Constitutive NKG2A levels and timing of antiretroviral therapy initiation impact the potential role of NK cells after treatment interruption

-the pVISCONTI study-

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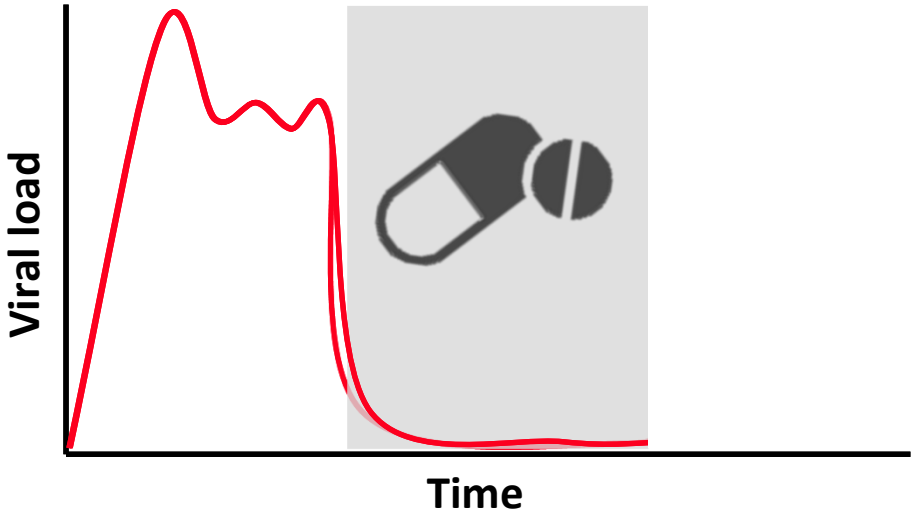
- December 2022, 14

Martin Delaney Collaboratories for HIV Cure Research
NIAID/NHLBI/NIDDK/NINDS/NIDA
1UM1AI164562-01

No conflit of interest to disclose

Post-treatment control of HIV

VISCONTI
(Viro-Immunological Sustained CONtrol after Treatment Interruption)



- Early treatment

→ Estimated delay to treatment initiation : 31 days

- Treatment for ~3 years
- 30 patients who maintained control for >12 years

5%

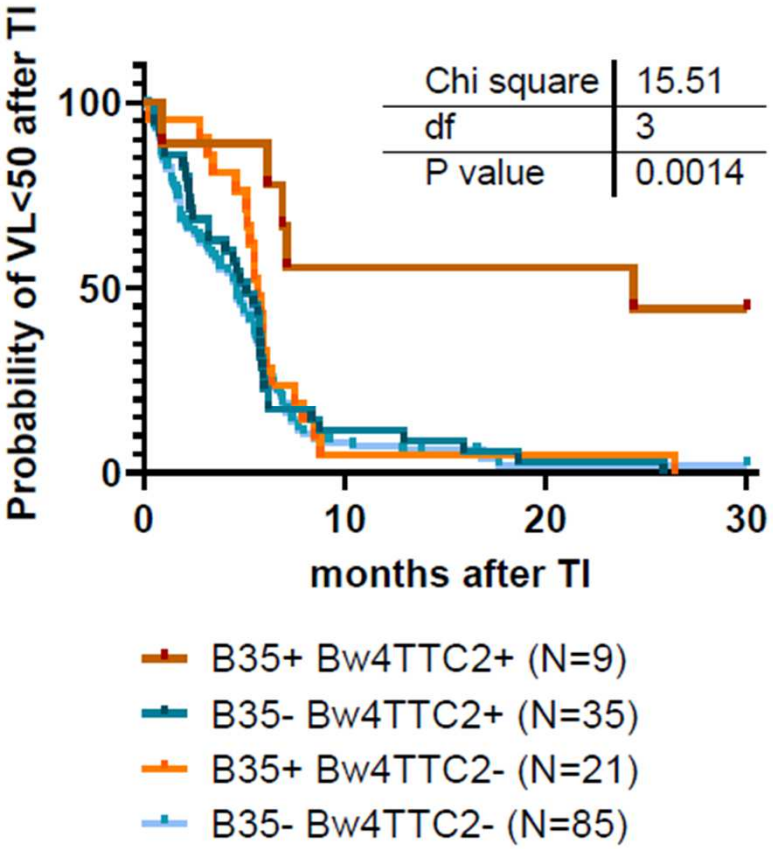
Saez-Cirion *et al.*, Plos Path 2013

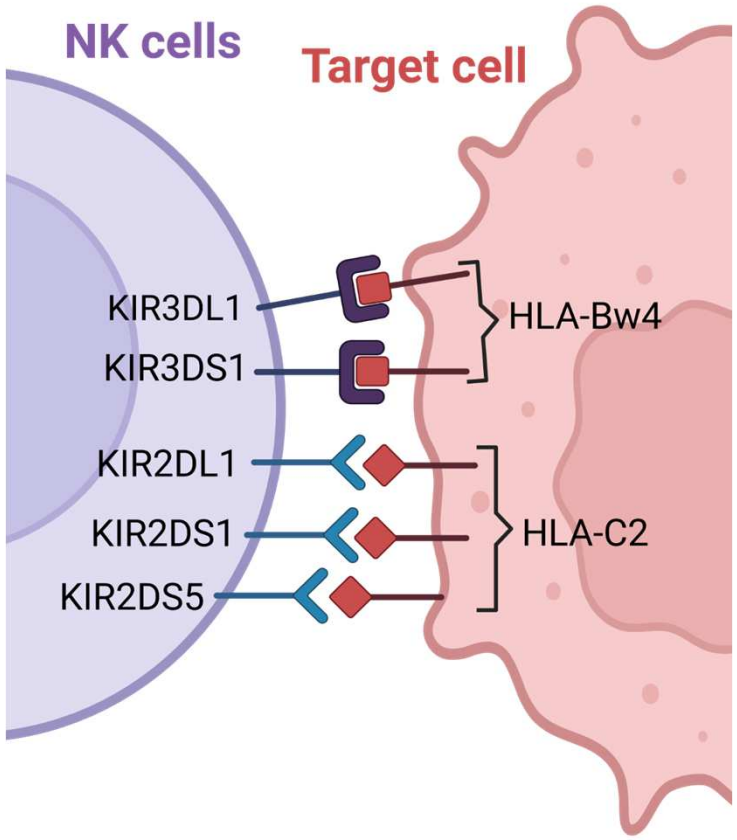
Understanding the immune mechanisms underlying the post-treatment control of HIV could help develop HIV remission strategies.

Characteristics of the VISCONTI Post-Treatment Controllers (PTC)

Genetic background

Enrichment in HLA-B35/Bw4TTC2





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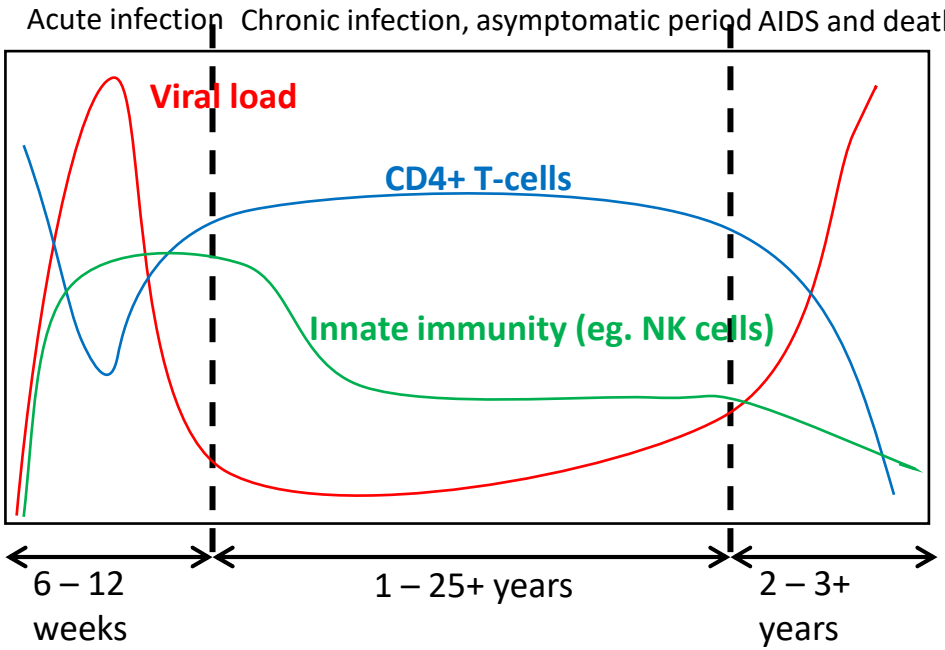
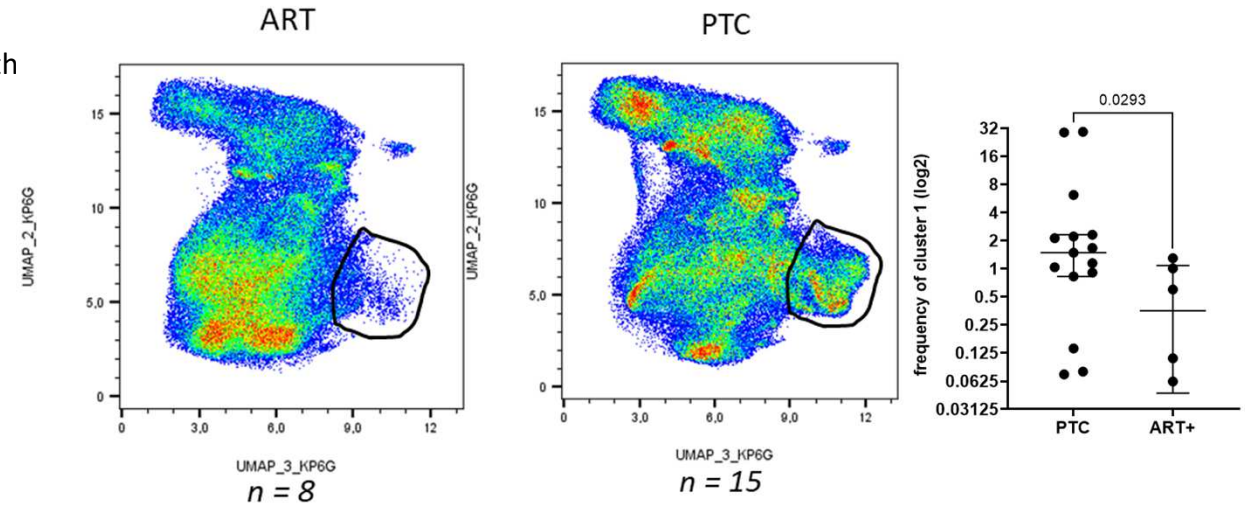
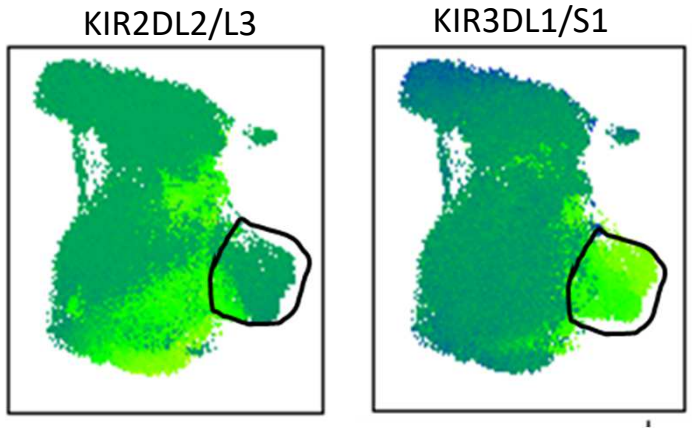
Sáez-Cirión, A et al (2013). PLoS Pathogens

NK cells could be involved in the post-treatment control of HIV







→ Strong cytotoxicity against virus infected cells *(CD16+ CD56dim)*

→ Immune-regulatory role (production of cytokines) *(CD16+/-CD56bright)*

Essat, Chapel et al submitted

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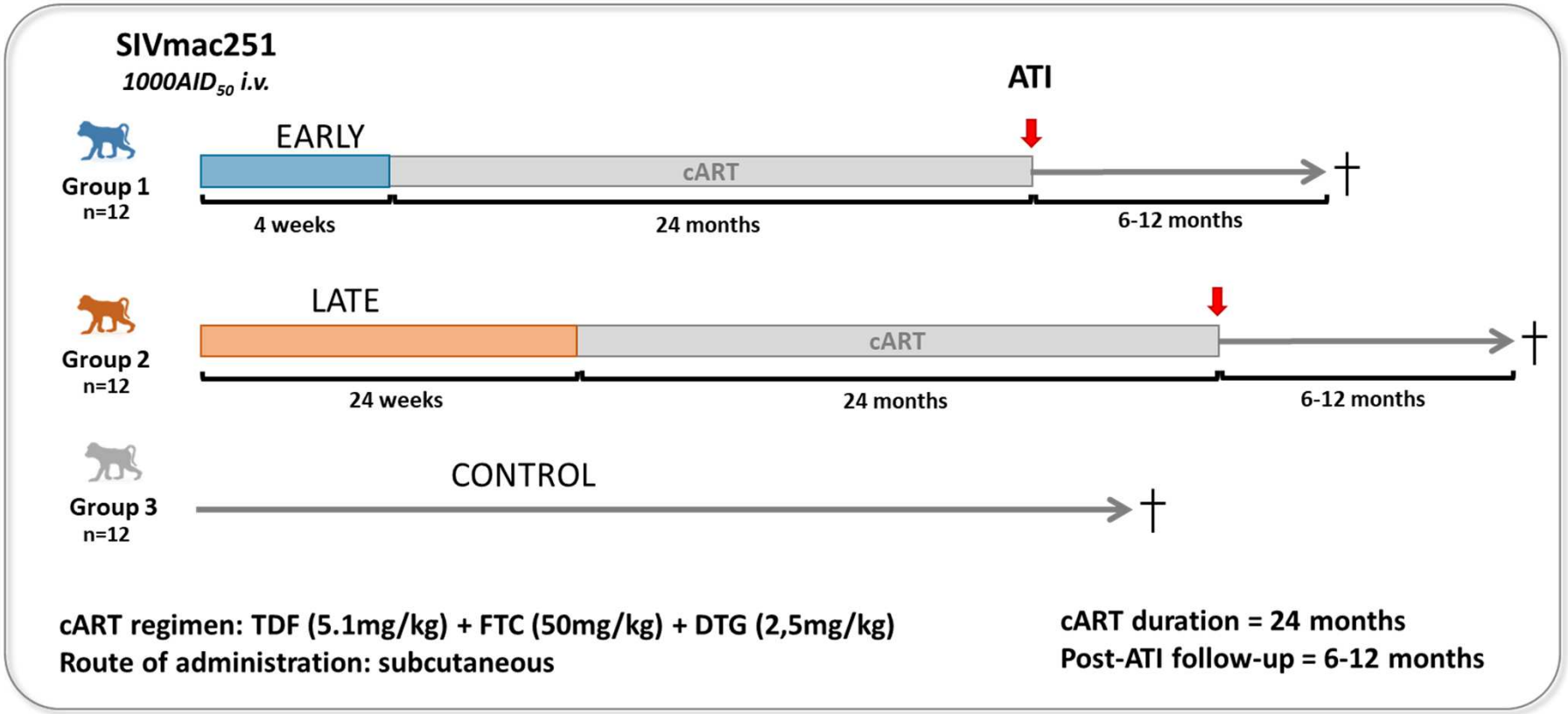
The pVISCONTI study goal & design

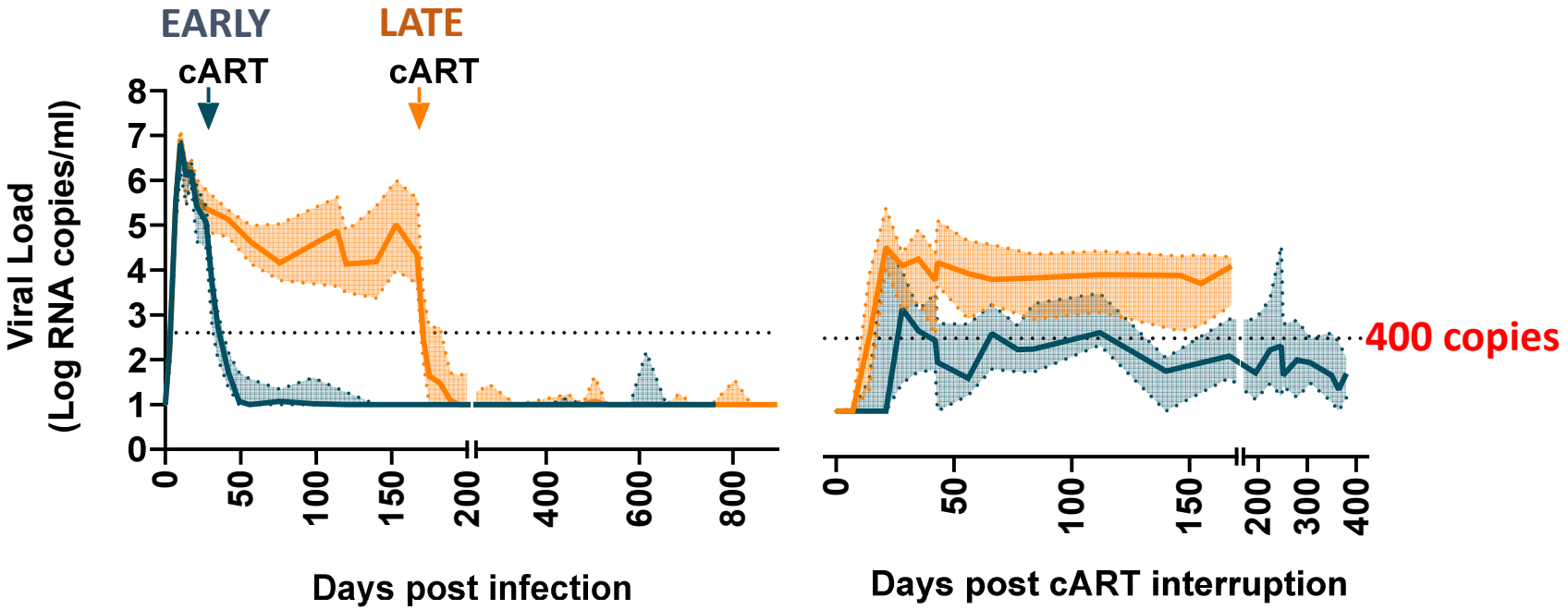
p(rimate)VISCONTI

To assess, in standardized conditions, the impact of early versus late cART initiation on the immune responses and the outcome after analytical treatment interruption (ATI).

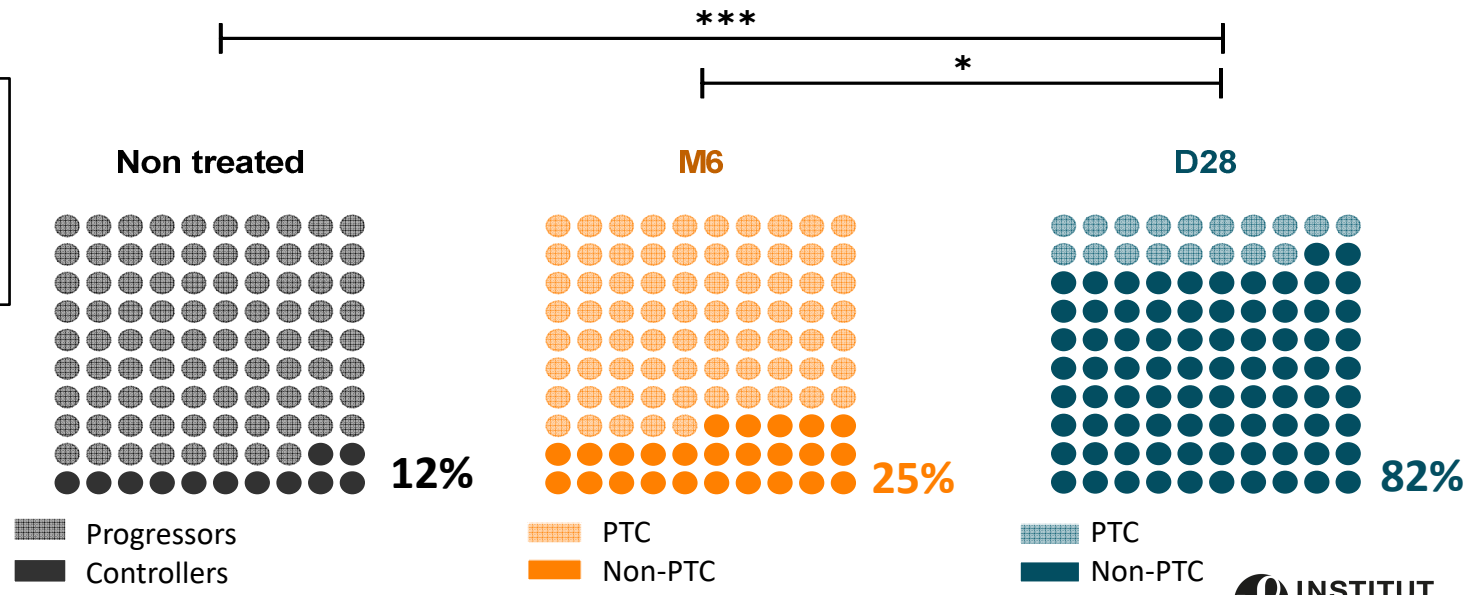


MHC H6 haplotype associated with natural control was excluded

Early antiretroviral treatment favored a delayed viral rebound and lower viral setpoint after treatment interruption



Higher rate of post-treatment controllers (VL<400 copies) among early treated macaques, at the end of the study



Passaes et al IAS 2021

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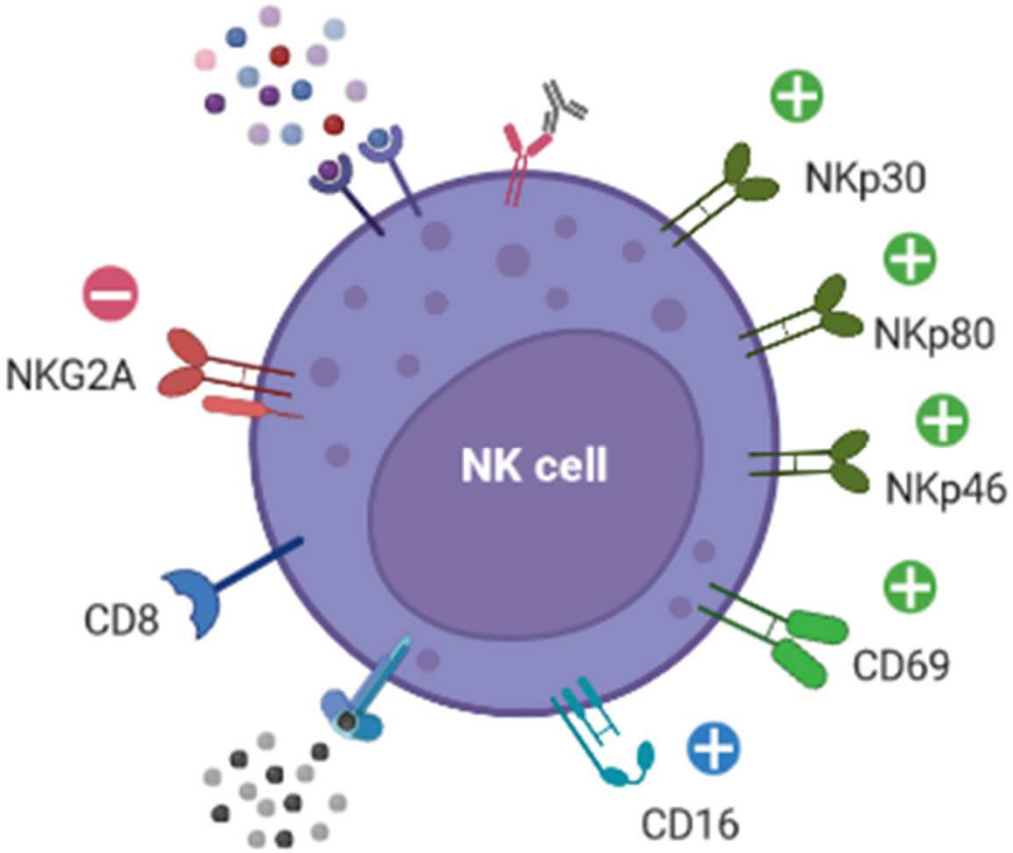
Analysis of the impact of NK cells on post-treatment control

- ✓ Phenotypic analysis by flow cytometry blood, LNP, BM, BAL



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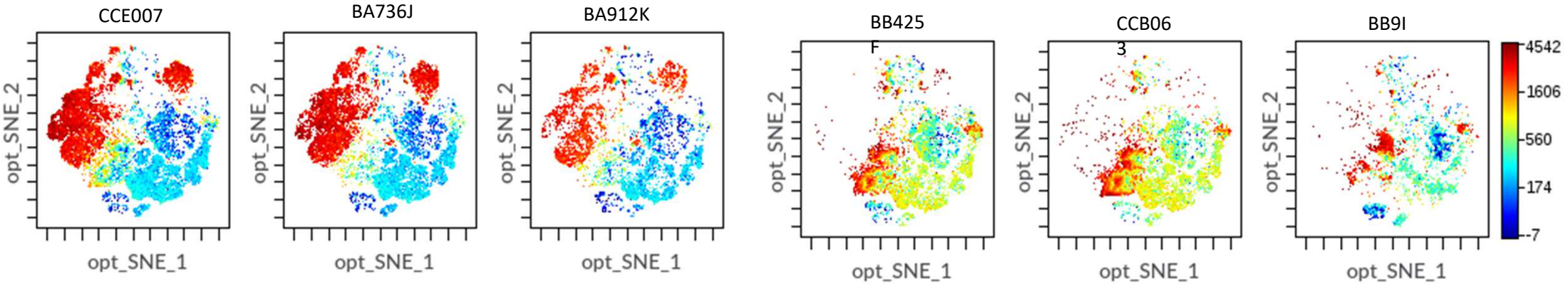
NK cells from CyMs constituvely express differentials levels of NKG2A in blood, lymph nodes and bone marrow

Individuals monkeys -Blood



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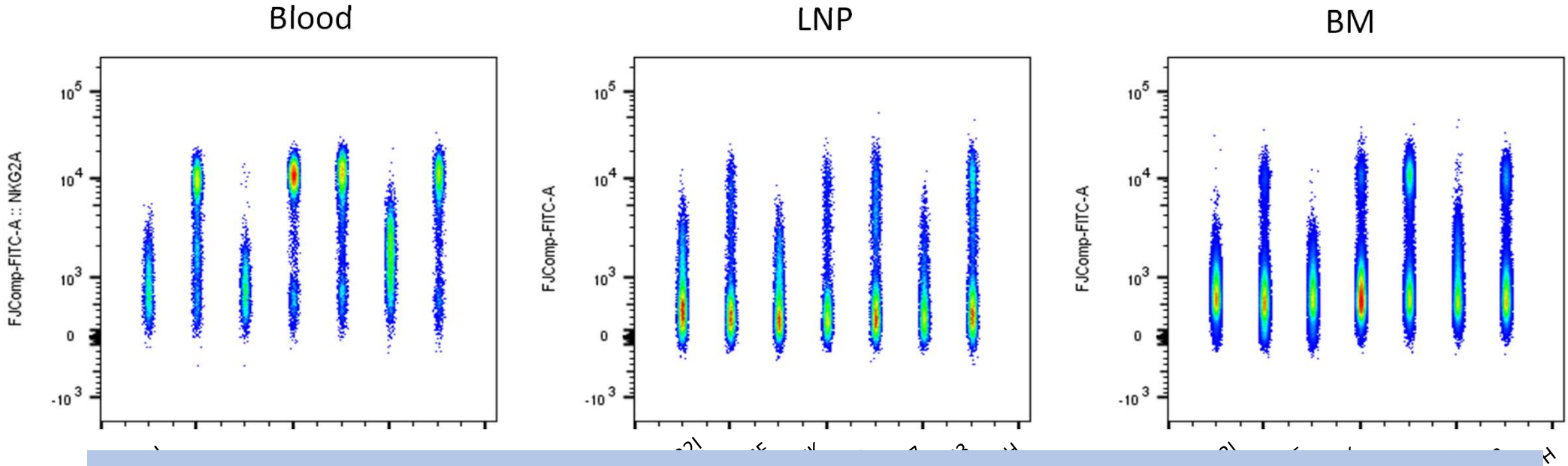
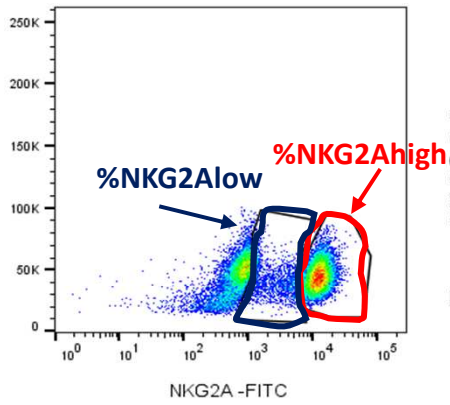


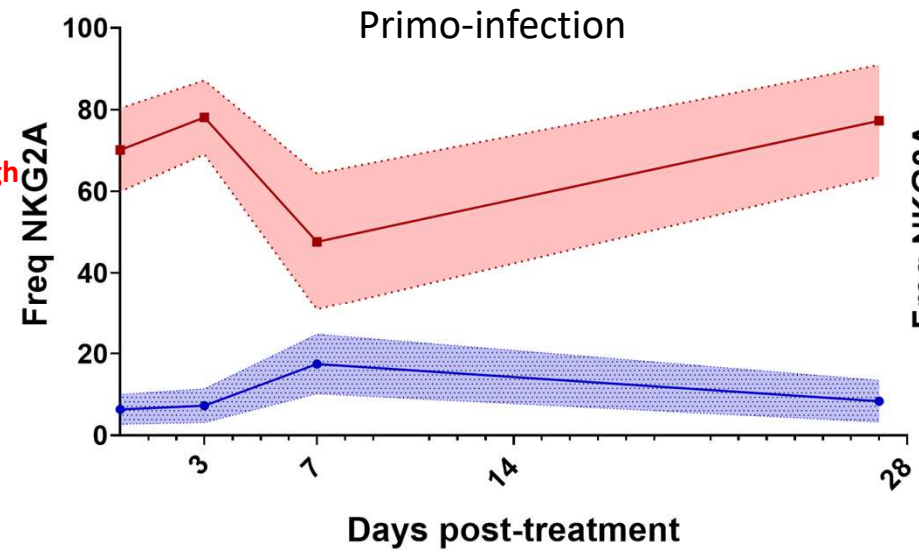
Preliminary data showed association between NKG2A level and MS277+ located in MHC type I region

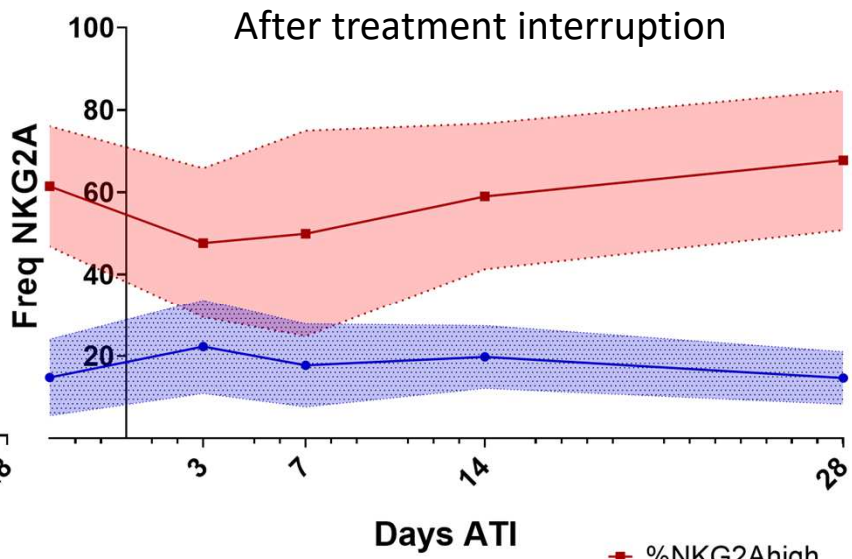
AC0

The NKG2A populations remain stable longitudinally in the blood

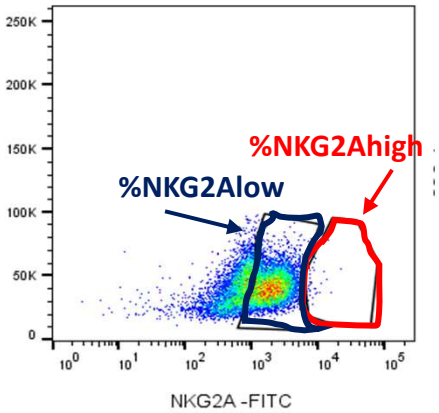
1. Group with high expression of NKG2A

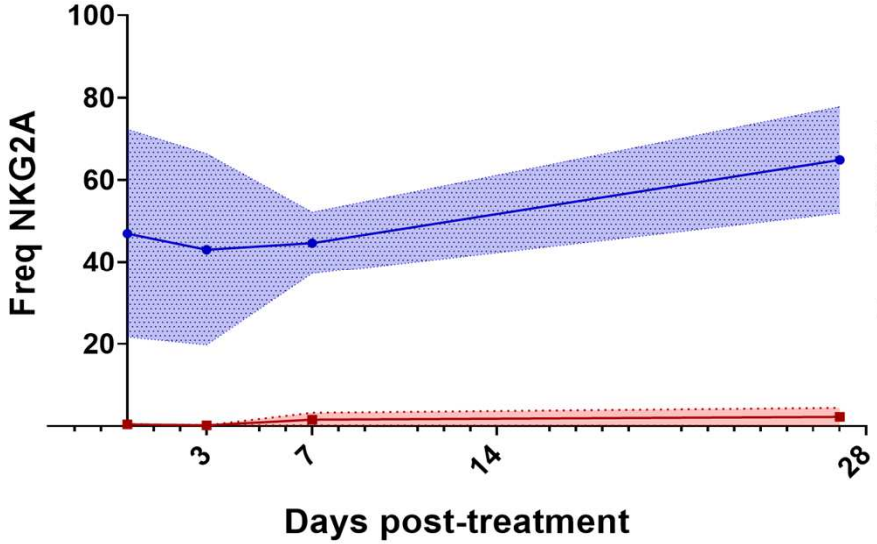


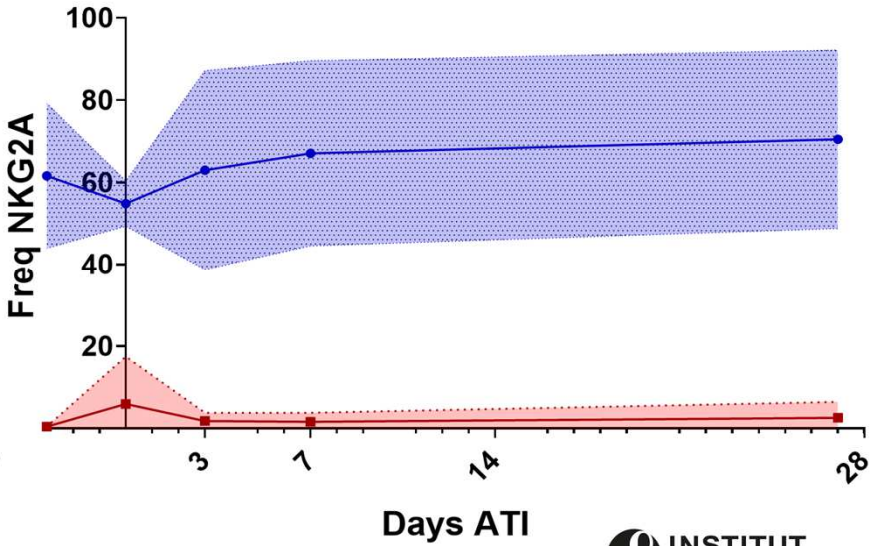




2. Group with low expression of NKG2A







%NKG2Ahigh
%NKG2Alow

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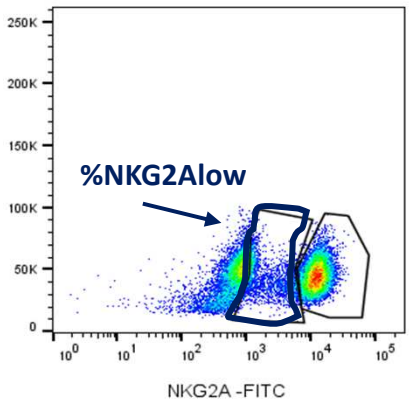
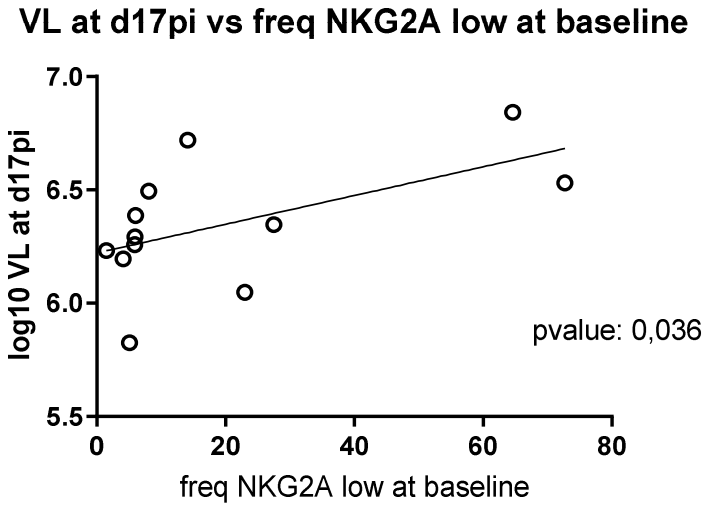
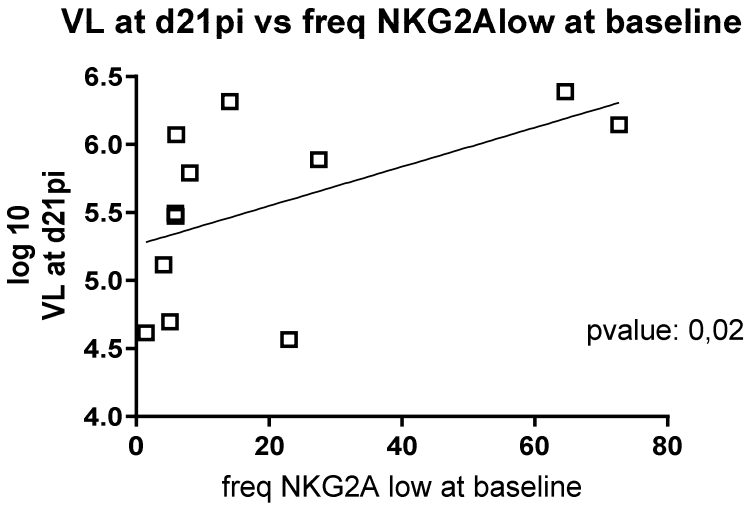
Diapositive 10

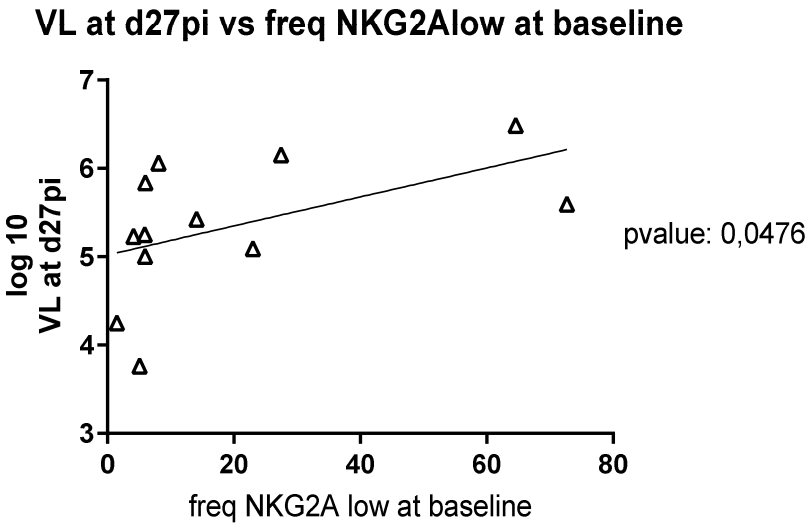
AC0 Changer les graph ?
Anais Chapel; 2022-09-07T20:24:28.672

A high frequency of NKG2A^{low} at baseline in the blood correlated with a higher viral load during primo-infection









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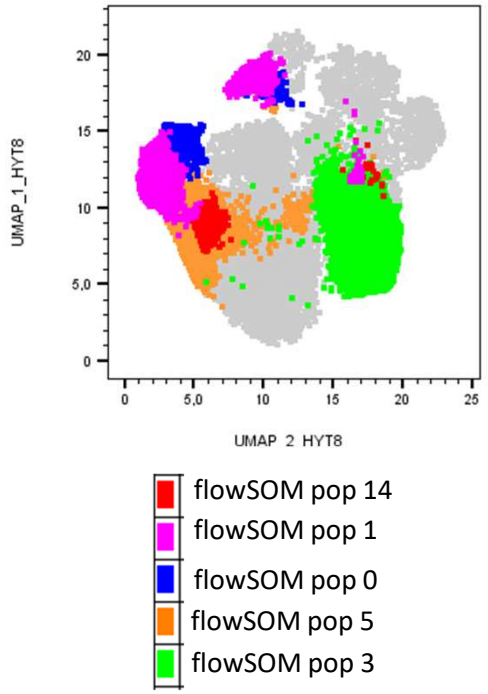
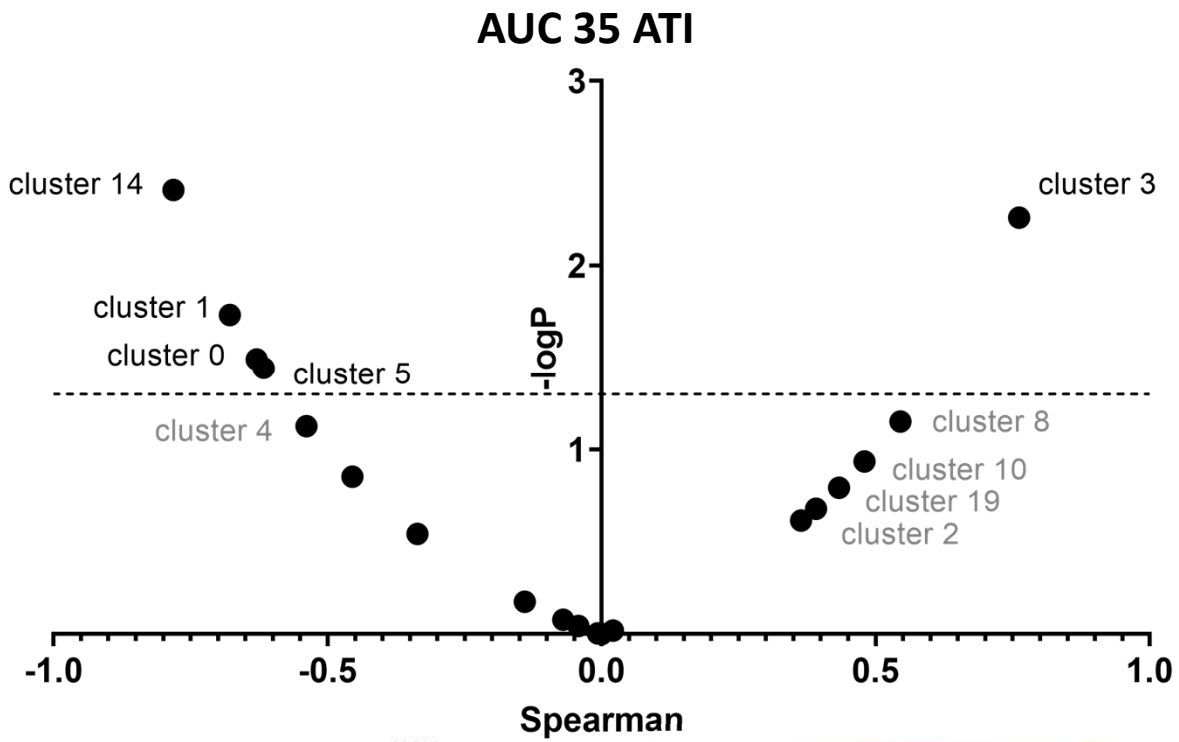
NK cell subsets constitutively expressed at baseline correlate with viremia during the first 35 days after treatment interruption



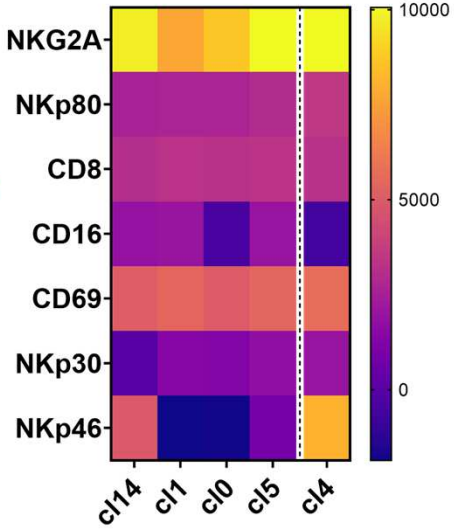


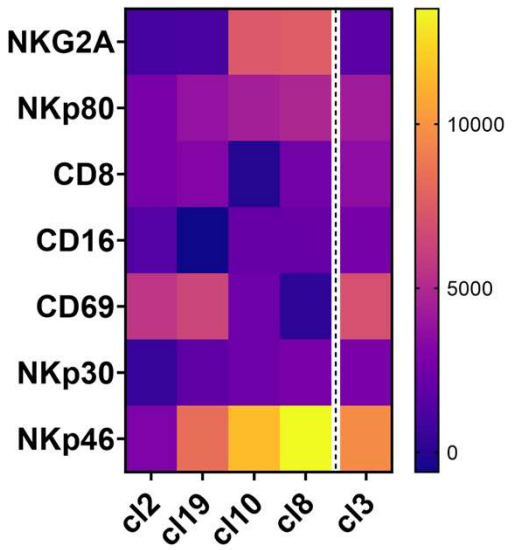
NKG2A^{high}NKp46^{low}

NK cell subset correlate

negatively with

the viral load





NKG2A^{low}NKp46^{high}

NK cell subset correlate

positively with

the viral load

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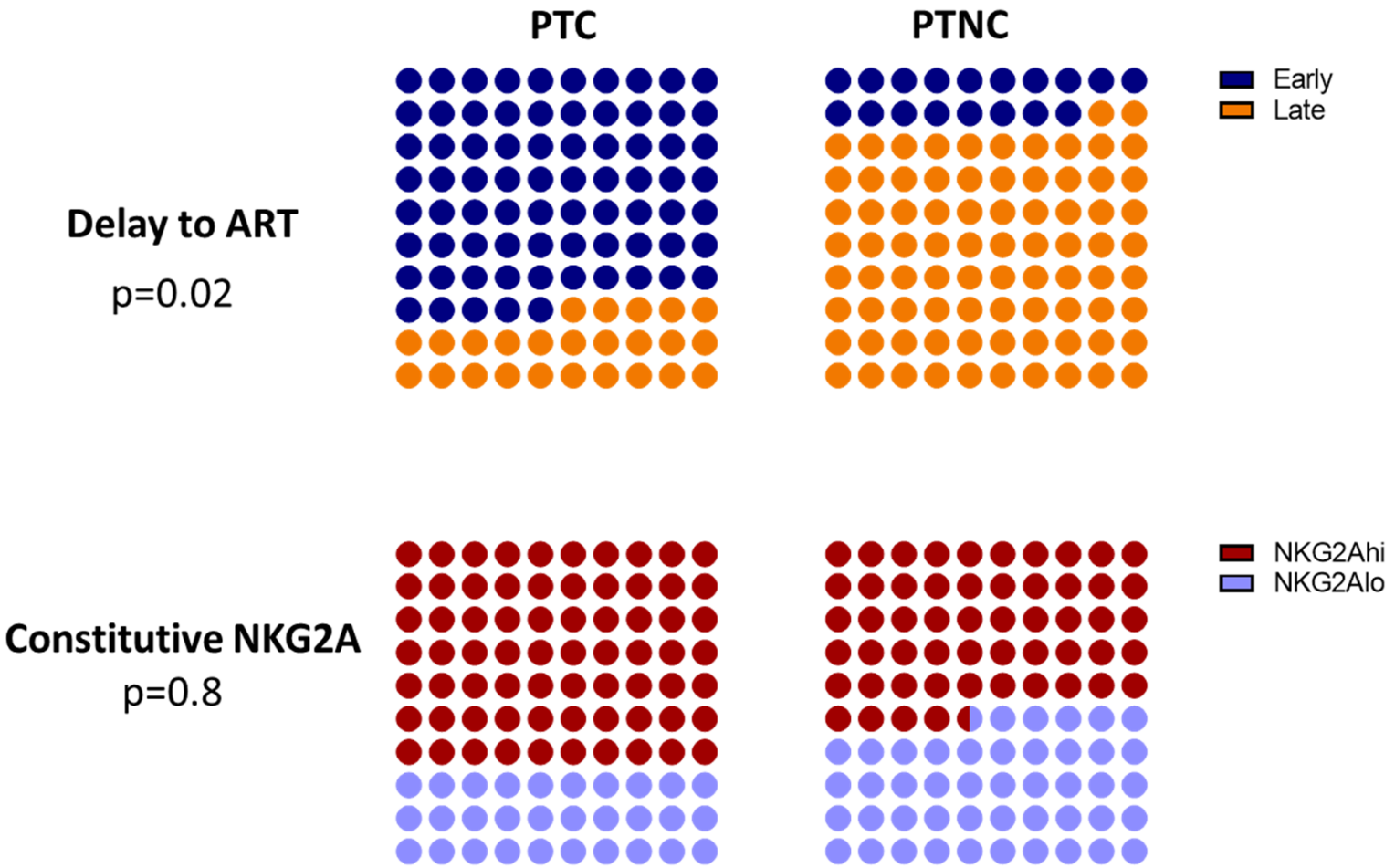
The constitutive expression of NKG2A did not determine the rate of post-treatment control

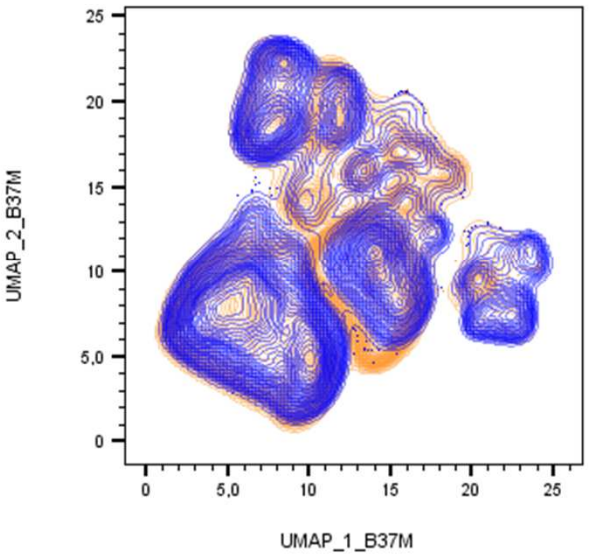
Correlation between baseline frequencies of NK cells and viremia was lost at later times after treatment interruption

Same proportion of NKG2A^{high} and NKG2A^{low} animals in early treated and late treated groups

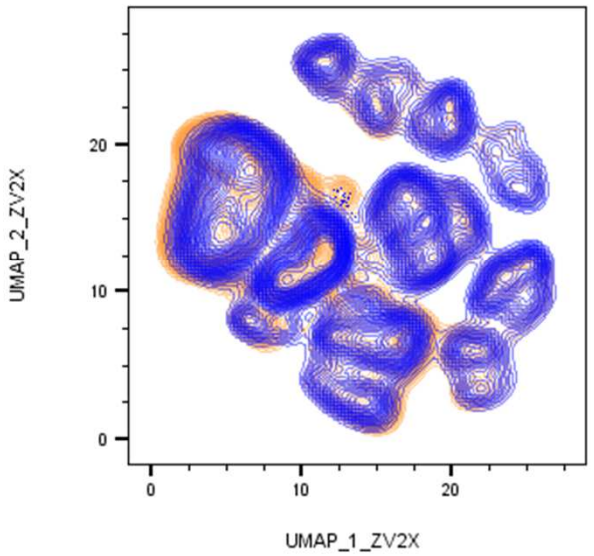


The timing of the treatment has an impact on NK cell phenotype during and after treatment interruption

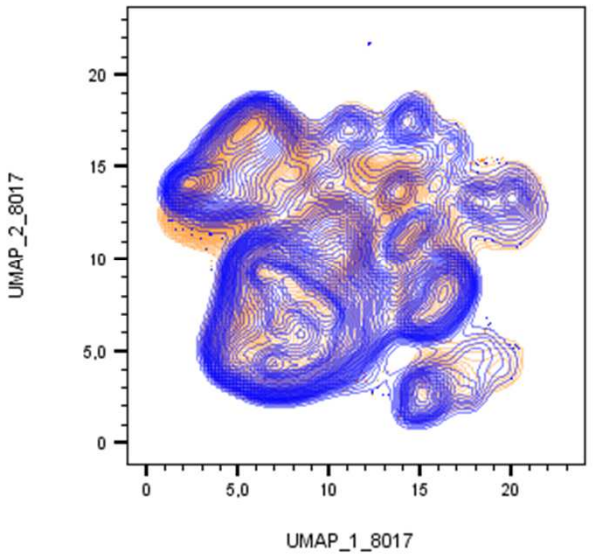
Baseline



7 days post-infection



28 days post-infection



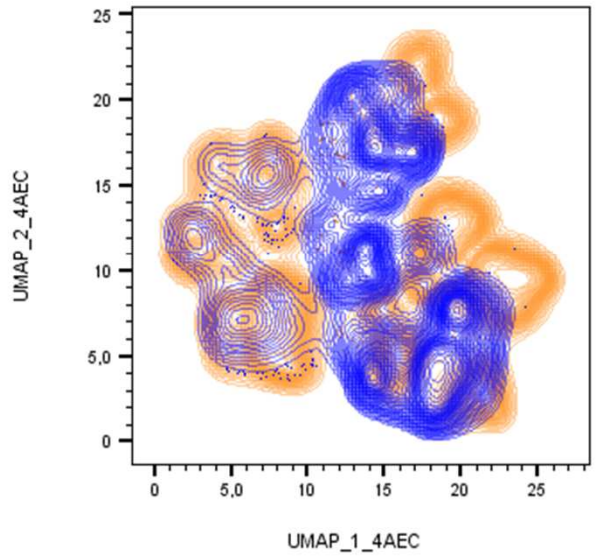
Legend

Early treated monkeys

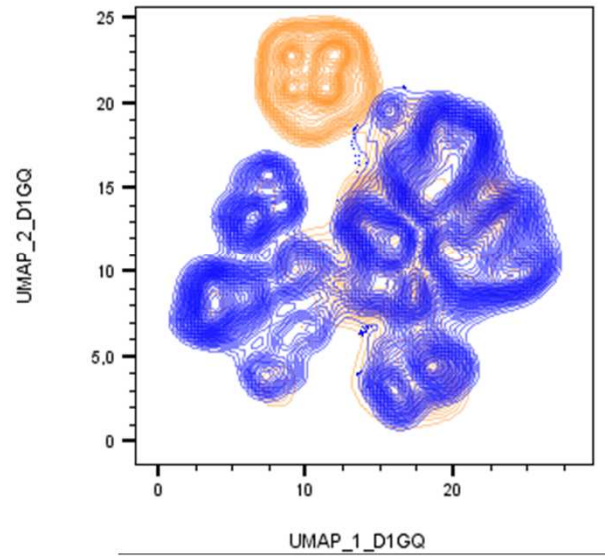
Late treated monkey

No difference observed during primo-infection

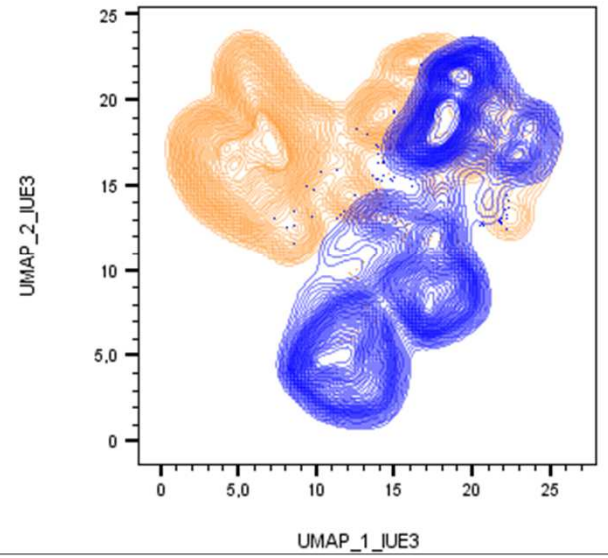
100 weeks post-treatment



7 days post-treatment interruption



28 days post-treatment interruption



Different phenotype after treatment interruption

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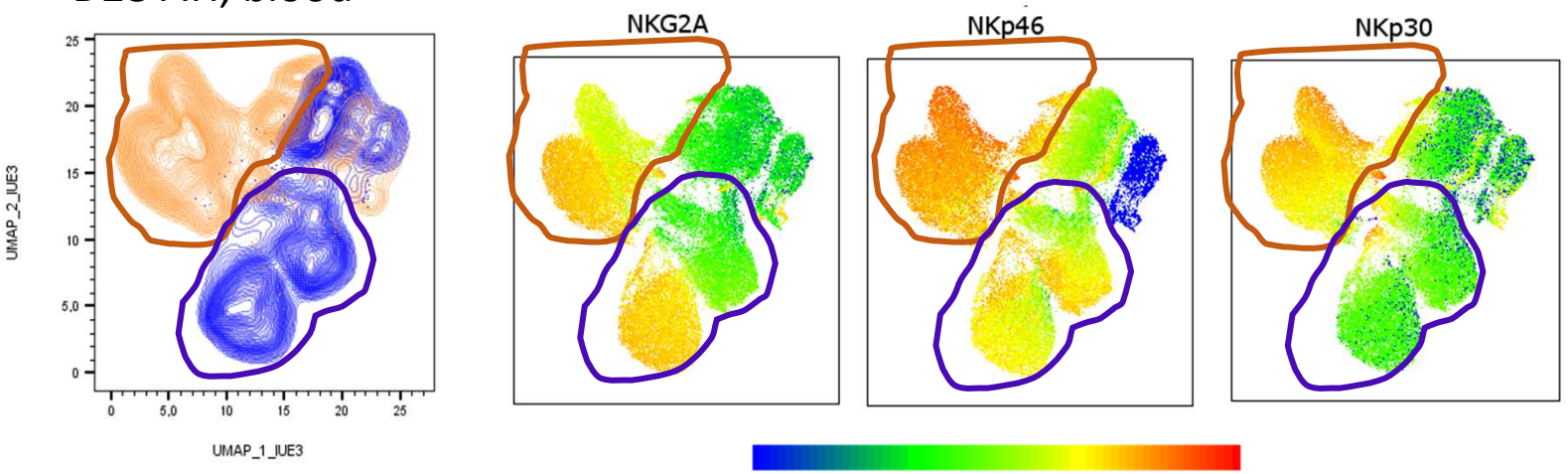
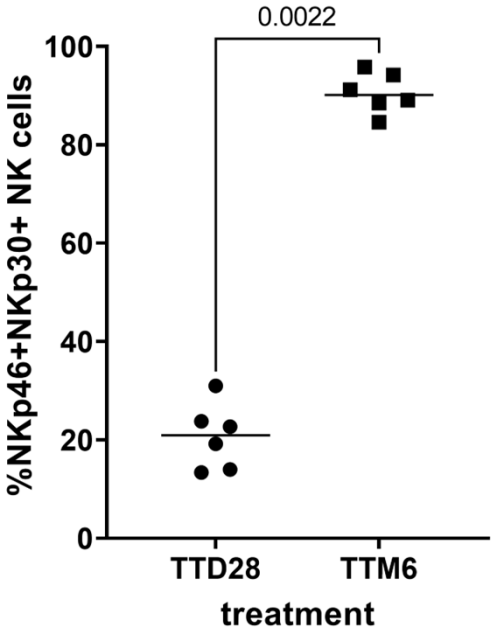
Late treated animals showed a higher frequency of NK cells expressing the activating marker NKp46 and NKp30

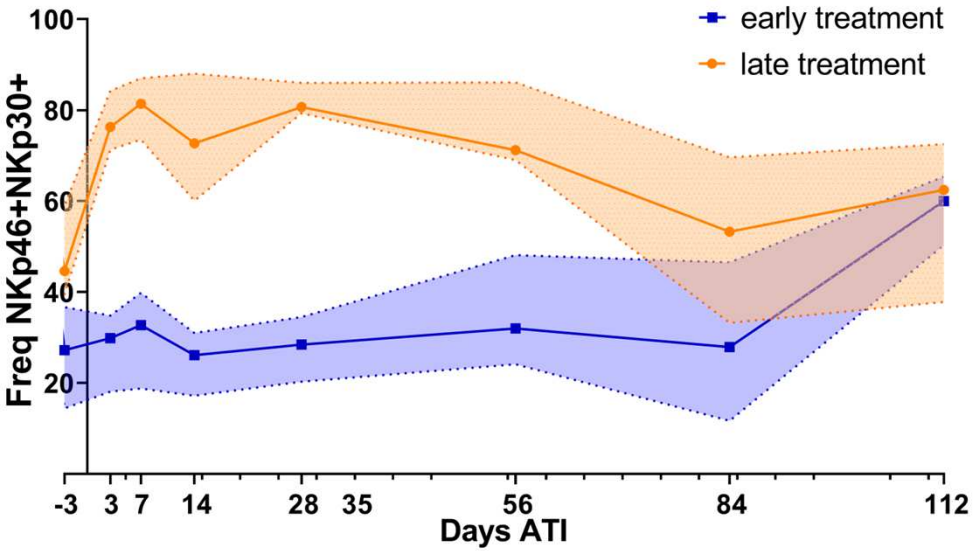
D28 ATI, blood



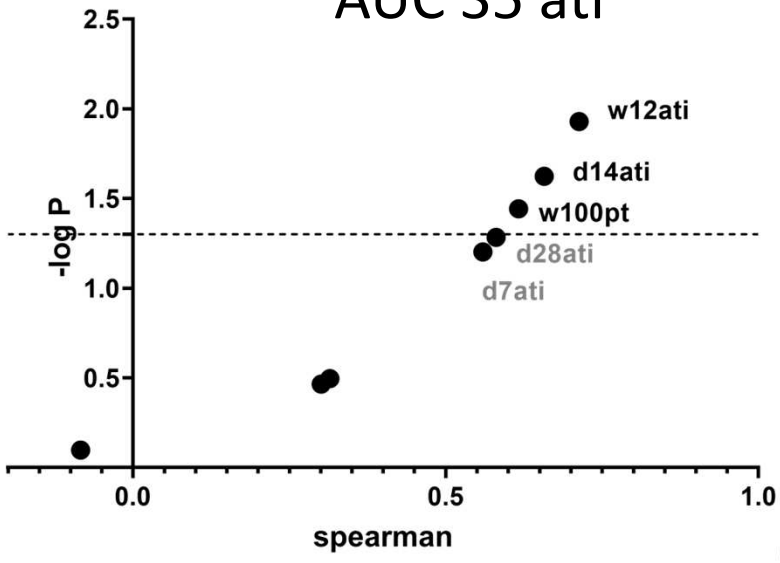
Early treated monkeys (TTD28)

Late treated monkeys (TTM6)





AUC 35 ati



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Take home message

- Constitutive differential expression of NKG2A may influence the viremia during the primo-infection and after treatment interruption.
- Ultimately, the timing of treatment appear to have a stronger impact on the achievement of post-treatment control than the constitutive expression of NKG2A.
- The timing of ART impact the distribution of the NK cells subsets and their mobilization after treatment interruption.
- Higher of $NKp46^{+}NKp30^{+}$ NK cells are observed in late treated animals and are associated with a higher viral load.

COMMUNITY SUMMARY

Key question :

What is the role of Natural Killer (NK) cells in the **post-treatment control** of HIV ?

→ Use of a non human primate model to mimic the post-treatment control of HIV in standardized conditions.

Key findings :

1) Before infection, the non human primates **differently express** some markers (NKG2A) which could **influence their capacity to control the viral infection**. This could be linked to **genetics factors**
2) Early treatment seems to **better preserve** the **NK cells response** and **impact their mobilization** after treatment interruption.
3) A treatment initiated **early** favored **the rate of post-treatment controllers** among non human primates.

Next steps ? Determine the functional activity of the different NK cells subsets.

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HIV inflammation and persistence
Asier Saez-Cirion

Reservoirs and control of infection


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Federico Perdomo Celis
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ERASE HIV

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HIViera
Remission of HIV infection era

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