Dynamics of the intact proviral DNA over two decades of antiretroviral therapy

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Disclosure of speaker's interest

(Potential) conflict of interests	None
Relations that could be relevant for the meeting	None

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Introduction

- Antiretroviral therapy (ART) inhibits viral replication, resulting in a decline of RNA & DNA in blood[1,2,3]
- No complete elimination of HIV DNA reservoir, which forms the major obstacle to HIV cure[2,3,4]

- **Little is known about the very early and late dynamics of the reservoir after start of ART**

1. Perelson et al. 1997, 2. Besson et al. 2014, 3. Peluso et al. 2020, 4. Finzi et al. 1997

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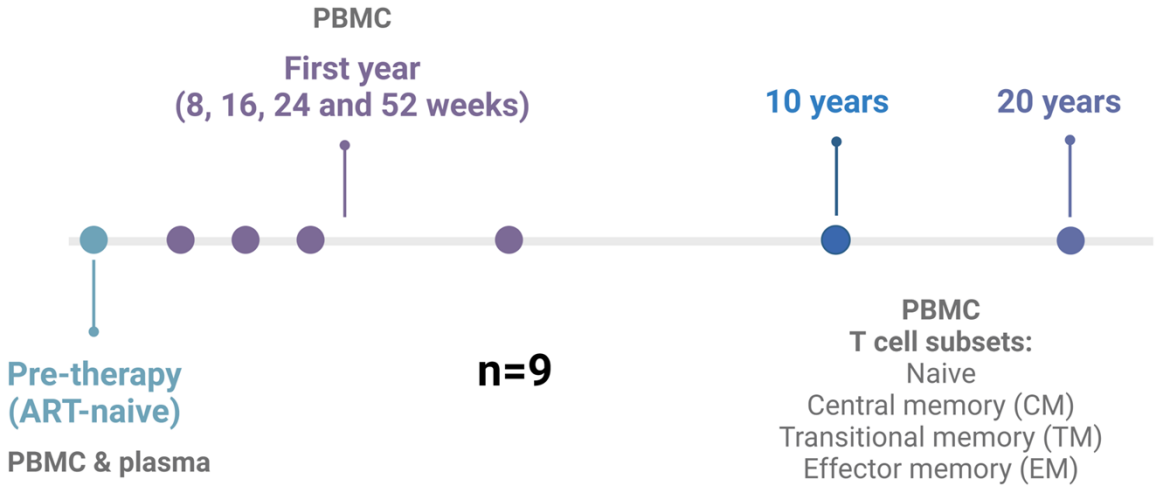
Study outline



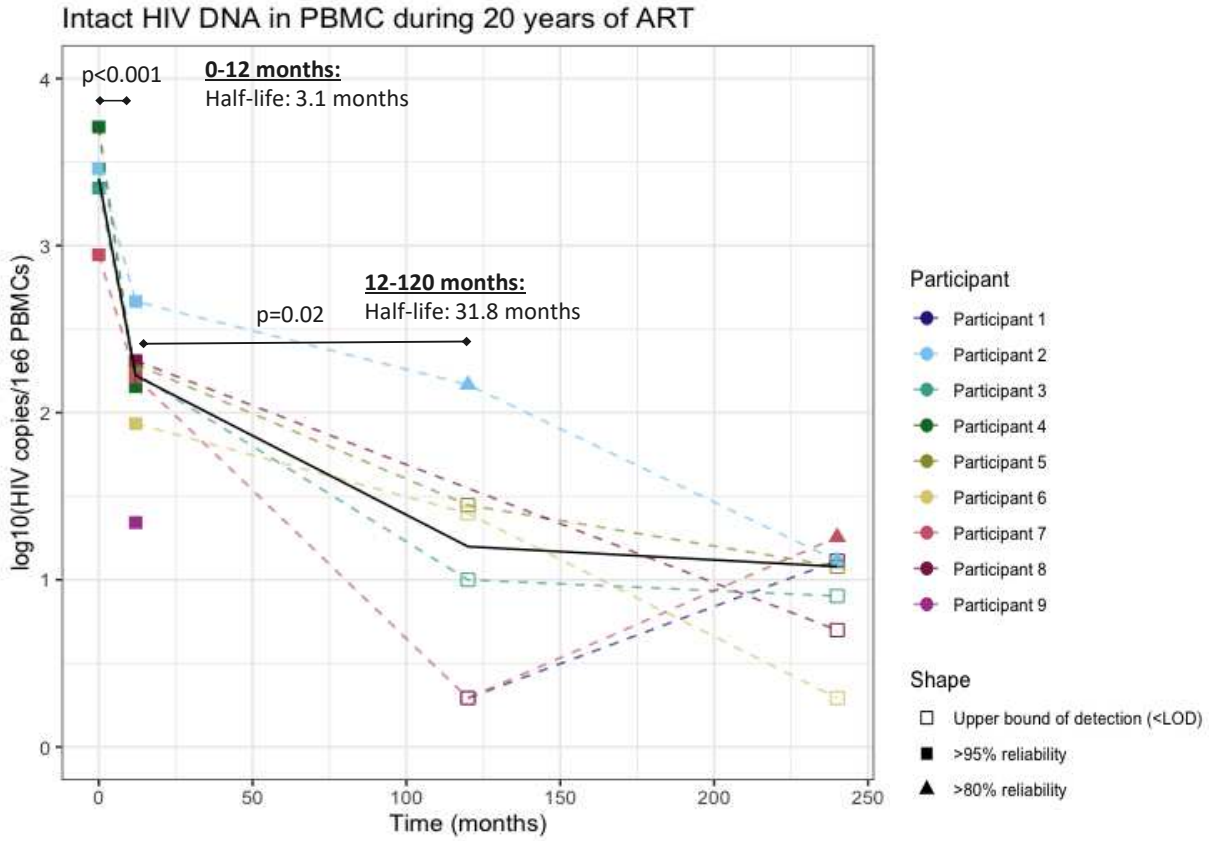
- Check for the presence of intact proviral DNA via the **Intact proviral DNA assay (IPDA)**
  - Separately quantify the intact and defective proviral reservoir

	Gender	100% Male
Start ART	**CD4 count (cc/mm3)**	290 *[40 - 210]*
	Viral load (copies/ml)	2.E5 *[5.E4 – 4.E5]*
10 years ART	**CD4 count (cc/mm3)**	883 *[575.5 - 1173.5]*
	Viral load (copies/ml)	<50 *[<50 - <50]*
20 years ART	**CD4 count (cc/mm3)**	1000 *[773.5 - 1111.5]*
	Viral load (copies/ml)	<50 *[<50 - <50]*

Median values and their IQR for the CD4 count and the viral load are shown

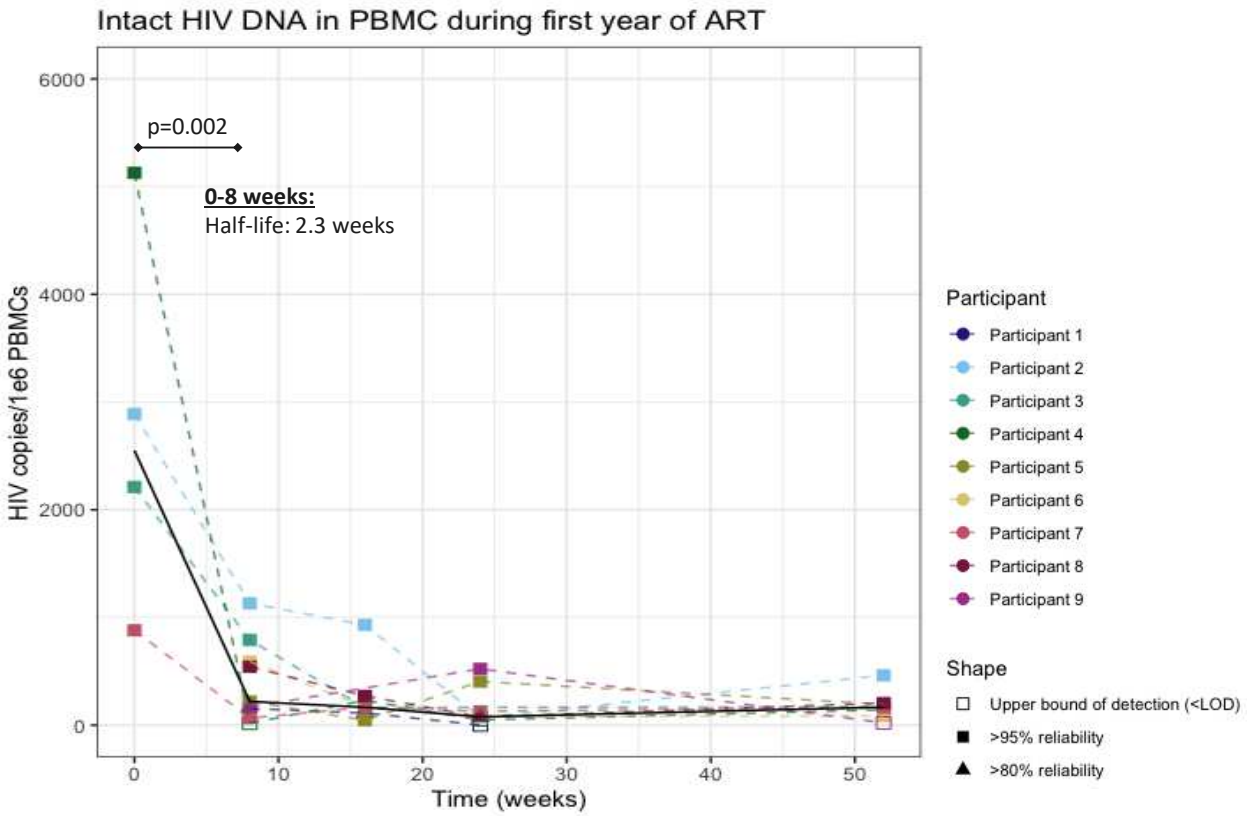
Decline of intact proviral DNA over 10 years of ART

- Significant decline of intact proviral DNA **continuously up to 10 years** after start therapy
  - 10 to 20 years flattening (non-significant)
  - LOD limits the detection between 10 and 20 years
- **Faster decline over the first year** compared to the decade after



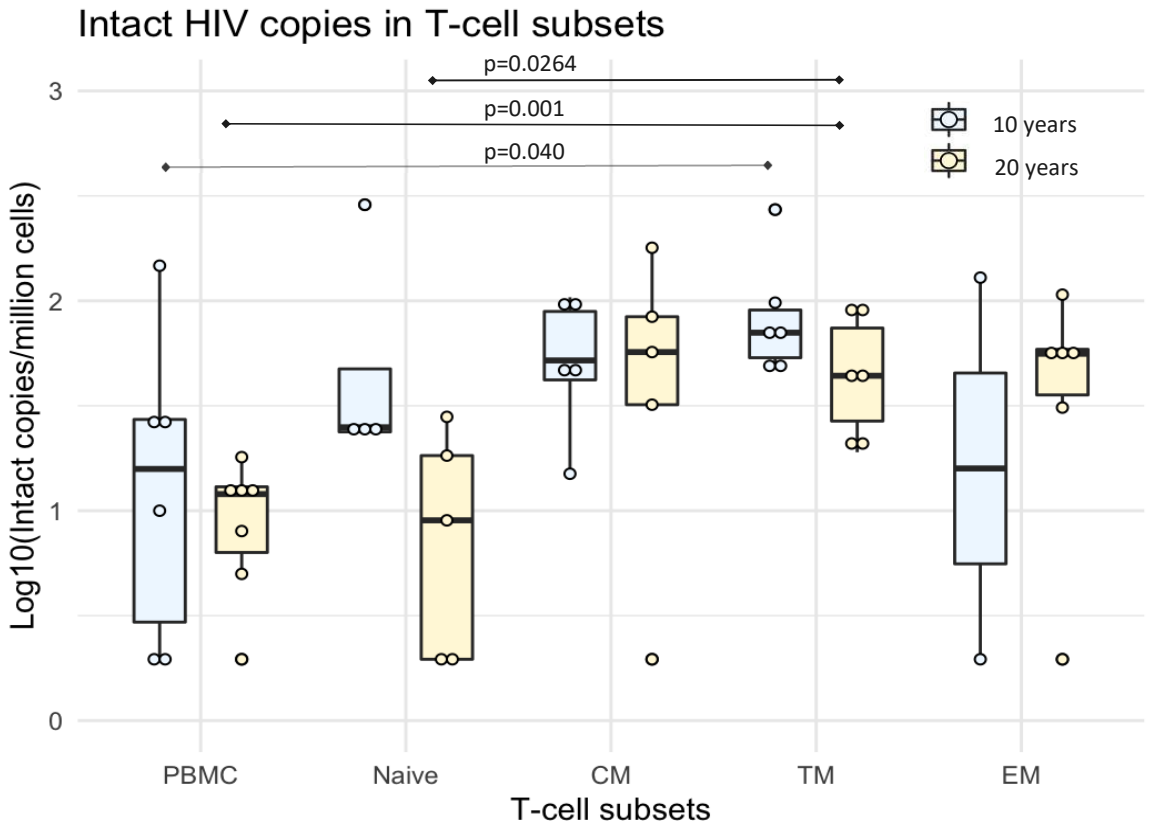
Decline of intact proviral DNA within first weeks of ART

- **Sharp decline** of intact proviral DNA **within first 8 weeks** of ART
- Later time intervals are not significantly different from each other
- **Continuous decline up to 10 years**



Proviral DNA enriched in memory CD4 T-cell subsets

- HIV-reservoir enriched in memory T-cell subsets compared to PBMCs & naive
  - Measured in copies per million cells of that subset
- No significant changes from 10 to 20 years



Community summary

Main question:

- Are the viruses which might contribute to new rounds of infection (intact viruses) after cessation of ART still decreasing in number after 20 years of therapy?

Key findings:

- Already within the first weeks after start of ART, there is a strong decline of the intact viruses.
- This decline continues up to 10 years after start of ART, probably up to 20 years after start of ART.
- There are limited dynamics within the HIV reservoir in T cell subsets during the last decade.
- *The reservoir in PBMCs is not maintained via ongoing replication (not shown)*
- *The defective reservoir stabilizes quicker than the intact reservoir (not shown)*

Poster: PP 1.7

Poster: PP 3.8

Next steps:

- Analyze larger cohorts to investigate the continuous decline up to decades after start of ART.
- Investigate the variation of the viral landscape after 20 years of ART.
- Subtype C dynamics and impact of the defective reservoir after start of ART.

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Study participants

aidsfonds

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ICD-ICK4HIVCure

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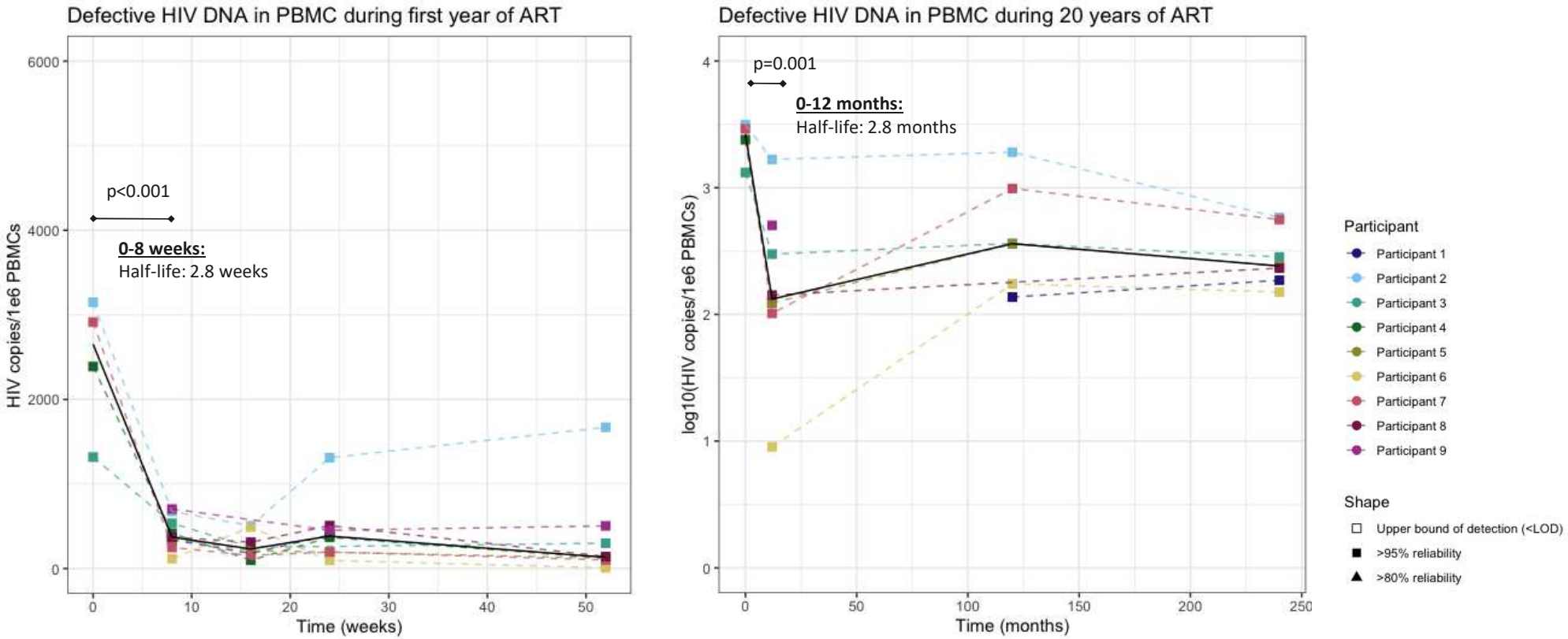
Stabilization of the decline in the defective proviral reservoir

- Decline in defective DNA over the first weeks
- **Stabilization of the decline in defective DNA over 20 years** of ART



Percent change

Intact:

- 0-8 weeks: 91%

- 0-12 months: 93.5%
- 12-120 months: 89.5%
- 0-120 months: 99.3%

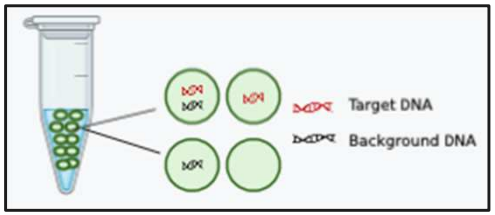
Defective:

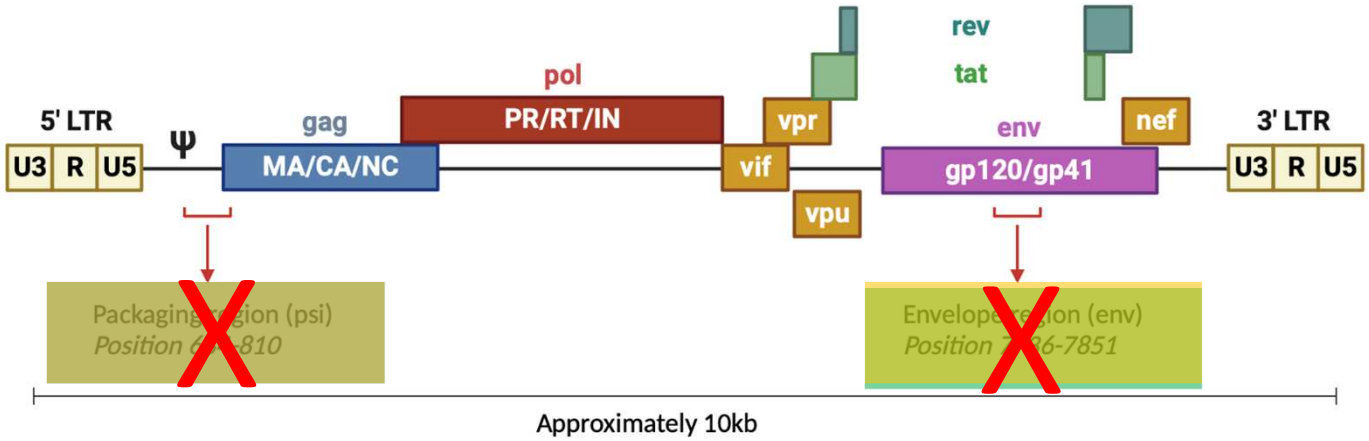
- 0-8 weeks: 86%

- 0-12 months: 95%
- 0-120 months: 86.4%

Intact Proviral DNA Assay (IPDA)

- Most widely-used PCR detects total proviral DNA (intact & defective)[1,2]
- Digital droplet PCR (ddPCR); sample in +/- 20.000 droplets
- IPDA: which droplet contains intact proviral DNA?[2]

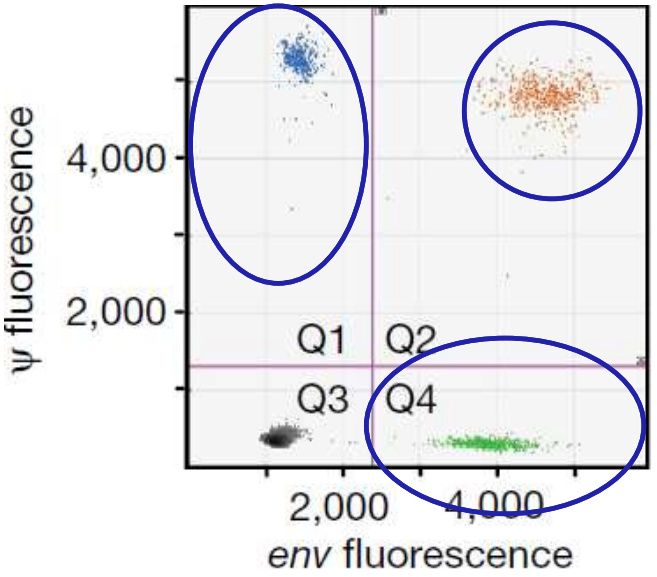




Psi present and 3' deletion/hypermutation

Env present and 5' deletion

Double positive →intact



1. Ho et al. 2013. 2. Bruner et al. 2019