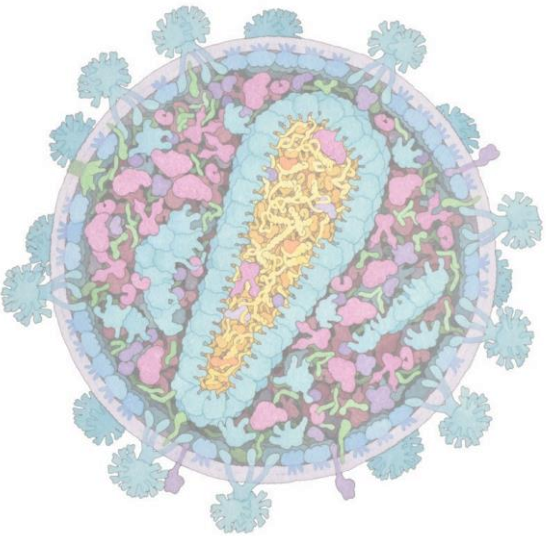


Resistance to HIV-1 pathogenesis in Viremic Non-Progressors (VNPs): a multiomics perspective

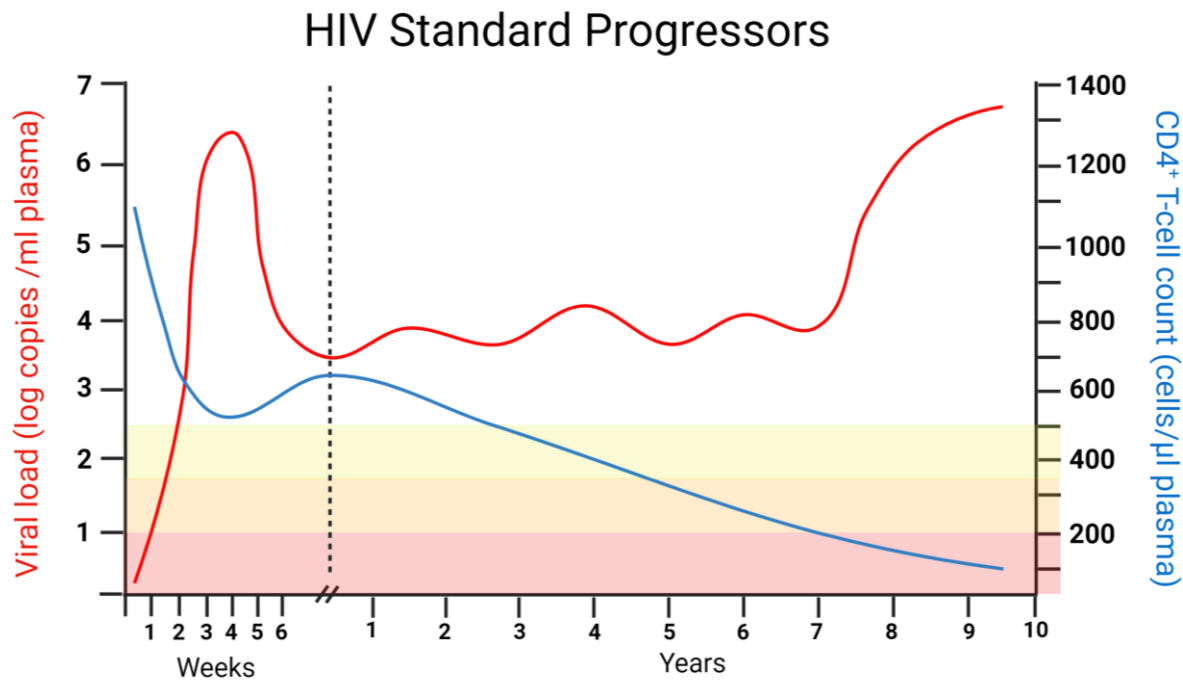
Ángel Bayón Gil

IrsiCaixa - AIDS Research Institute

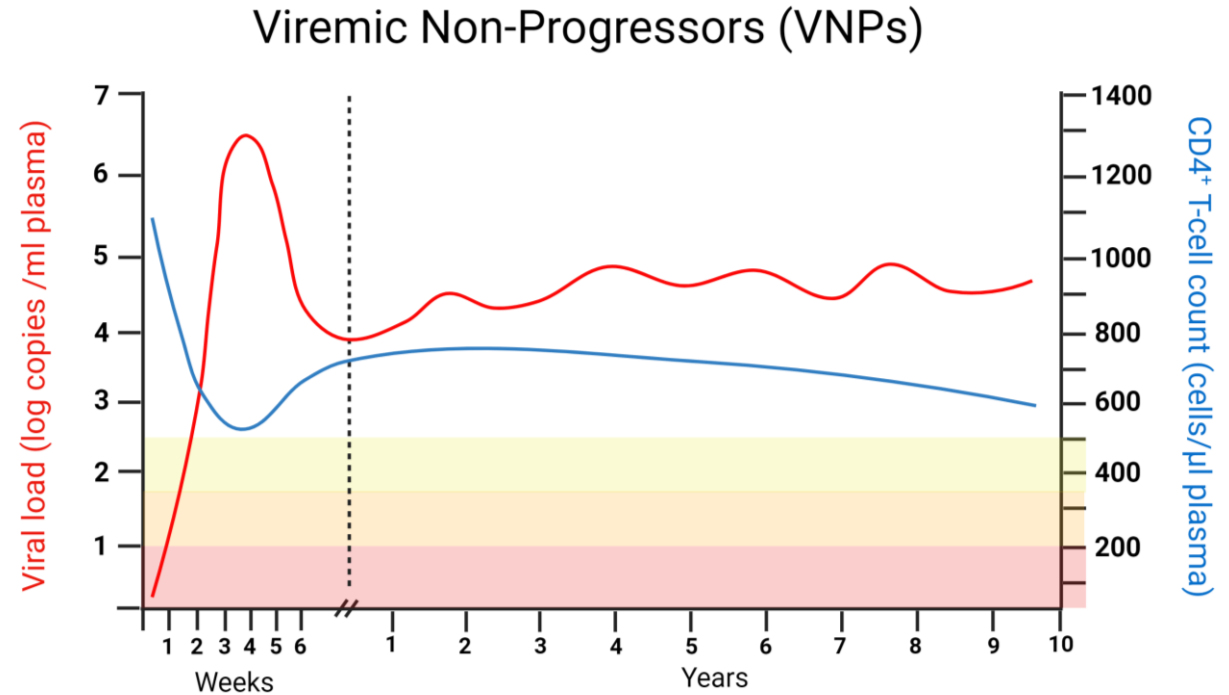
26th October 2023



Who are the VNP's? How do they differ from Standard Progressors?



≈90% PWH

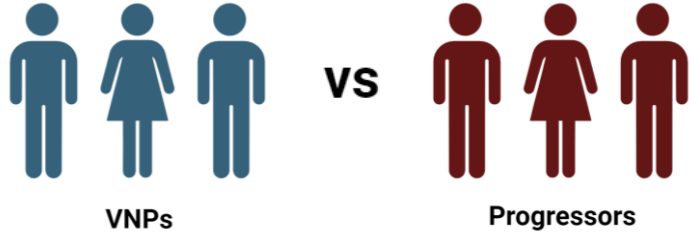


<0.1% PWH

Viremic Non-Progressors (VNPs) are an infrequent group of people with HIV who naturally preserve CD4⁺ T-cell counts despite uncontrolled viral replication.

What did we know about VNPs?

Studies in...



What did we know about VNPs?

Studies in...

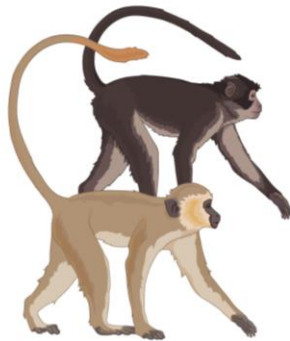


VNPs

vs



Progressors



Natural SIV hosts

African green monkey
Sooty mangabey

VNP-like

vs



Non-natural SIV hosts

Rhesus macaque

Progressor-like

VNP phenotype resembles that of natural SIV hosts.

What did we know about VNPs?

Studies in...

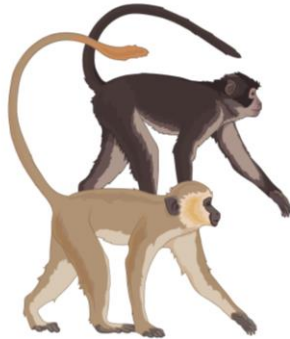


VNPs

vs



Progressors



Natural SIV hosts

African green monkey
Sooty mangabey

VNP-like

vs

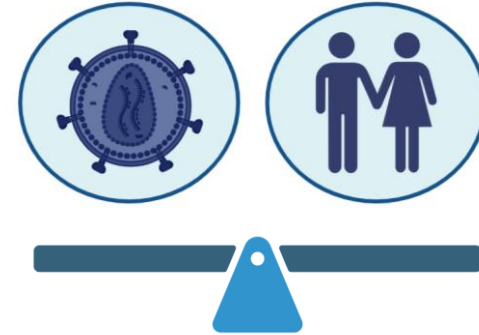


Non-natural SIV hosts

Rhesus macaque

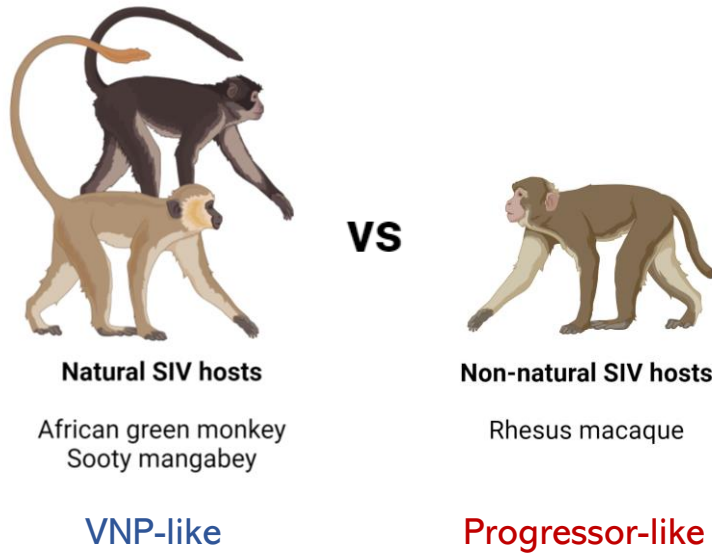
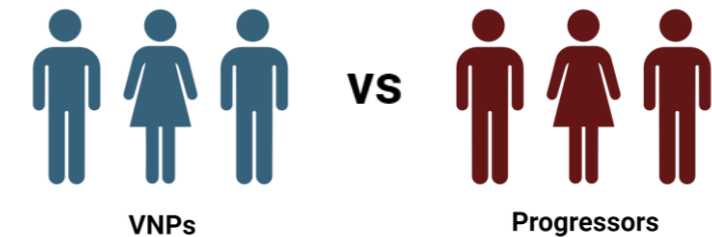
Progressor-like

Virus or host?

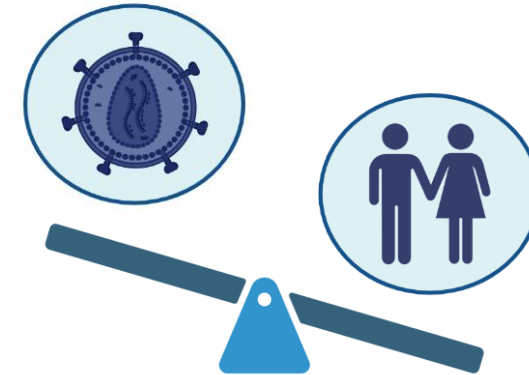


What did we know about VNPs?

Studies in...



Virus or host?



Similar viral properties

Different immune features

Important limitations

1. Very small studies
2. VNP / Control definition
3. Very specific focus



VNP phenotype is apparently determined by host-related factors rather than virus-related factors.

Our study group

Our study

1. Increased sample size
2. Early timepoints
3. Multiomics approach



Inclusion criteria

VNPs (n=16)

HIV Progressors (n=29)

Our study group

Our study

1. Increased sample size
2. Early timepoints
3. Multiomics approach



Inclusion criteria

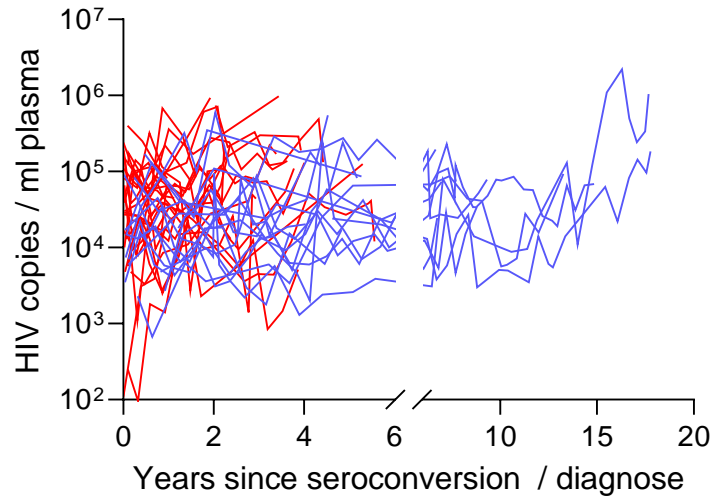
VNPs (n=16)

High VL (>10,000 cop/ml)

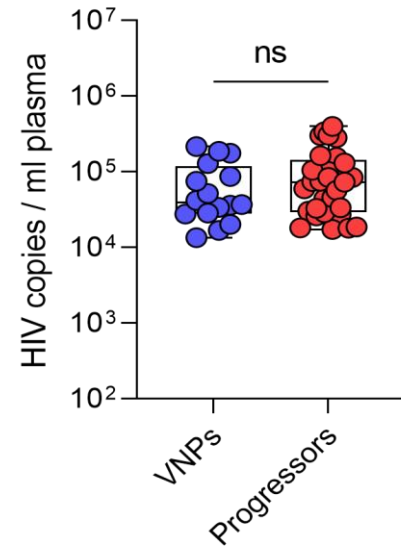
HIV Progressors (n=29)

High VL (>10,000 cop/ml)

Viral load pre-ART



Viral load setpoint



Our study group

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Inclusion criteria

VNPs (n=16)

High VL (>10,000 cop/ml)

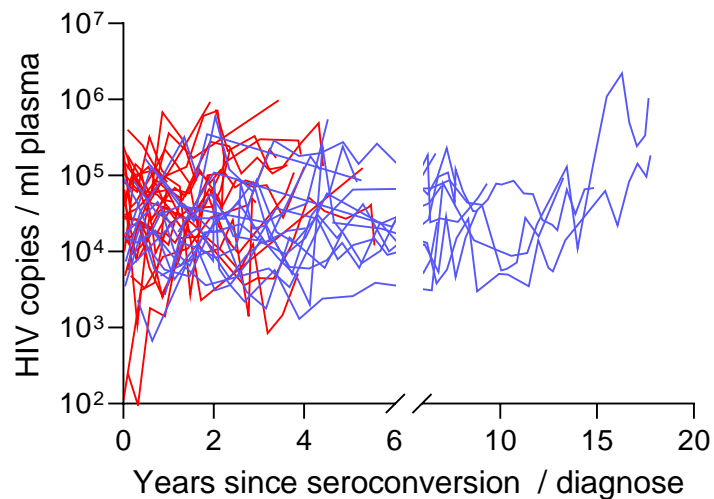
Slow CD4 decay
(<10% annual CD4 loss)

HIV Progressors (n=29)

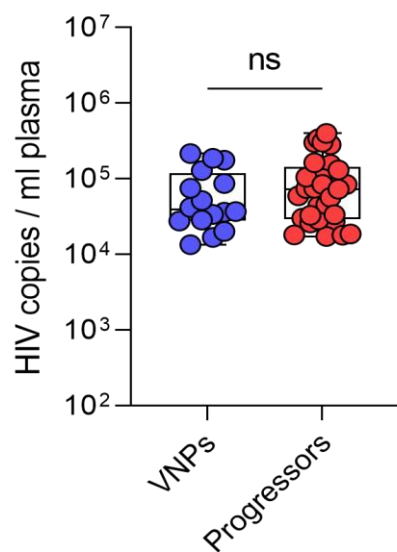
High VL (>10,000 cop/ml)

Quick CD4 decay
(>10% annual CD4 loss)

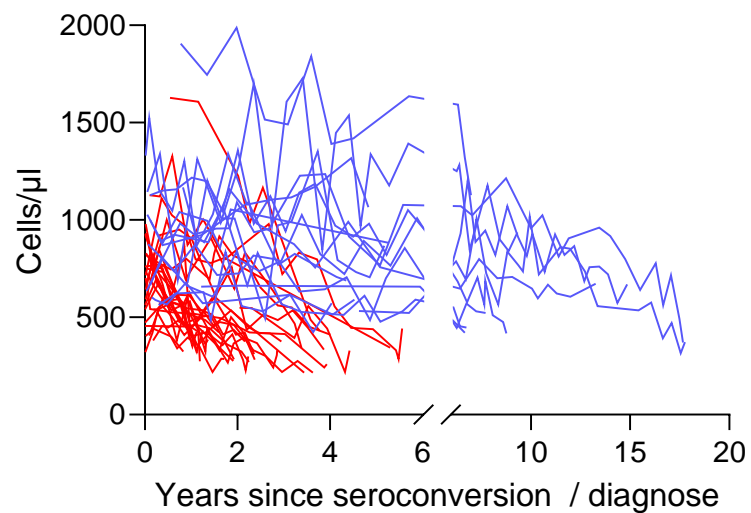
Viral load pre-ART



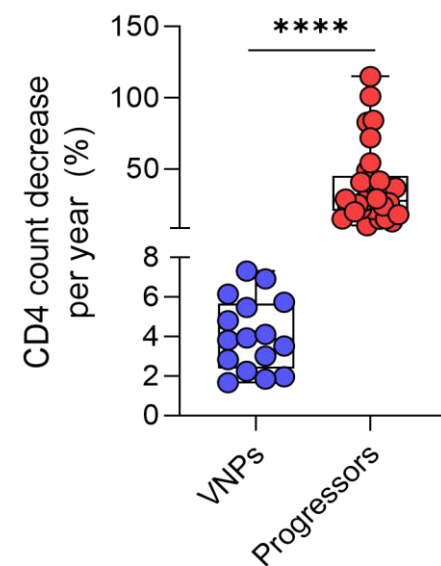
Viral load setpoint



CD4 counts pre-ART



CD4 decay rate



Our study group

Our study



1. Increased sample size
2. **Early timepoints**
3. Multiomics approach

Inclusion criteria

VNPs (n=16)

High VL (>10,000 cop/ml)

Slow CD4 decay
(<10% annual CD4 loss)

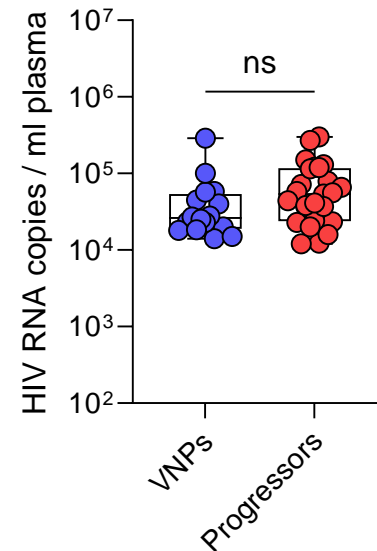
HIV Progressors (n=29)

High VL (>10,000 cop/ml)

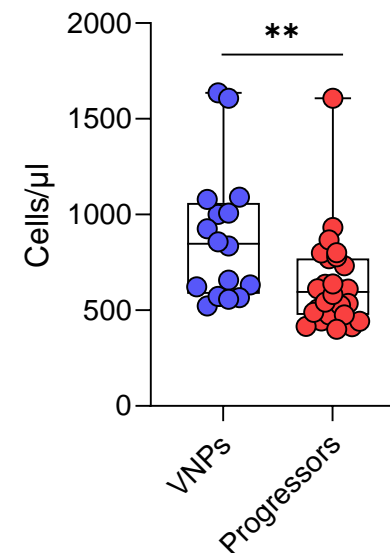
Quick CD4 decay
(>10% annual CD4 loss)

Samples pre-ART

Viral load pre-ART



CD4⁺ T-cell count pre-ART



VNPs: old questions, new solutions

Our study

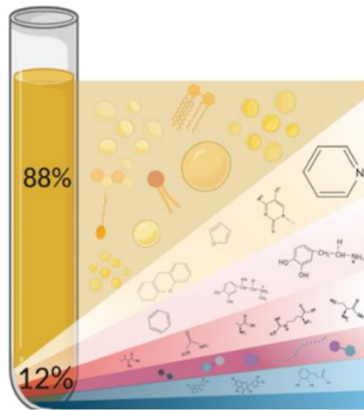
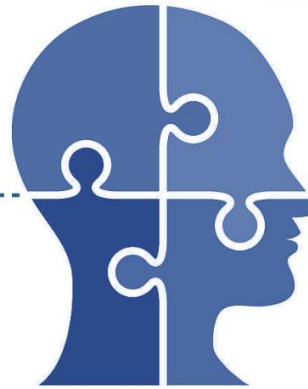
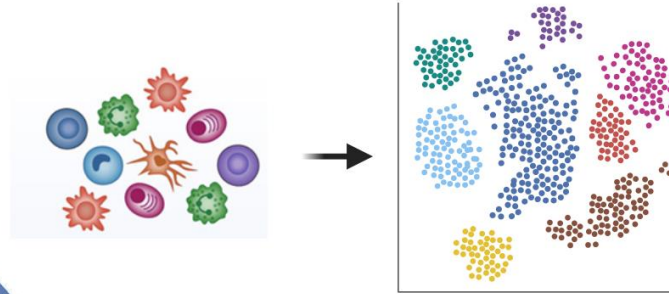


1. Increased sample size
2. Early timepoints
3. **Multomics approach**

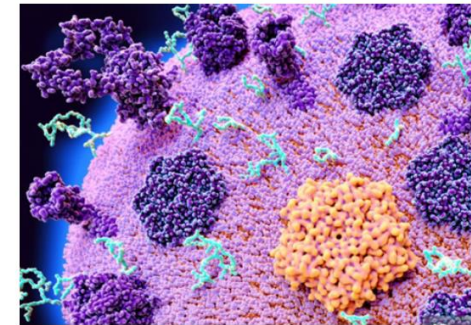
Genomics



Transcriptomics

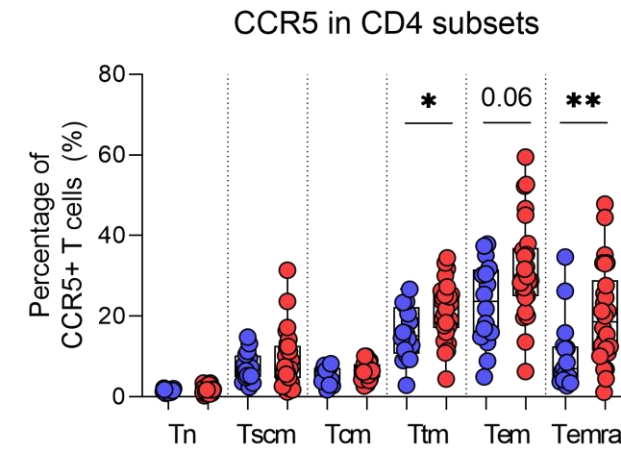
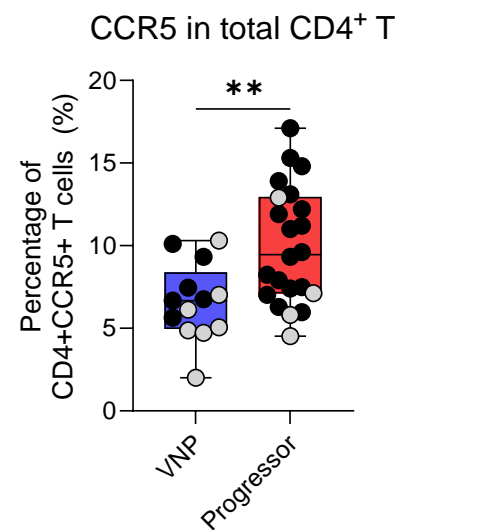
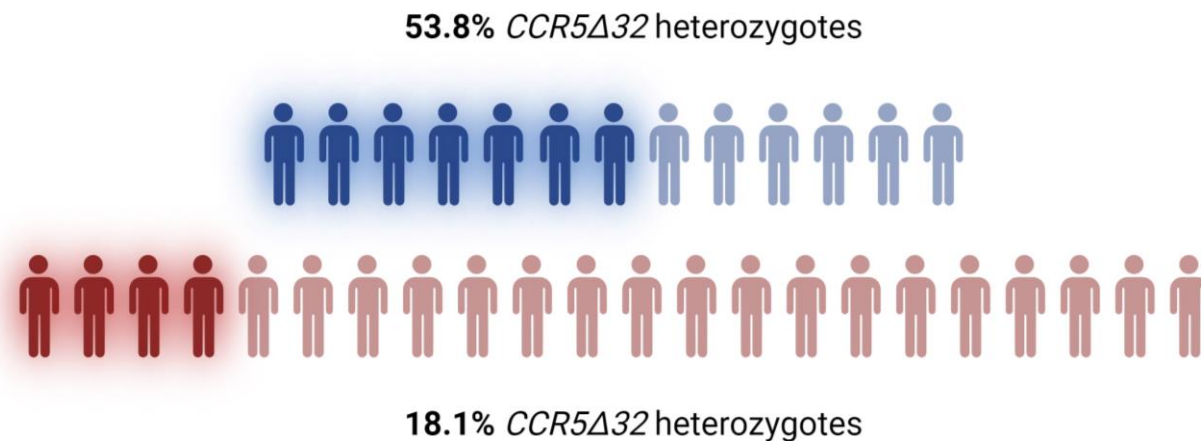
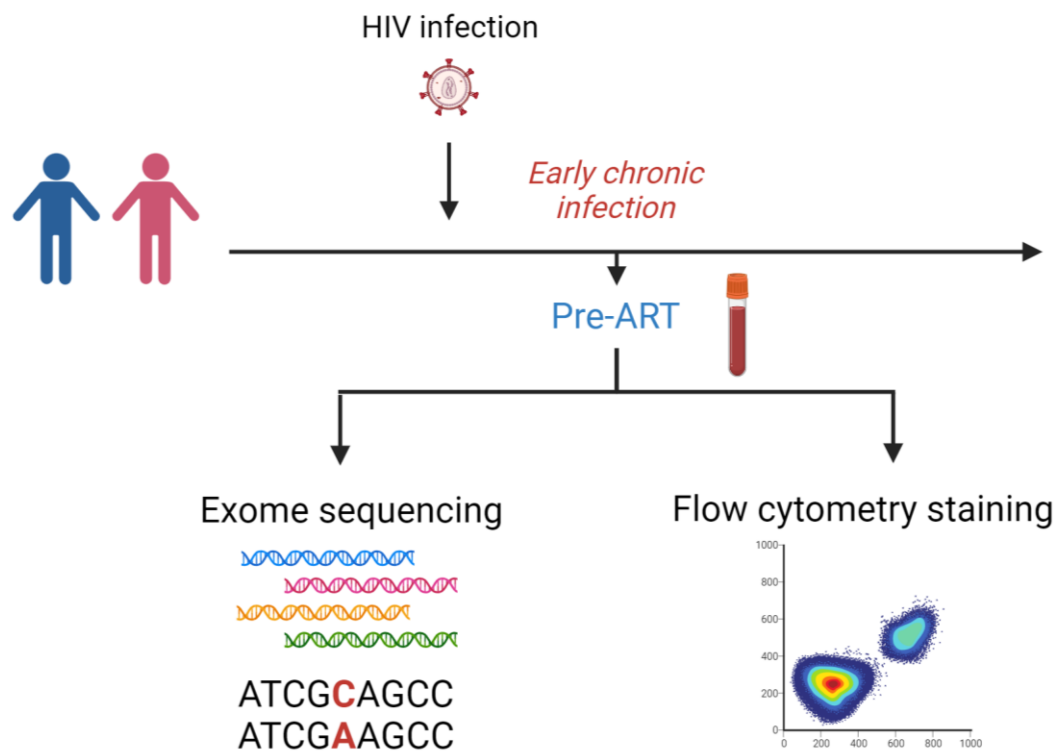


Metabolomics



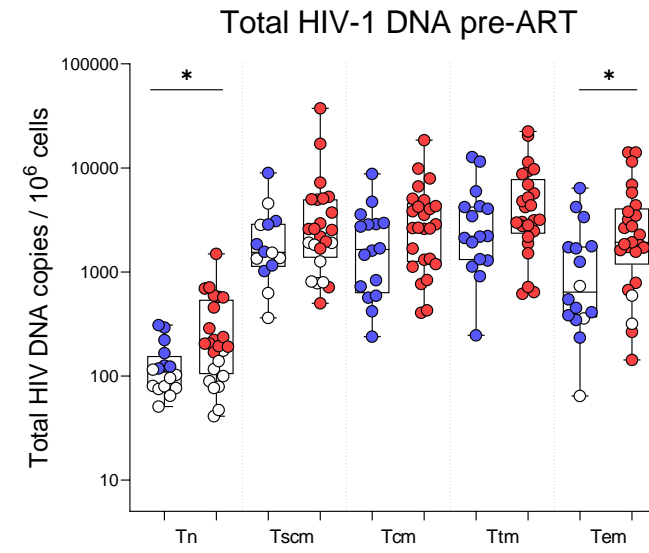
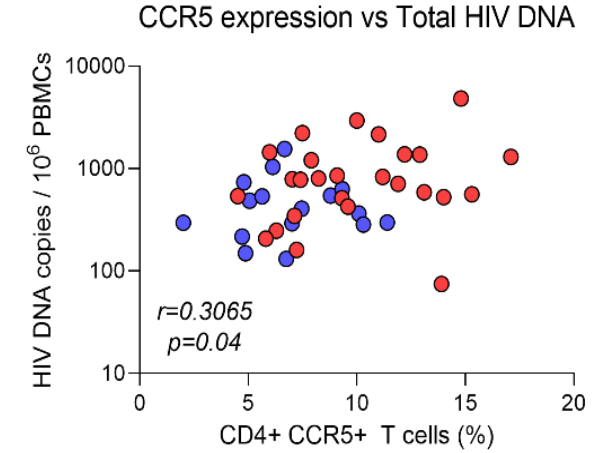
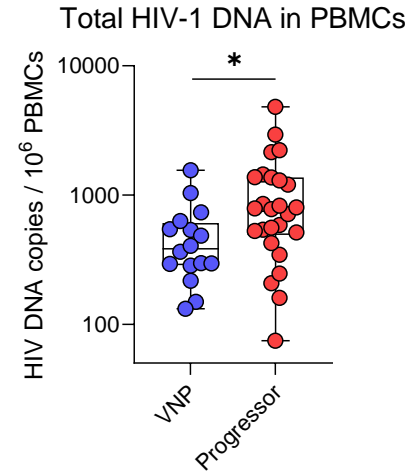
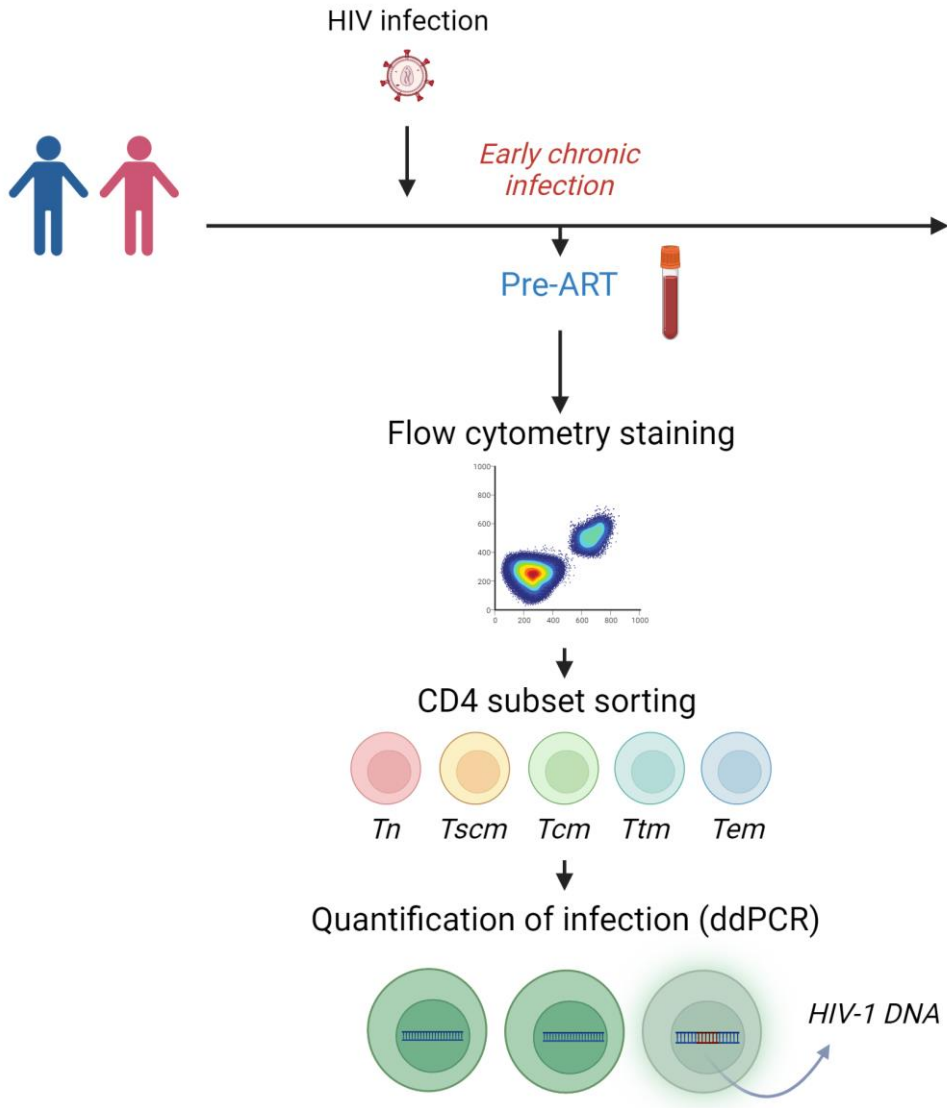
Plasma/cell marker validation

Looking at VNPs from genomics



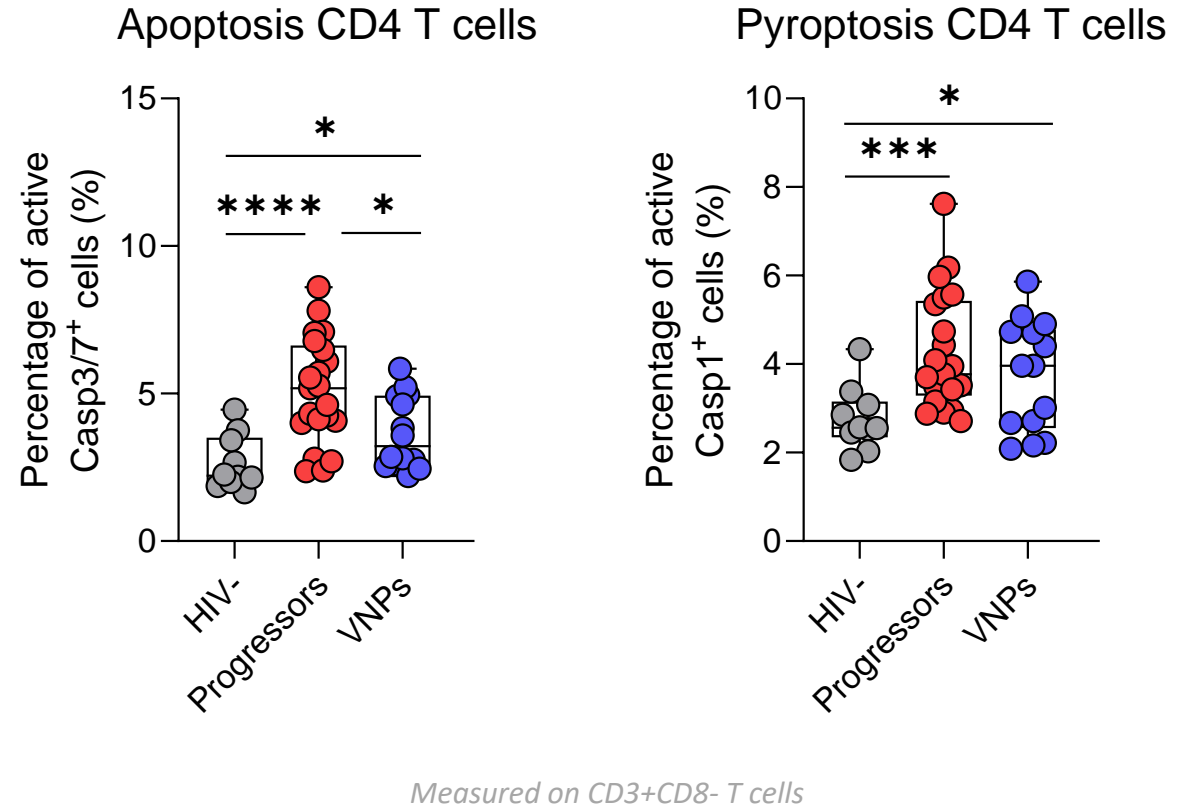
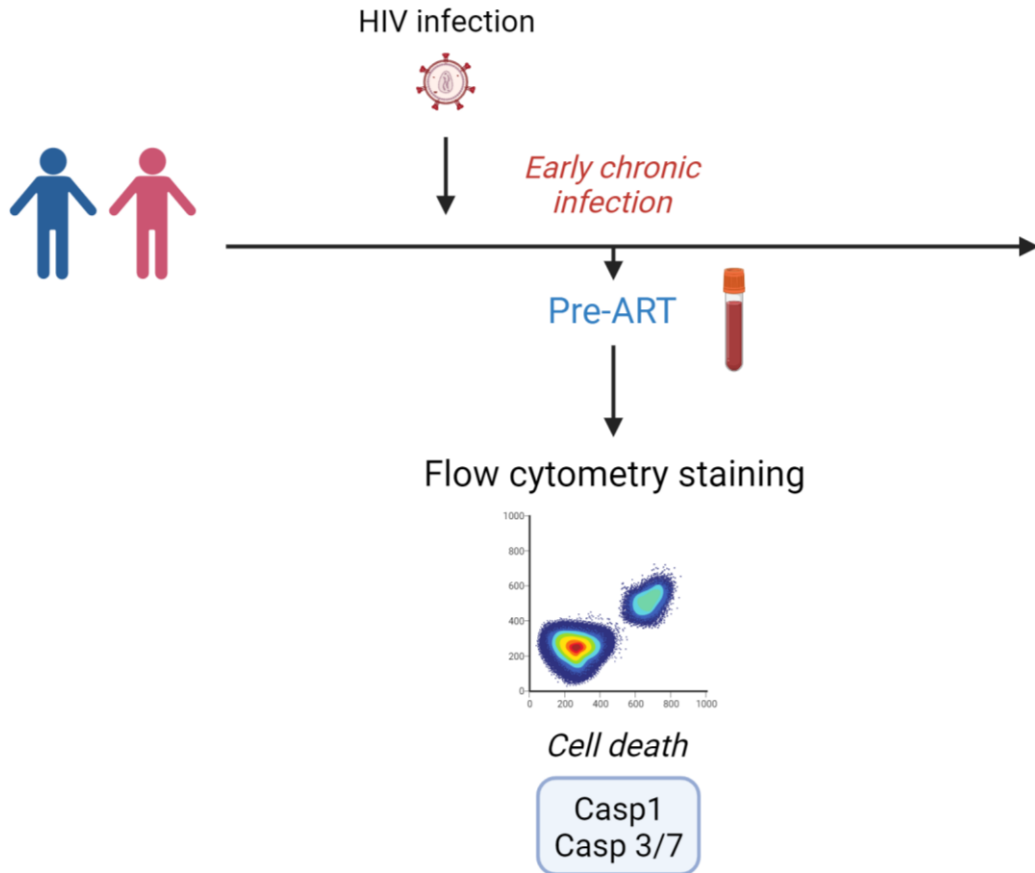
CCR5Δ32 deletion in heterozygosity is more frequent in VNPs, and CCR5 protein expression is lower.

Does CCR5 genotype affect rates of cellular infection?



VNPs have lower rates of cellular infection in absence of ART.

Do VNPs have different levels of CD4⁺ T cell death?

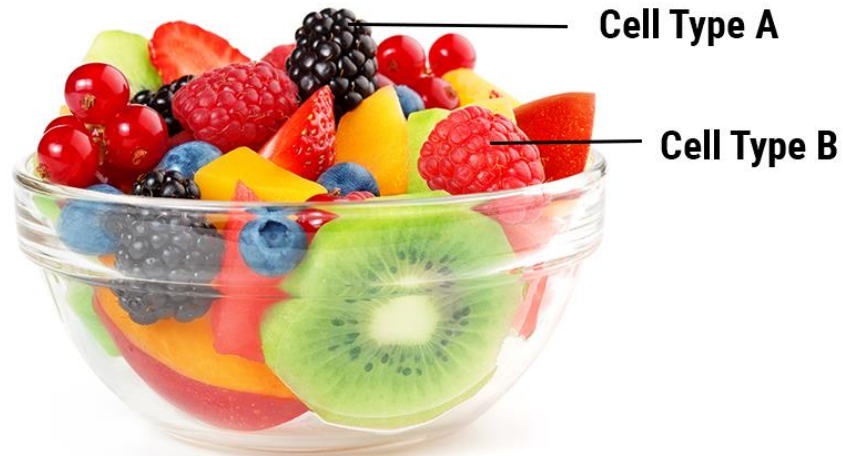


VNPs have lower levels of bystander apoptosis in the CD4 compartment.

Looking at VNPs from transcriptomics

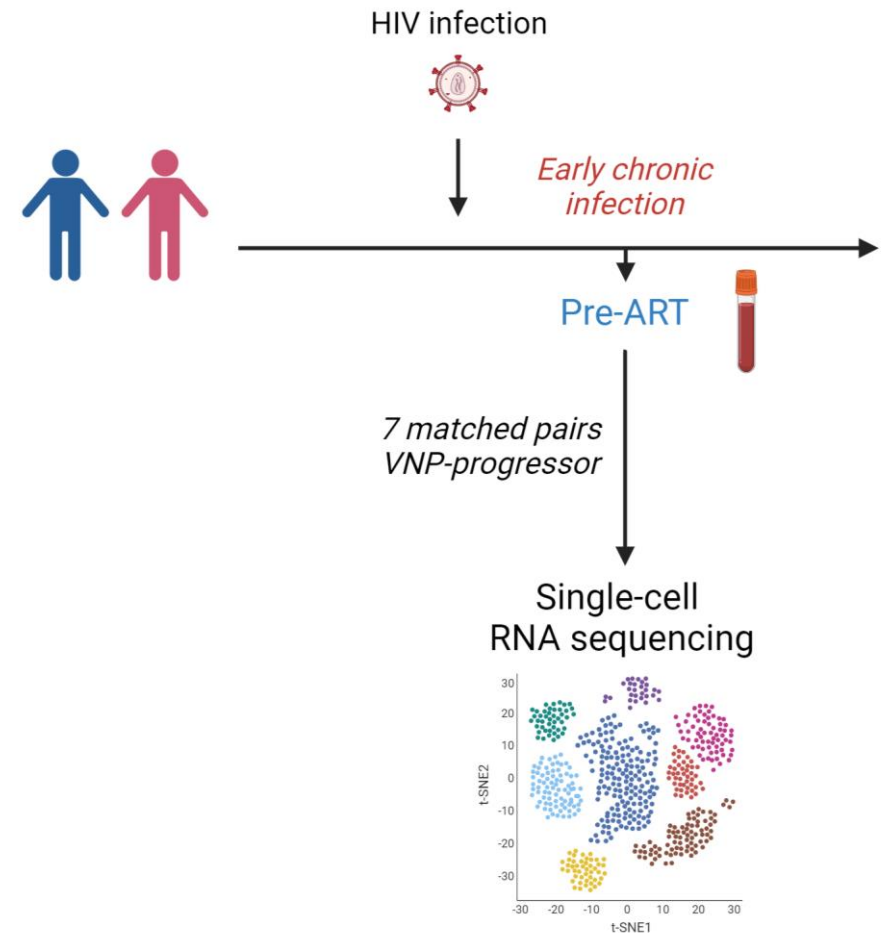


Bulk RNA Seq



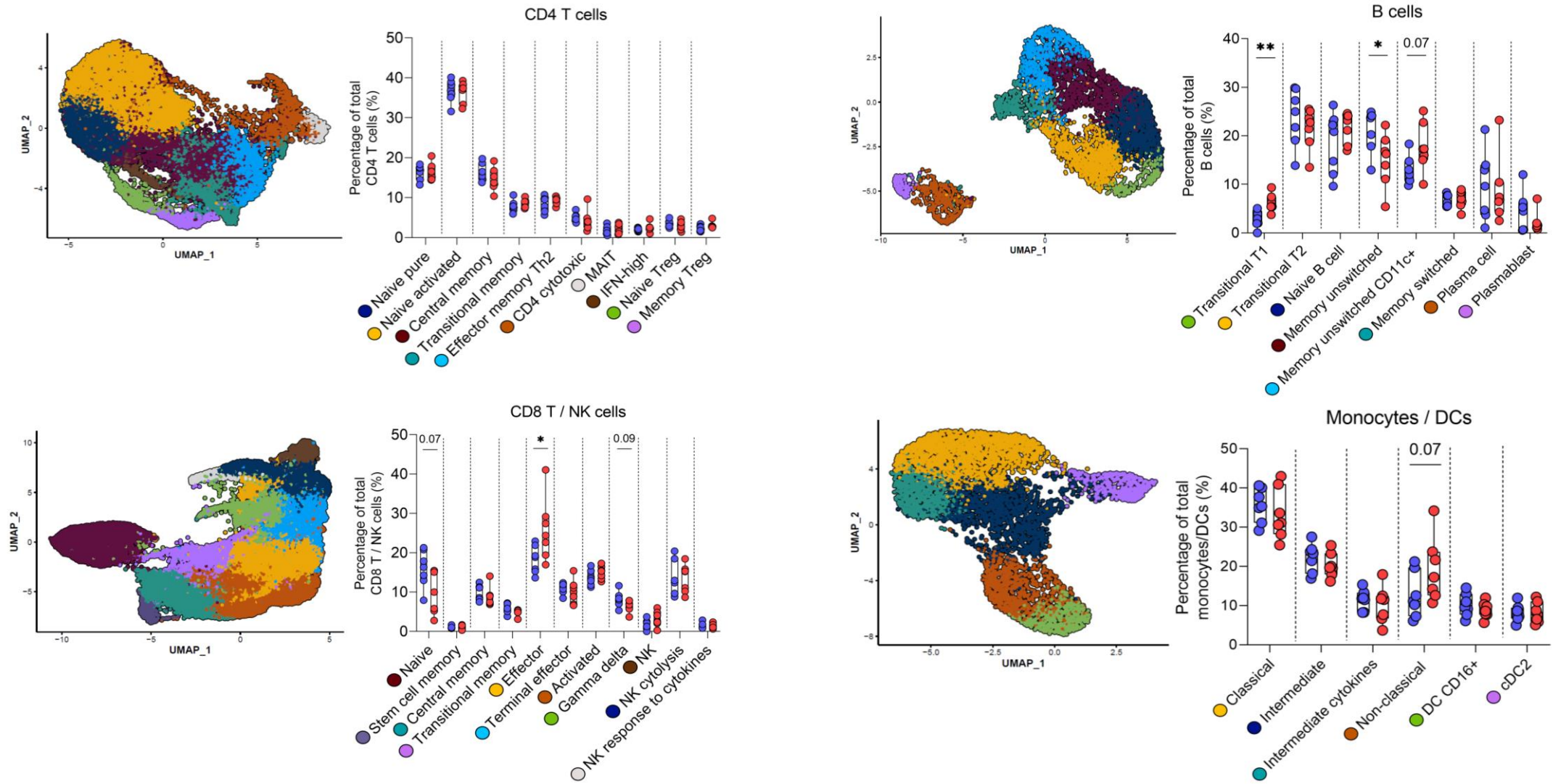
SCRNA Seq

<https://perkinelmer-appliedgenomics.com/>



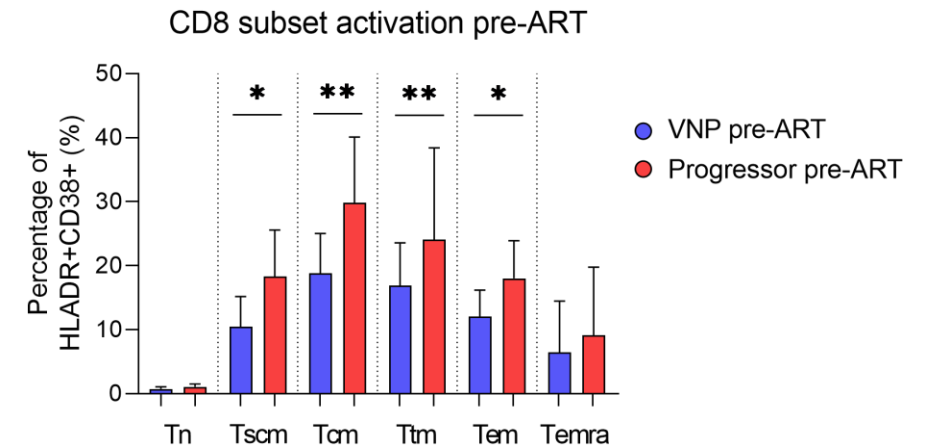
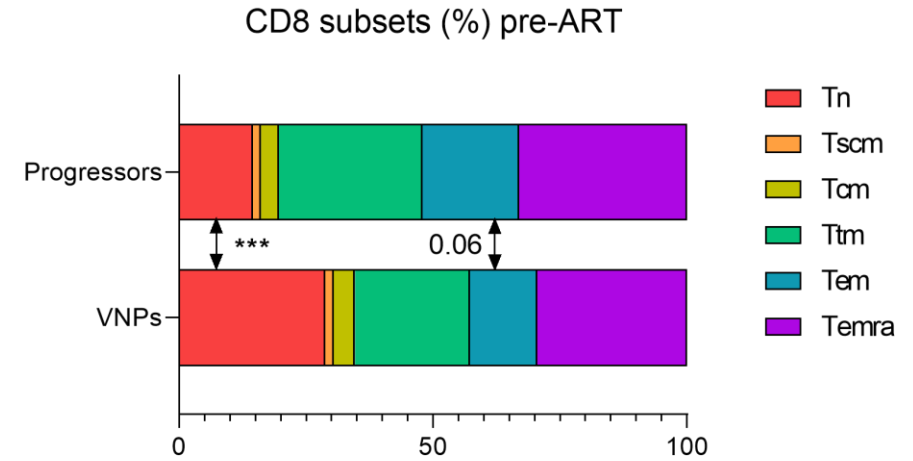
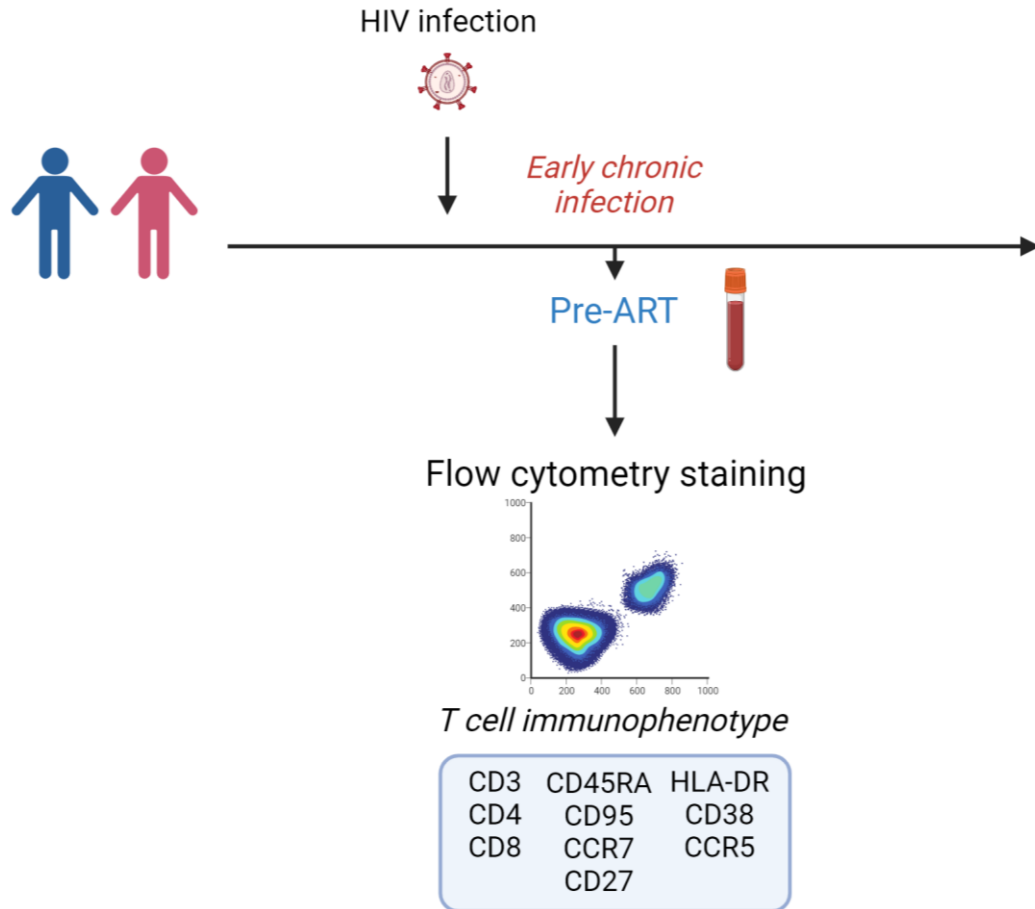
Single-cell RNA sequencing (scRNA seq) permits the identification of the transcriptome of individual cells.

Do VNPs differ in the proportion of cell subsets?



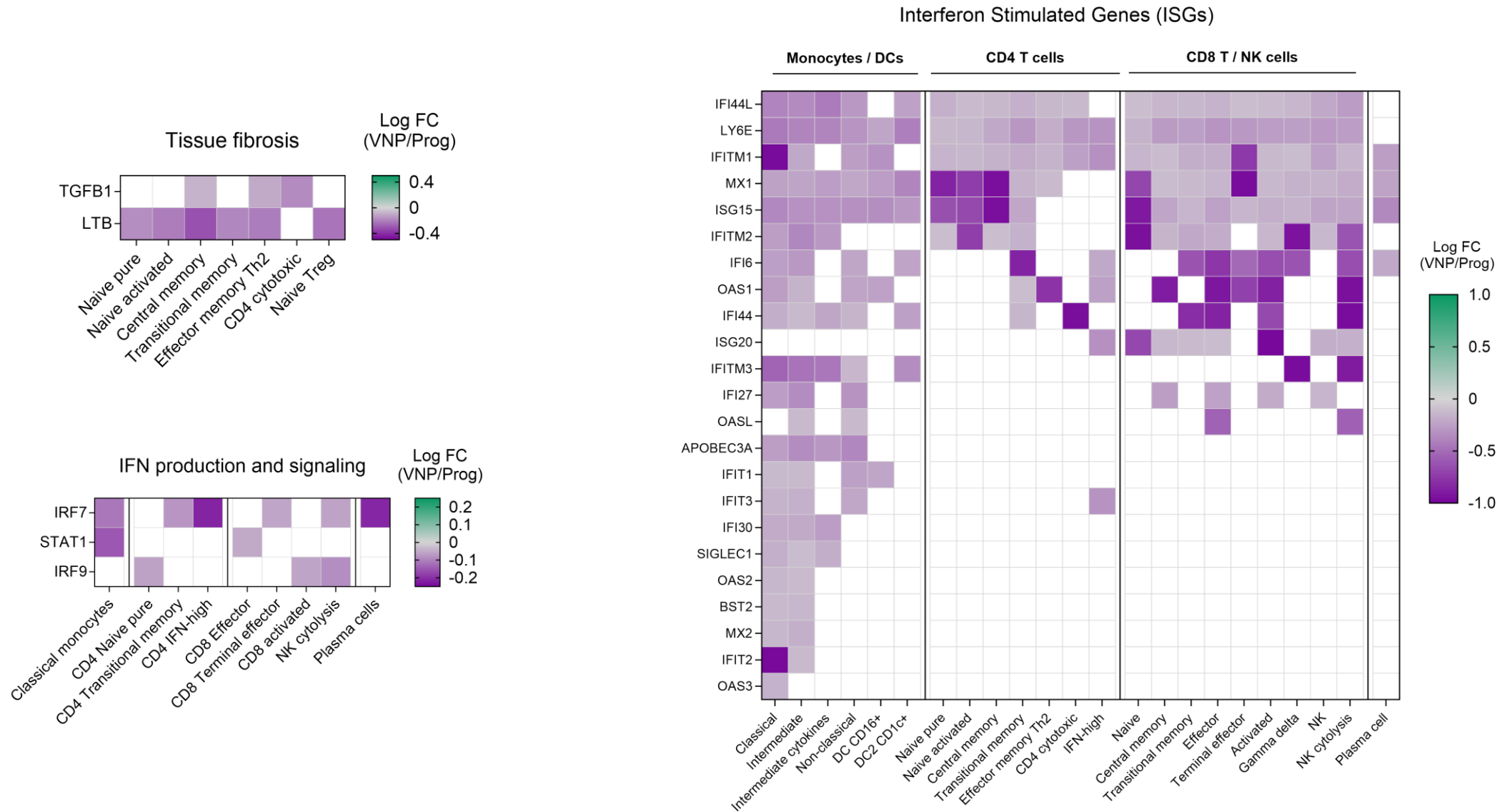
VNPs have a similar CD4 T cell compartment as Progressors, but a less differentiated CD8 T cell compartment.

Do CD8⁺ T cells from VNPs differ in their phenotype?



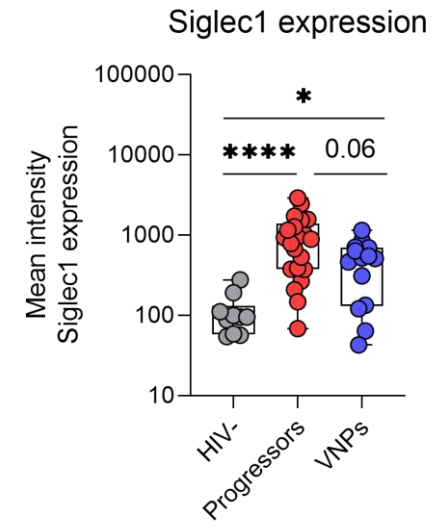
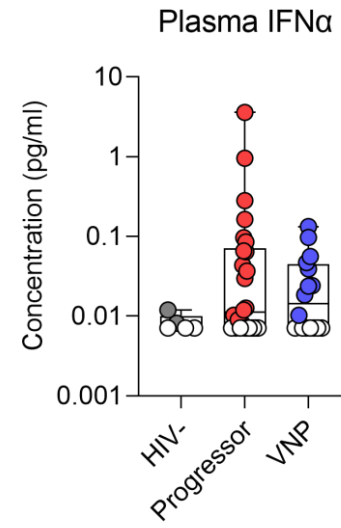
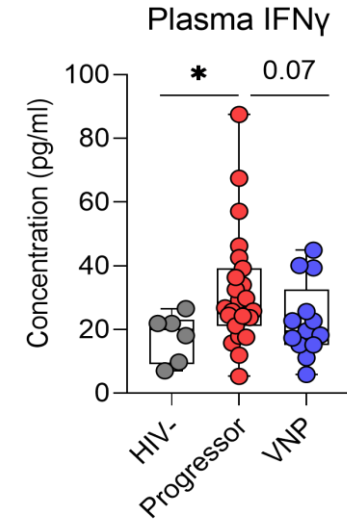
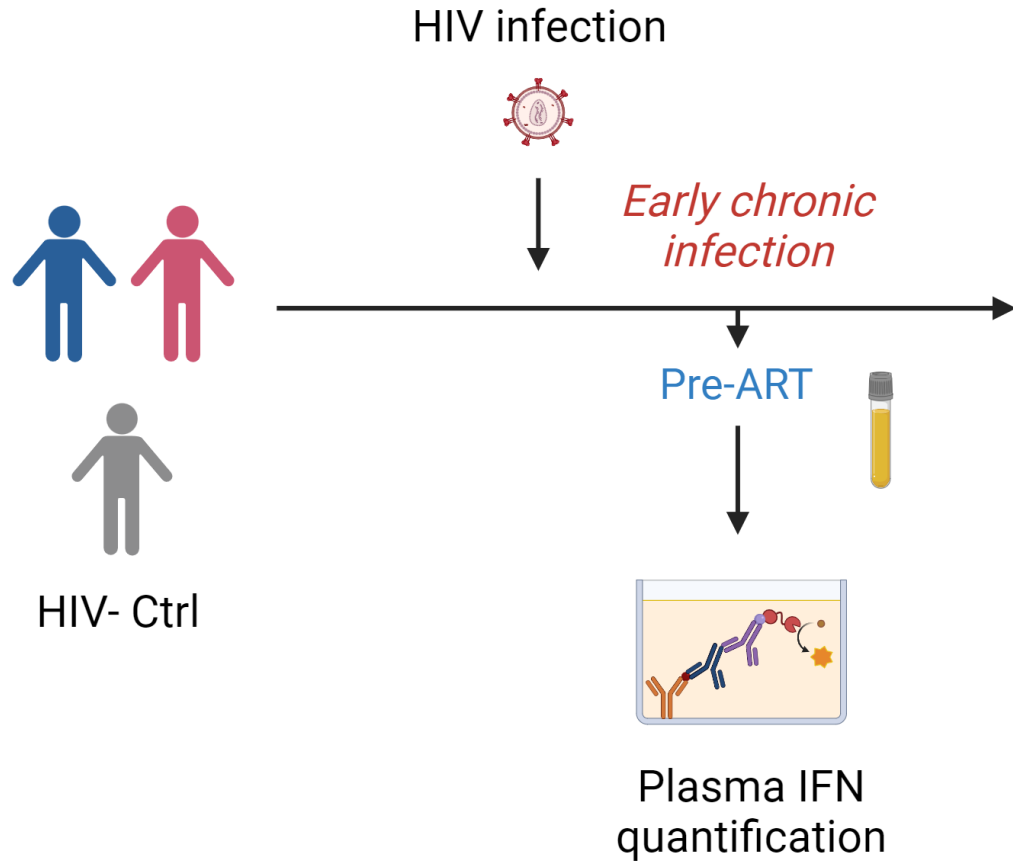
VNPs have lower differentiation and activation of the CD8⁺ T cell compartment.

Which gene expression signatures are associated with VNPs?



VNPs show downregulation of genes involved in interferon pathway and tissue fibrosis.

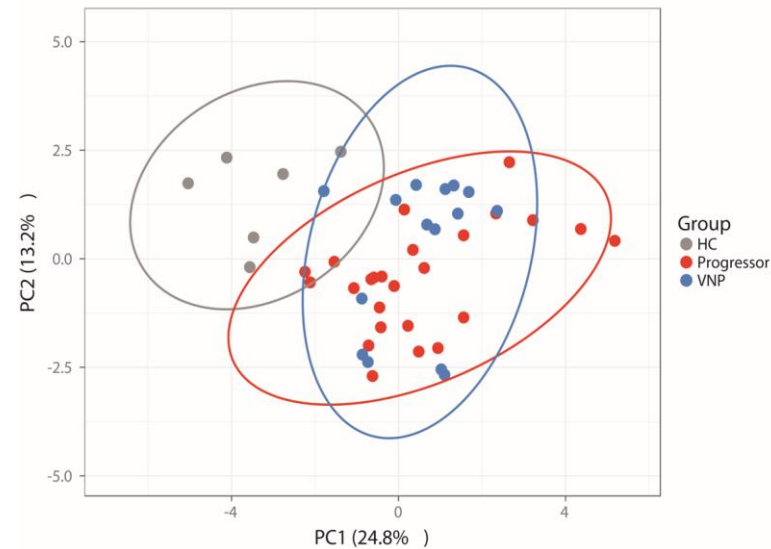
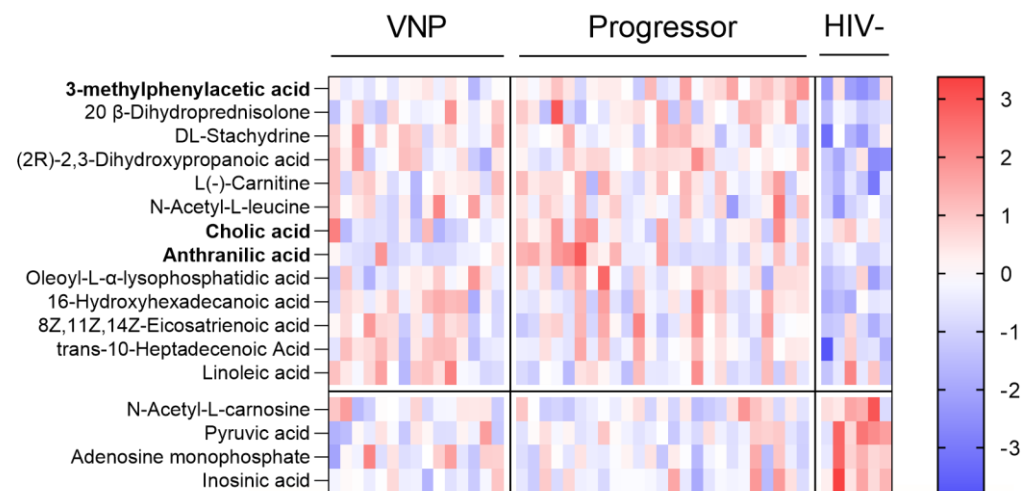
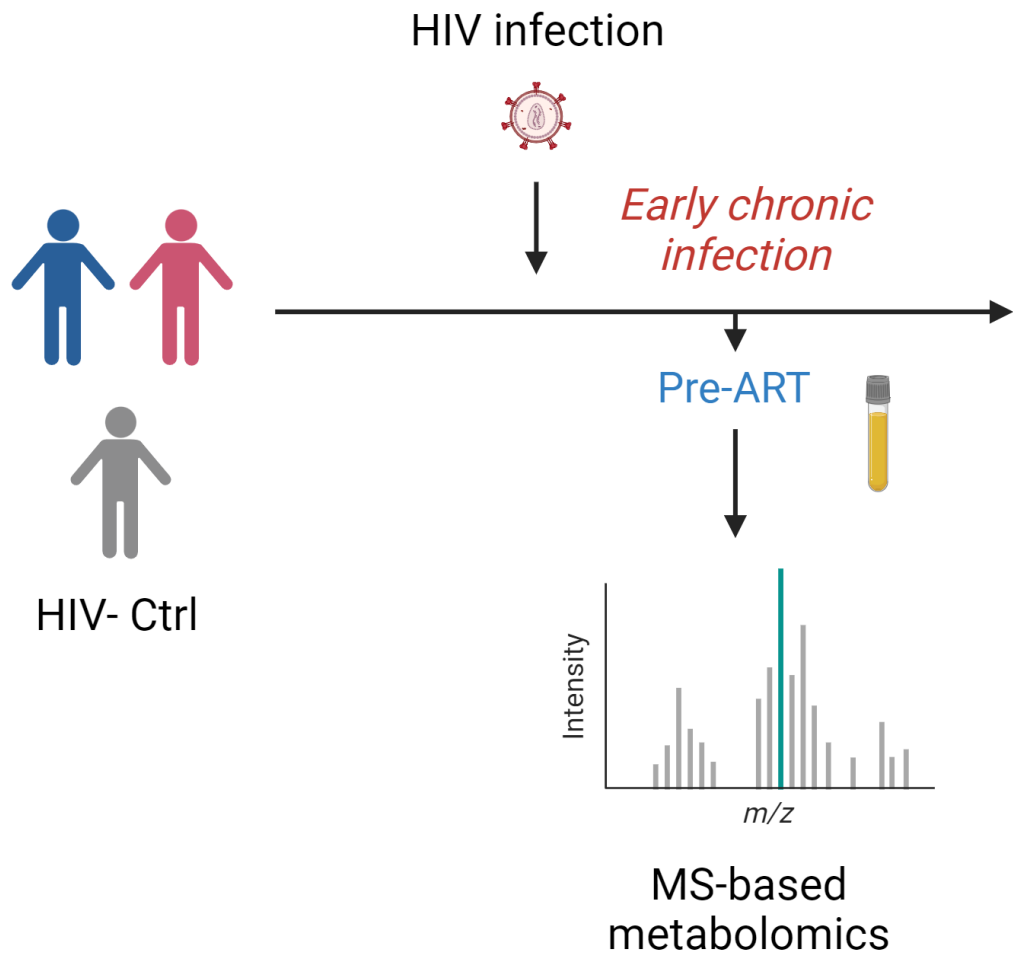
Do VNPs differ in the plasma levels of IFN in chronic infection?



Measured on CD14⁺ myeloid cells.

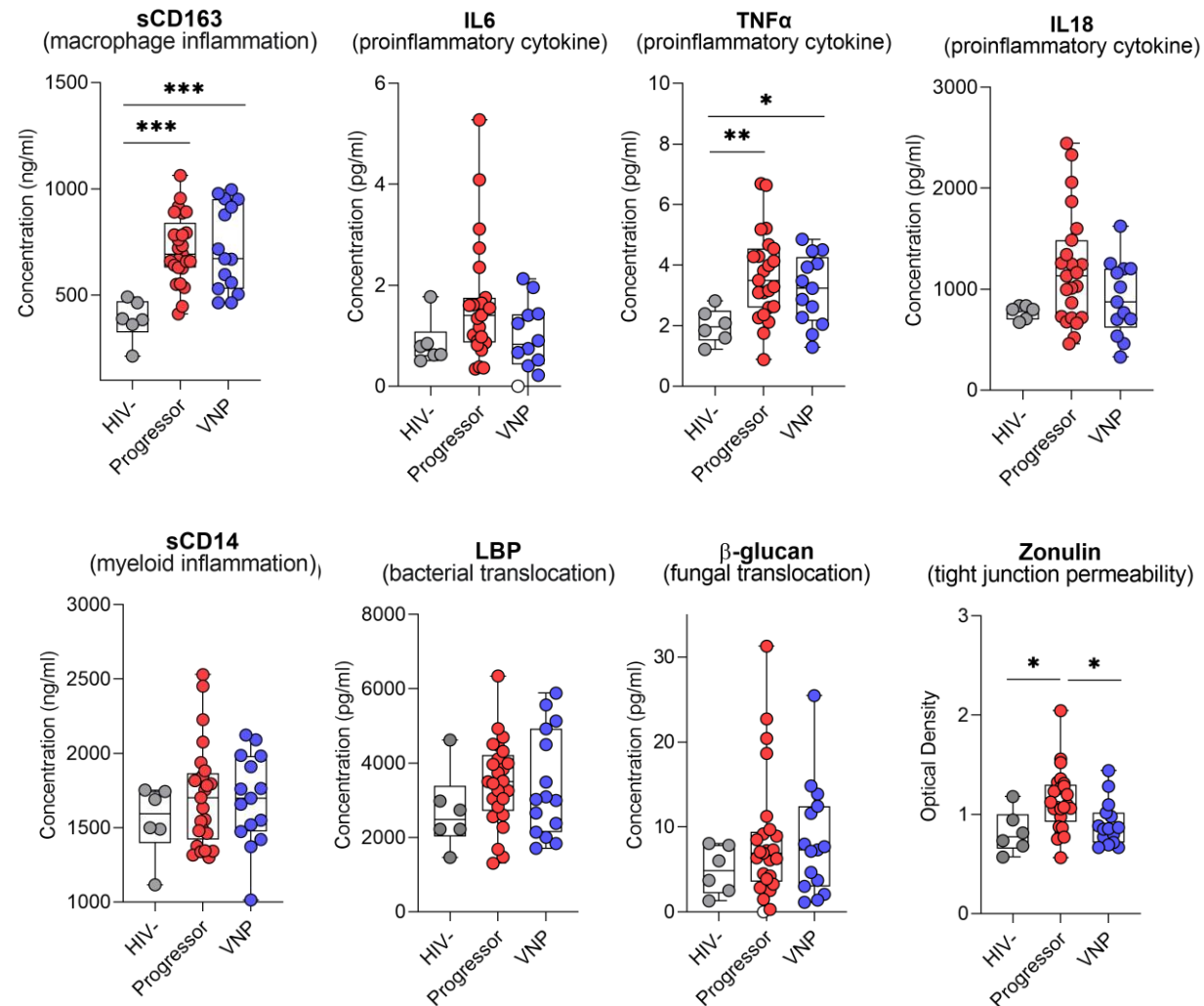
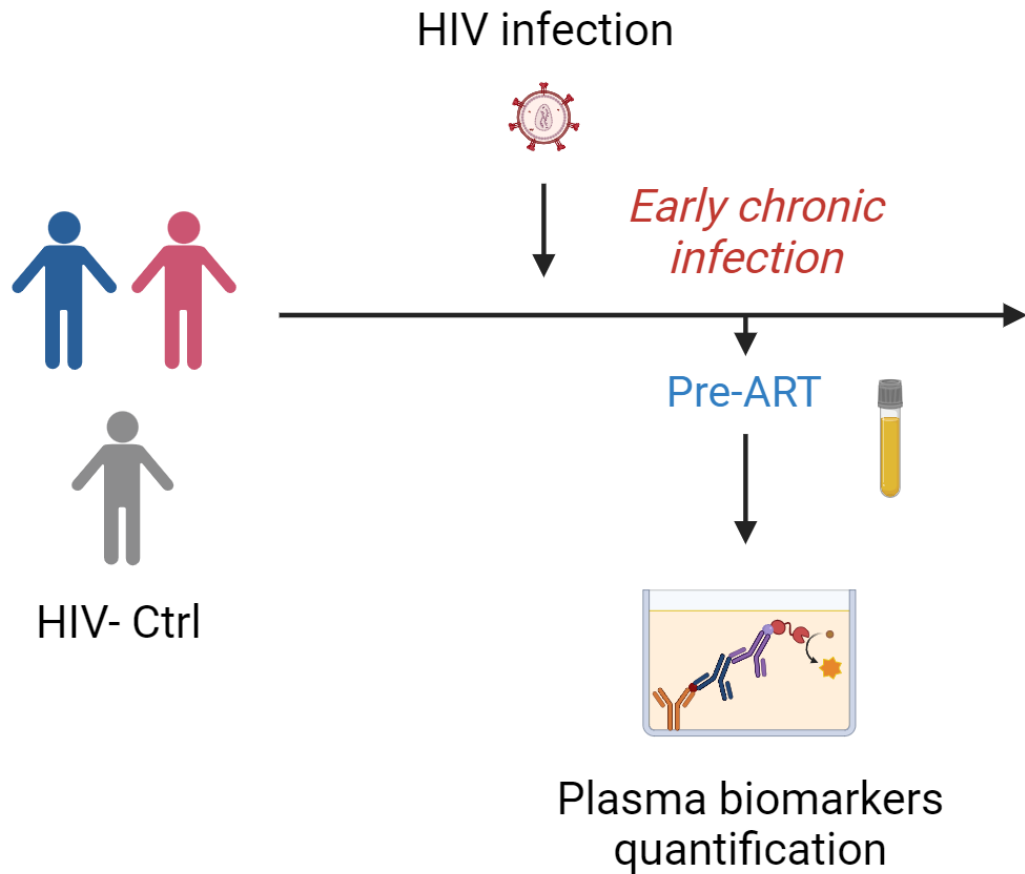
VNPs show lower plasma levels of IFN during chronic infection.

Looking at VNPs from metabolomics



VNPs and Progressors share important similarities in the plasma metabolomic profile.

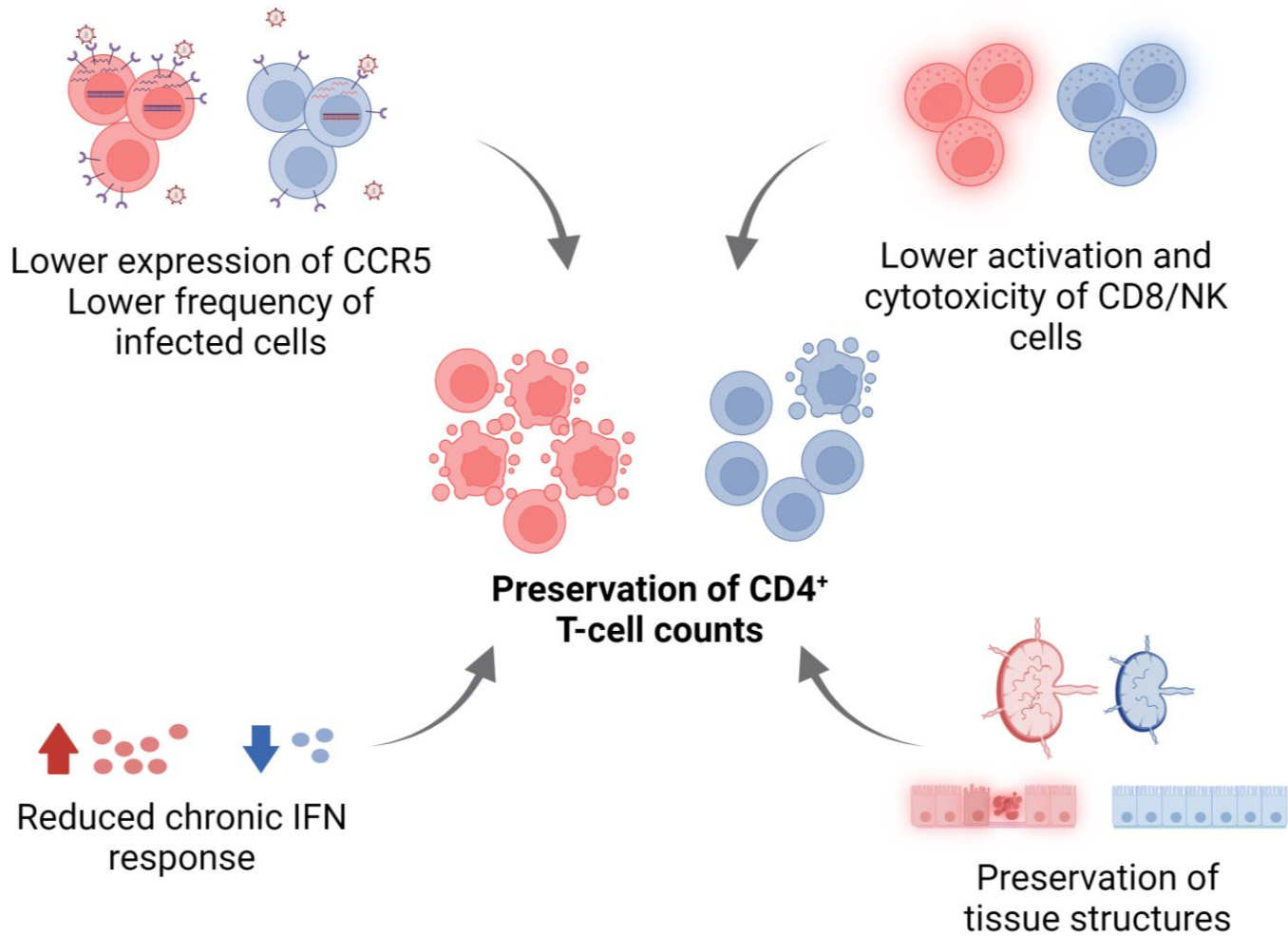
Do VNPs differ in other inflammatory pathways?



VNPs show lower plasma levels of zonulin than Progressors, but similar levels of other markers of systemic activation.

Summary

The VNP phenotype is complex, multifactorial...
...and might be heterogenous.



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