How do you measure HIV cure

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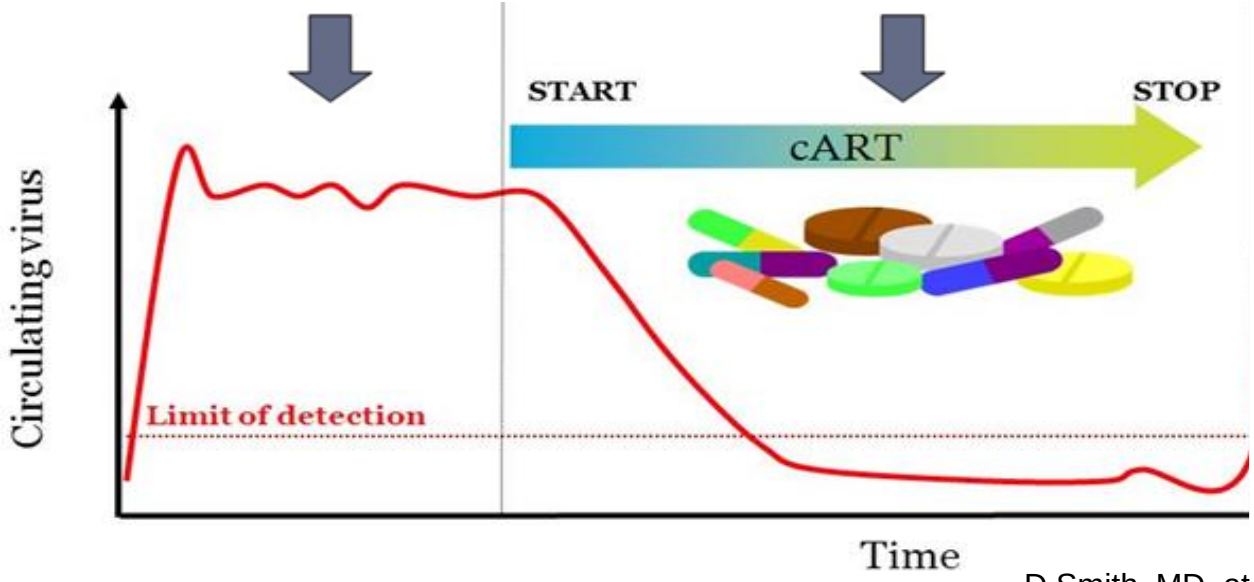
Background

Active ongoing HIV replication

Antiretroviral drugs suppress HIV replication



D Smith, MD, at Los Angeles, CA: April 25, 2016, IAS-USA

Background

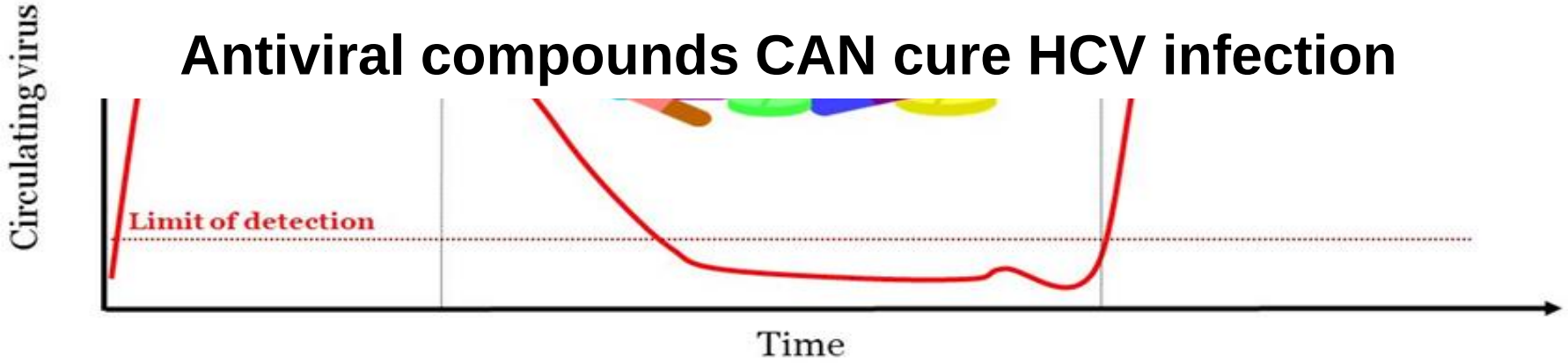
Active ongoing HIV replication

Antiretroviral drugs suppress HIV replication

HIV rebounds

Potent antiretroviral compounds can NOT cure HIV infection

Antiviral compounds CAN cure HCV infection



Background

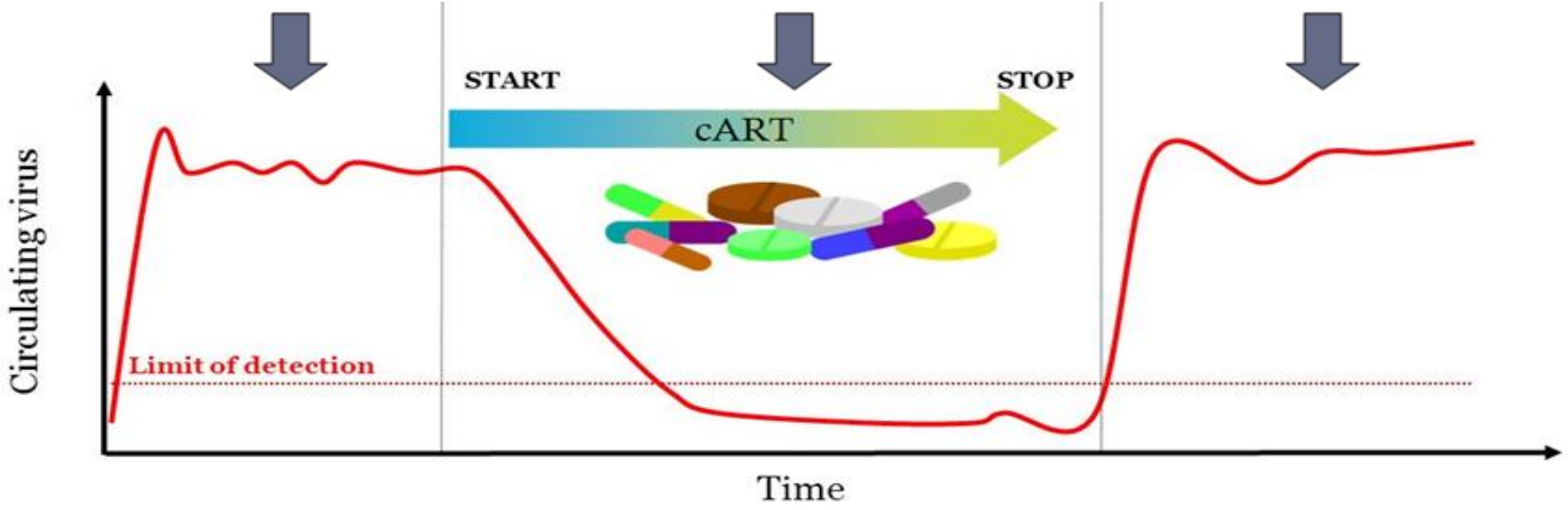
Active ongoing HIV replication

Establishment of viral reservoir

Antiretroviral drugs suppress HIV replication

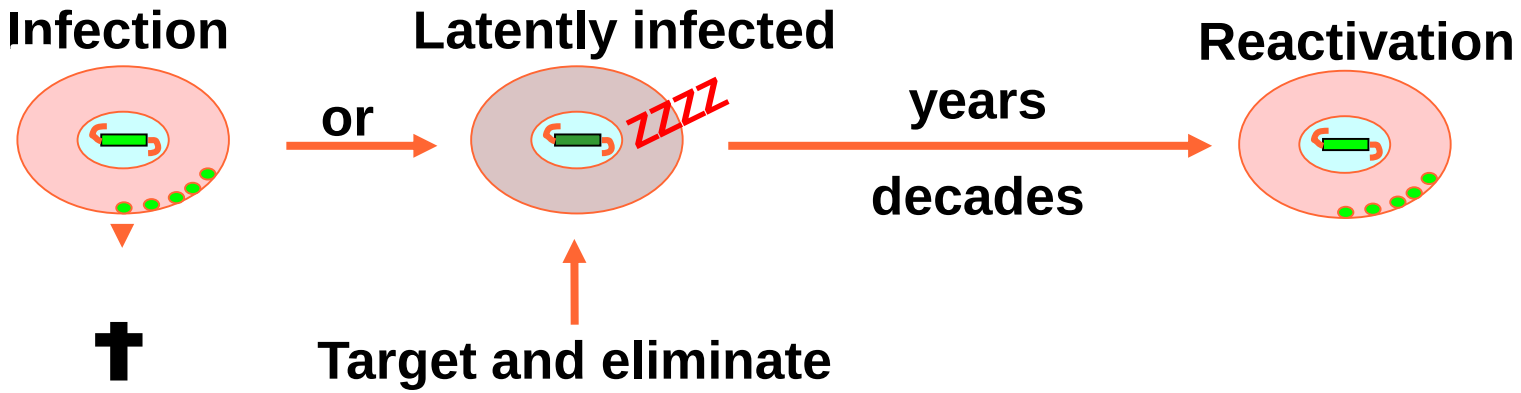
HIV rebounds

HIV rebounds from viral reservoir

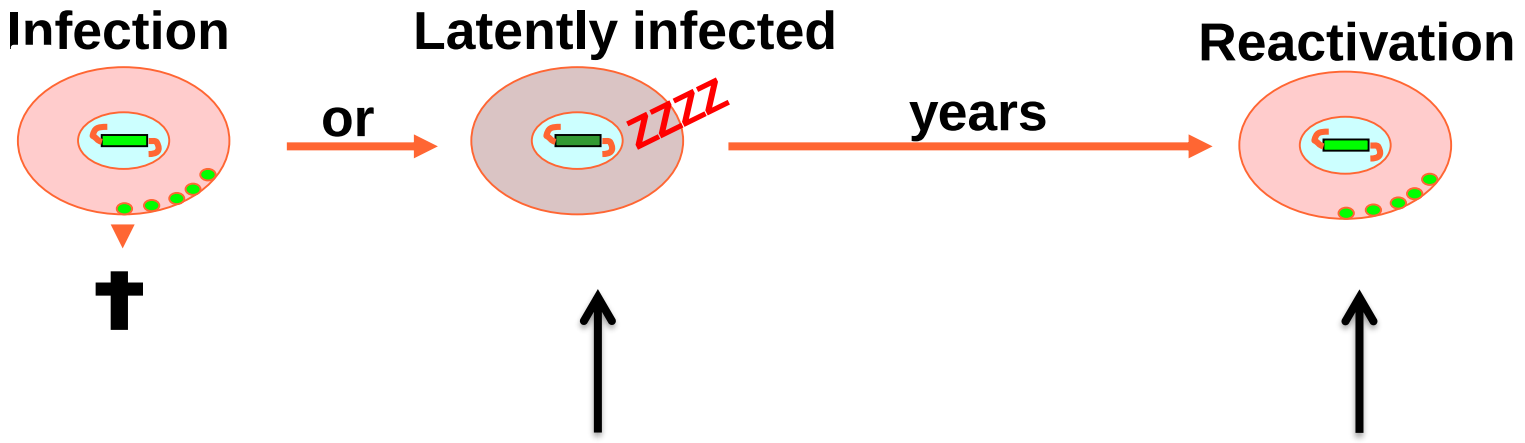


Major hurdle towards HIV cure

- HIV reservoir of latently infected cells
- How is the viral reservoir been formed



Measure of HIV Cure = Measure the viral reservoir



How much HIV DNA can we detect inside the latent cells

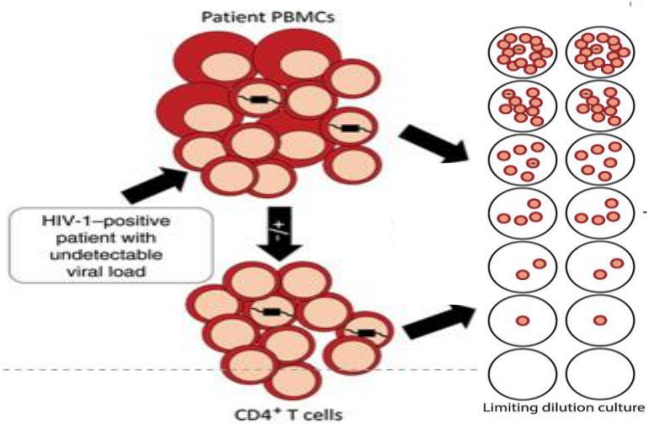
How many cells can reactivate infectious virus

What do we know about the viral reservoir?

eeks et al, Nature Med, 2016

Measure the viral reservoir: HIV reactivation

Quantitative viral outgrowth assay (QVOA): infectious virus



Measure the viral reservoir: HIV reactivation

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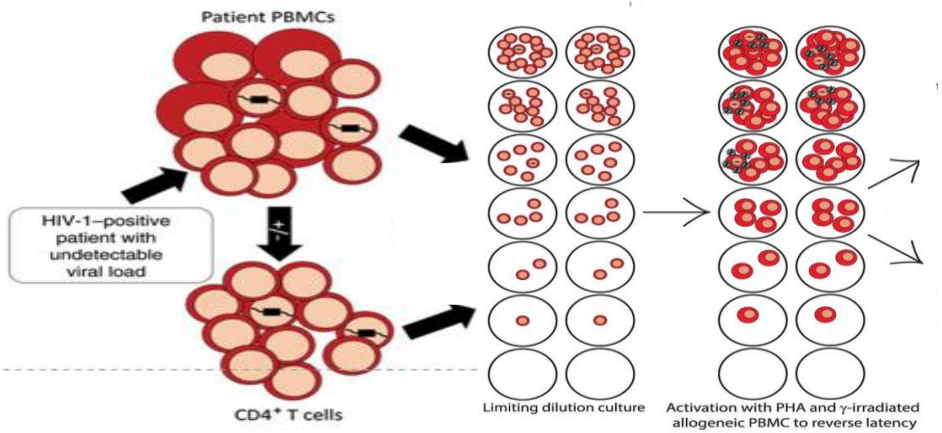

Measure the viral reservoir: HIV reactivation

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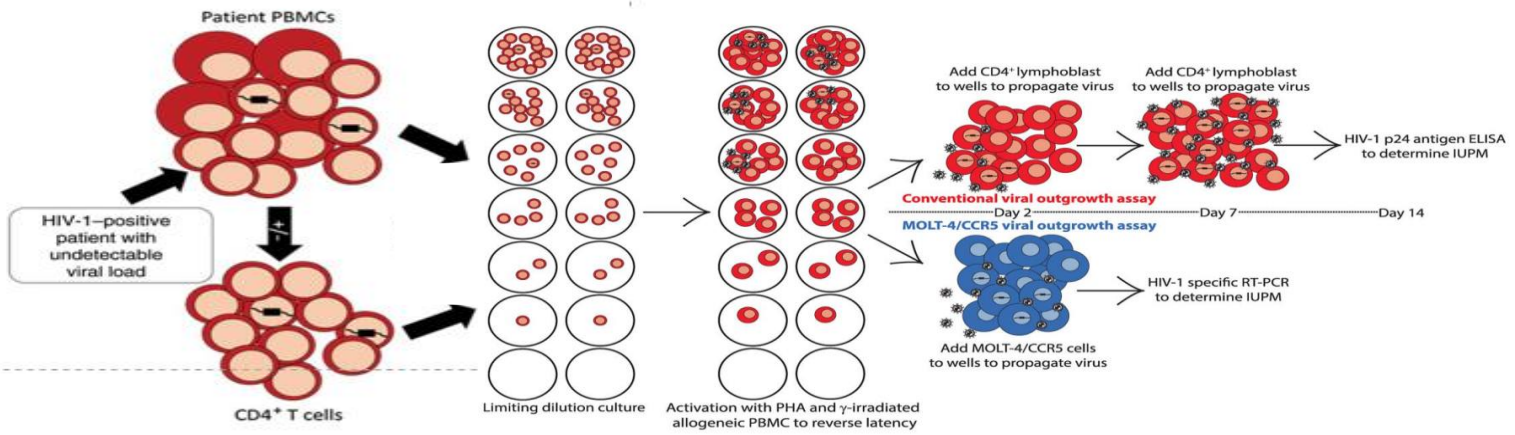
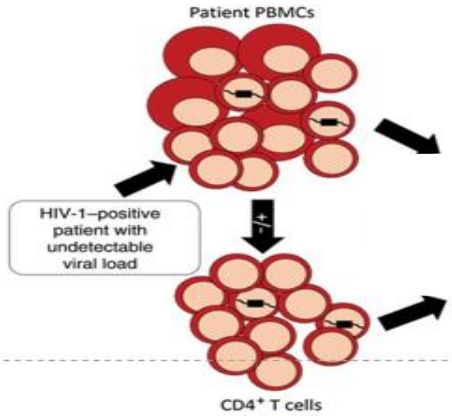


Measure the viral reservoir: HIV reactivation

Mouse viral outgrowth assay (MVOA): infectious virus

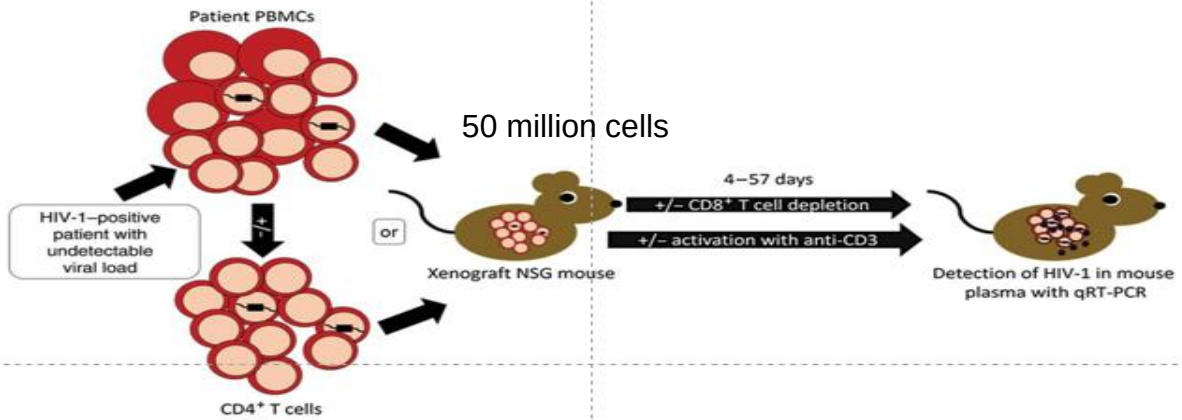


Metcalf Pate et al, JID, 2015

Measure the viral reservoir: HIV reactivation

Mouse viral outgrowth assay (MVOA): infectious virus

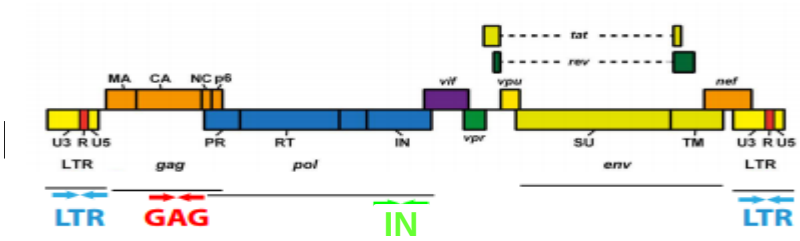
Humanized immune system

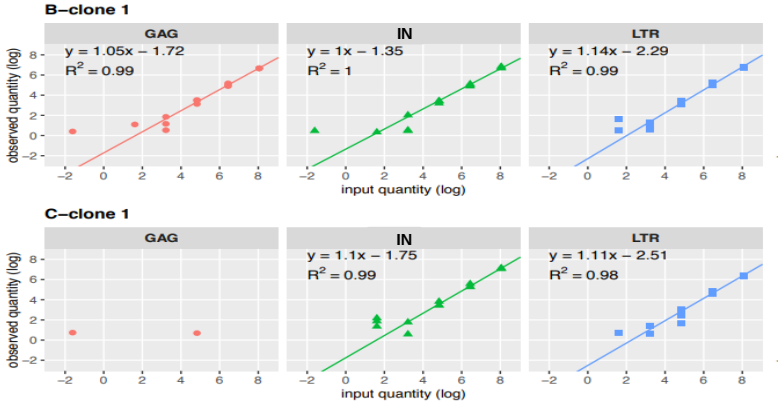


Metcalf Pate et al, JID, 2015

Measure the viral reservoir: HIV DNA

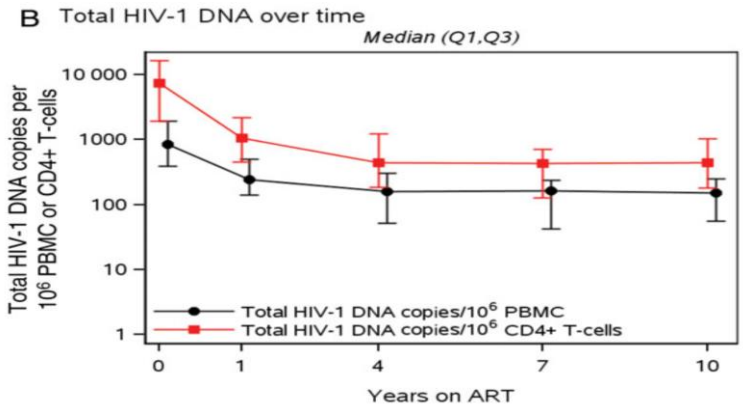
- Development of ultra-sensitive techniques (LTR-IN)
- Detect large majority of HIV subtypes and CRFs > 95% infections worldwideHIV-1 subtypes

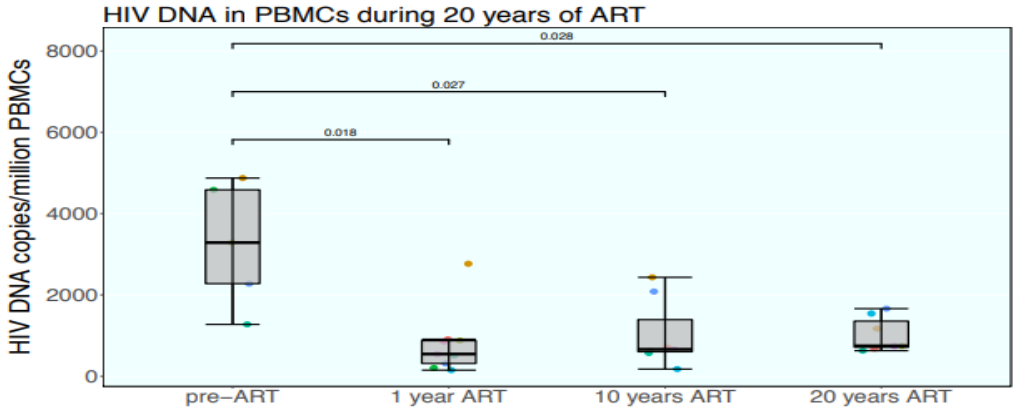




Bosman et al, JIAS, 2018

Measure the viral reservoir: HIV DNA





Besson et al, CID, 2014; Bosman et al, manuscript in preparation, Poster AIDS2018, WEPEA030

Apply measure of HIV reservoir in a Cure strategy

Berlin Patient: HIV infected, on ARVs and diagnosed with AML

Transplantation with stem cells from a donor
lacking the CCR5 receptor for virus entry into the cell

ARVs were stopped at transplantation

No sign of HIV replication afterwards (>10 years)

Hutter et al, NEJM, 2008

HIV Cure: stem cell transplantation: IciStem

International collaboration to guide and investigate the potential for HIV cure in HIV-infected patients requiring allogeneic stem cell transplantation for hematological disorders

ICISTEM

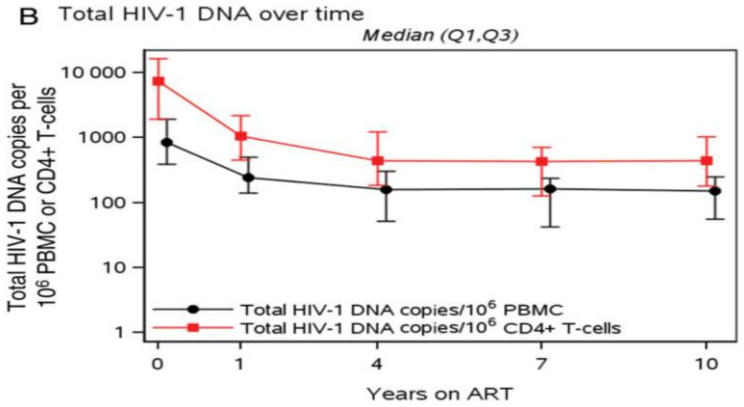
HIV Cure: stem cell transplantation: IciStem

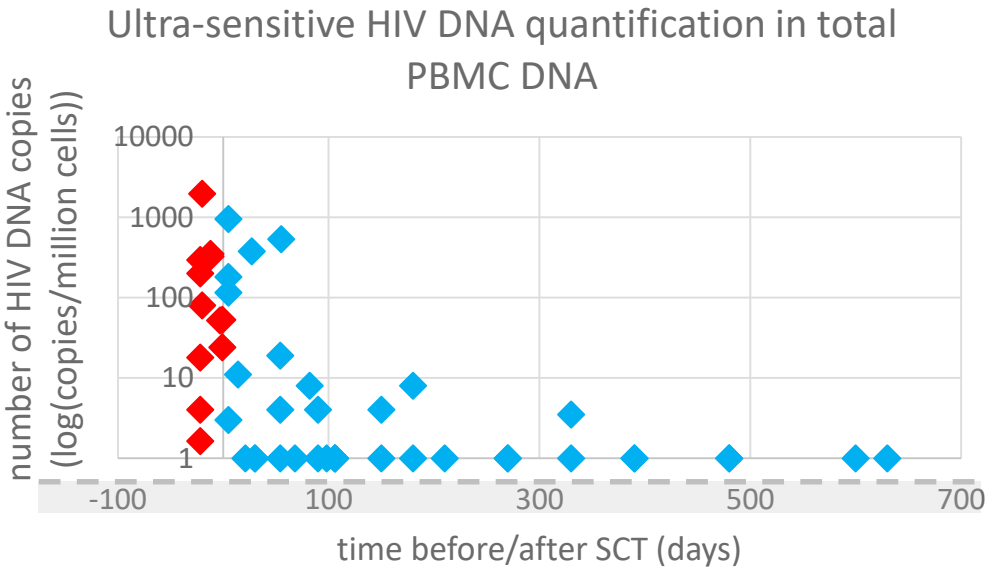
- 37 patients registered from 9 different countries
- 30 patients transplanted
- All patients are on ARVs
- Mean follow-up: 887 days
  -12 patients beyond 2nd year post-SCT

	CCR5WT/WT	CCR5Δ32/Δ32			alive
Adult Donor	20*	7	27	→	17
Umbilical Cord	1	2	3	→	1
	21	9			
	↓	↓	*3 CCR5 Δ32/WT		
alive	13	5			

ICISTEM

HIV Cure: stem cell transplantation: IciStem





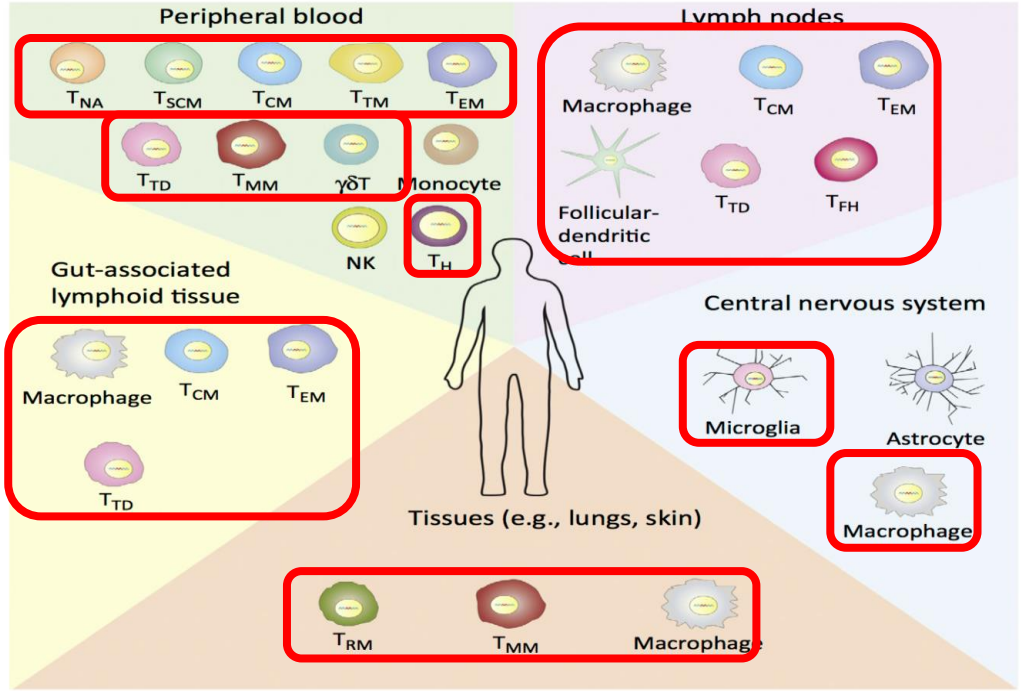
Besson et al, CID, 2014

HIV Cure: stem cell transplantation: IciStem

	IciS-19 CCR5d32 GvhD	IciS-03 CCR5WT GvhD
HI		
Measure of HIV reservoir = Measure of HIV cure		
Tot		
QVOA (IUPM)	undetectable	undetectable
MVOA	undetectable	undetectable

Salgado et al, Annals of Internal Medicine, 2018

Measure of viral reservoir



Autopsy studies (FIND study in SA)

Barton et al, T*rends in Microbiology,* 2016.

HIV Cure: stem cell transplantation: IciStem

NO HIV detected in CSF, gut and LN

HIV

Tot

Measure of HIV reservoir = Measure of HIV Cure

QV

Analytical treatment interruption

MV

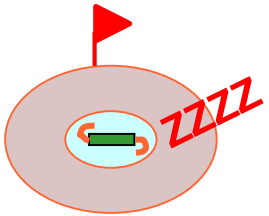
Salgado et al, Annals of Internal Medicine, 2018

Concluding remarks

- We have very sensitive techniques to measure the viral reservoir
- We can not measure the viral reservoir in the whole body

- Measure of HIV reservoir ≠ Measure of HIV cure

- A specific biomarker to identify the reservoir
  - Quantify and characterize the reservoir
  - Can be used in total body PET scan
  - Can be used in specific HIV targeting and elimination



Acknowledgements

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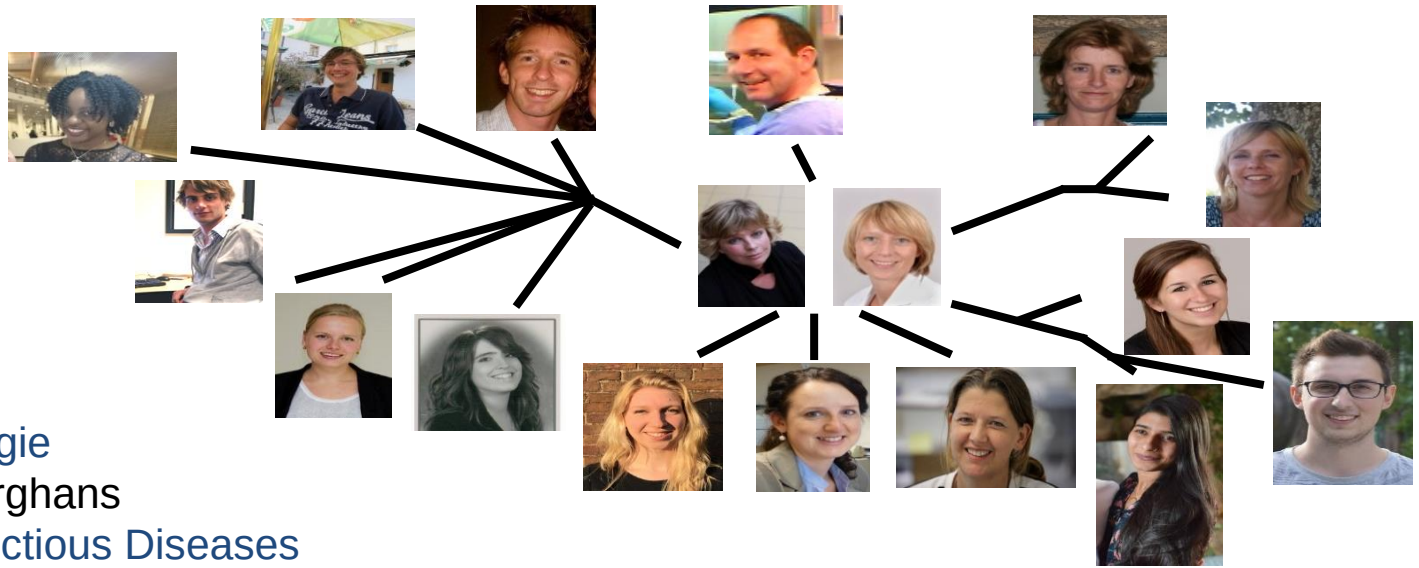

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MAKING AIDS HISTORY

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