed association) than 0.