# Functional clustering and association of HLA class I alleles to viral load in HIV-positive and ART-naïve participants from the INSIGHT START study

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## Background

- **Human Leukocyte Antigen (HLA) class I** alleles are the main host genetic factors involved in **HIV viral load (VL) control** and other viral infections due to its role in immune presentation of intracellular epitopes (1, 2).
- Statistical analyses of HLA alleles have been challenging due to **high polymorphism and variable allele frequencies among populations.**
- **Consensus clusters of HLA class-I alleles** based on **predicted epitopes** facilitate the study **HLA functional relationships** in HIV infection and can **increase statistical power** in statistical analyses.

## Methods

- **1.03 million putative HIV-1 peptides** (9-mers) were generated from HIV consensus sequences of **3785 HIV+ participants** across **35 countries** in the START study (3).
- **Consensus clustering** (4, 5) was implemented using **predicted binding affinities** of putative peptides to **259 HLA class-I alleles** by netMHCpan 4.0 (6).
- **Associations of $log_{10}$(VL)** to each node were tested by linear regression using **imputed HLA alleles from 2546 ART-naïve participants** and adjusted by sex, self-reported race and country.
- **Multiple testing** was controlled by a **false discovery rate (FDR)**-based procedure using a q-value < 0.05 to identify associations.

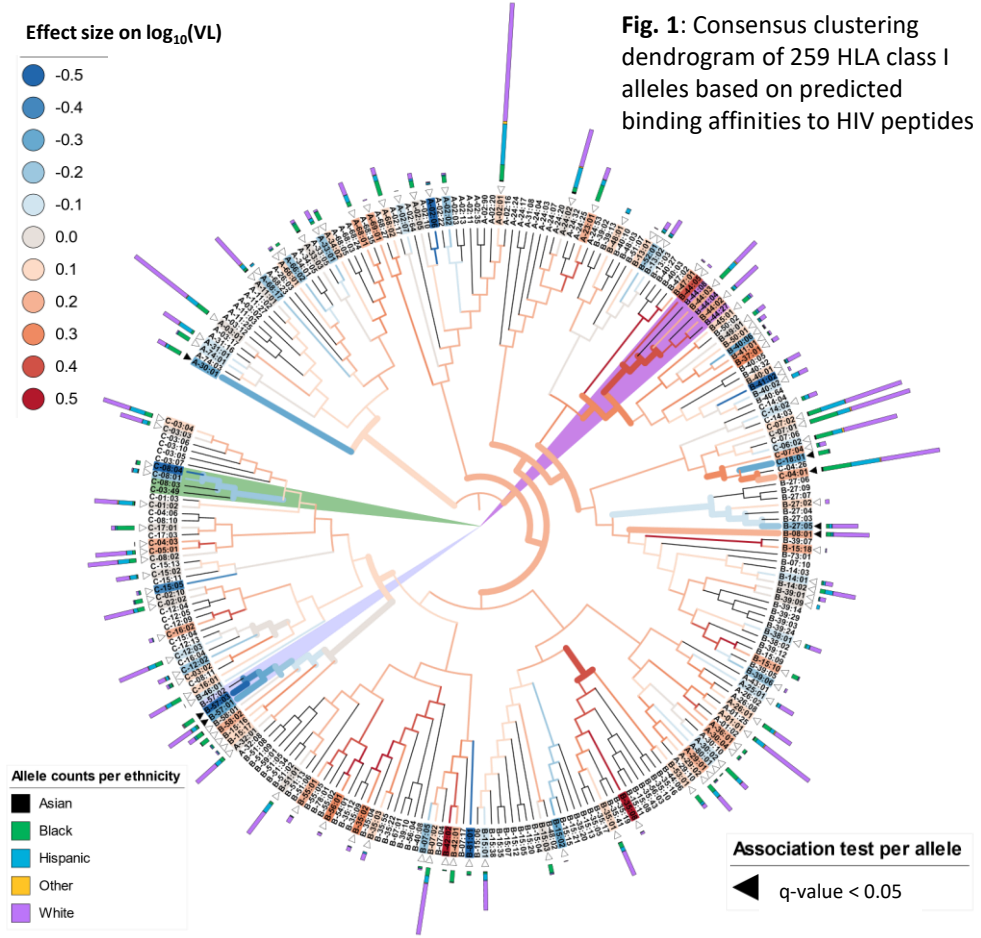
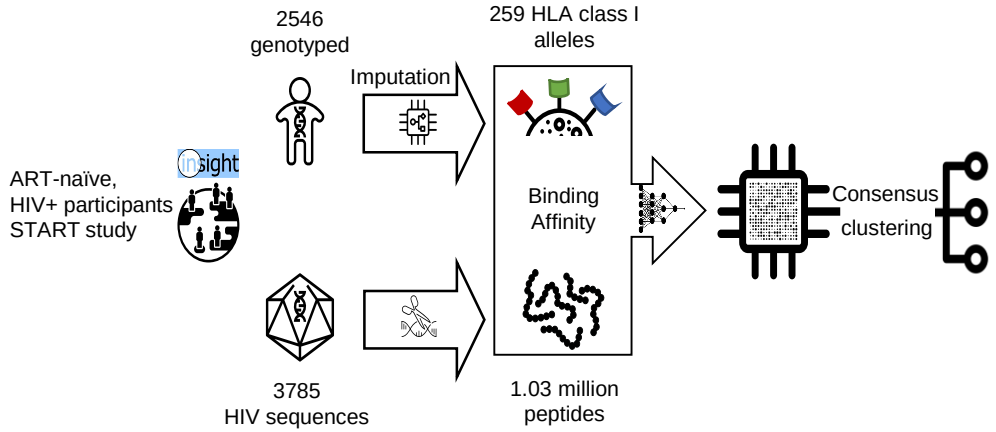



**Fig. 1**: Consensus clustering dendrogram of 259 HLA class I alleles based on predicted binding affinities to HIV peptides



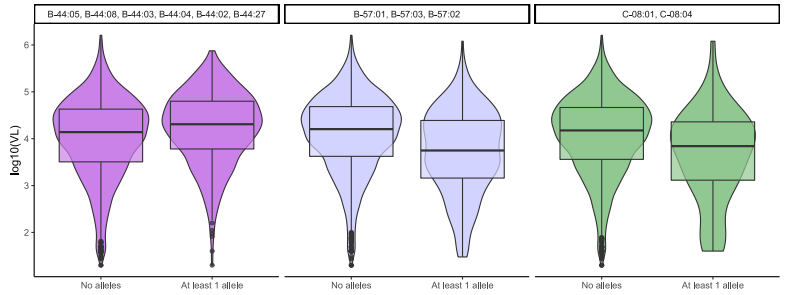




**Fig. 2**: Boxplots and violin plots of HIV-1 VL in carriers and non-carriers of the reported HLA nodes

## Results

- **Two functional groups** were **associated with a lower VL**, one composed of **HLA-B*57:01, B*57:02, and B*57:03** (β -0.32, q-value 1.77E-07, Fig. 2 center) and a pair of **HLA-C*08** alleles (β -0.29, q-value 0.043, Fig. 2 right).
- In contrast, an **HLA-B*44 cluster** showed an association with **higher VL** (β 0.15, q-value 0.005, Fig. 2 left).
- Among the **13 alleles implicated** by these 3 functional clusters, **only two** (HLA-B*57:01 and B*57:03) were **detected at individual allele level (Fig. 1)**.

## Conclusions

- Consensus clustering of HLA alleles based on predicted epitopes provides functional groups to efficiently explore associations with VL.
- Three functional clusters associated with viral load were found containing both previously reported HLA alleles (HLA-B*57) and novel candidates that were not detected at individual allele level.

## References

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