Analytical Treatment Interruptions in HIV Cure Clinical Trials

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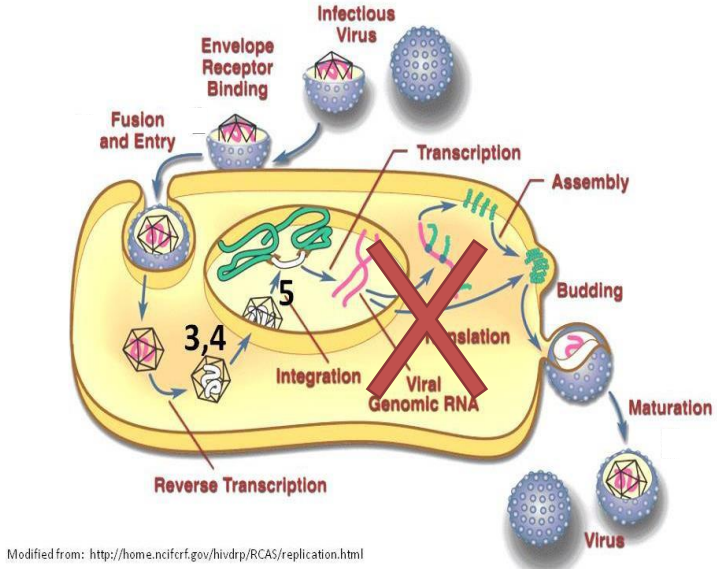
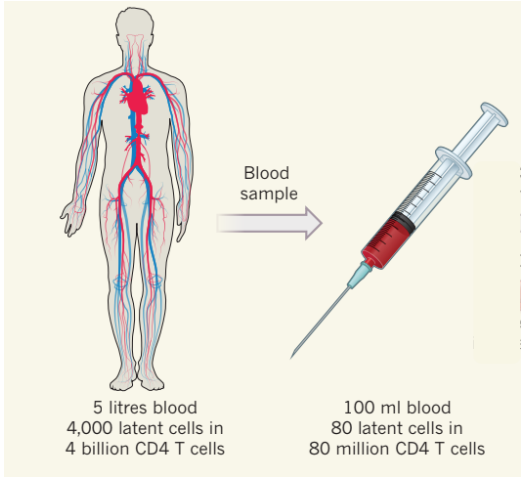
Overview

- What is the latent reservoir?
- How can we measure it?
- Analytical treatment interruptions
  - How they have been performed
  - For and against
  - Safety
  - PLHIV and provider attitudes towards ATI

HIV latency and infection of resting T-cells

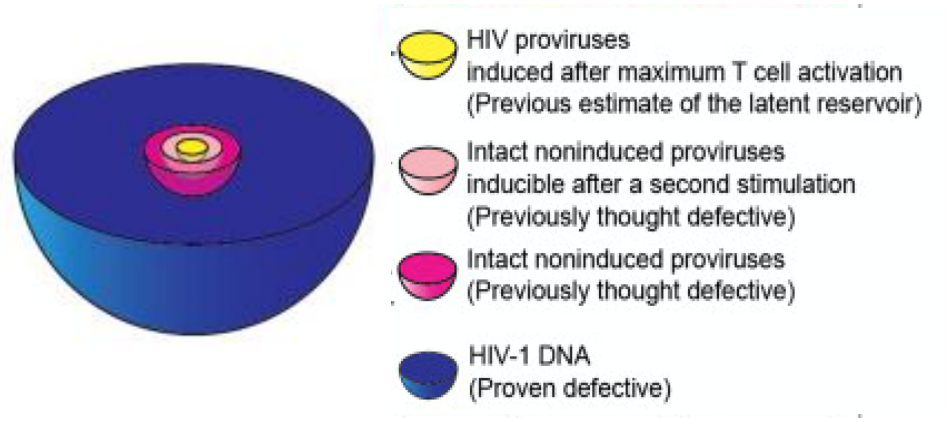


One in a million…



Adapted from Richman, Nature 2017

Intact versus defective virus



Ho, Cell, 2013

Measure	Method
Plasma RNA (HIV Viral load)	RT-PCR and single copy assay
Cell associated HIV RNA	RT-PCR
Total and integrated HIV DNA	HIV DNA by PCR
TILDA	RT-PCR to quantify multiply spliced HIV tat/rev transcripts using limiting dilutions of unstimulated or stimulated CD4 T cells
Viral DNA sequencing	Sanger sequencing or next generation sequencing
QVOA	Limiting dilutions of CD4 T cells co-cultured with uninfected cells to induce viral outgrowth and amplify infection. RT-PCR or p24 ELISA

What predicts virological control off ART?

- Lower pre-TI CA-RNA[1]
- Lower HIV-DNA[1-3]?
- Post treatment controllers more likely to have commenced ART in acute HIV infection[4-6]
- PD-1, Tim-3, Lag-3 strongly predict time to VL rebound[3]

[1]Li, AIDS, 2015; [2]Assoumou, AIDS 2015; [3]Hurst, Nature, 2015; [4]Saez-Cirion, PLoS Pathog. 2013; [5]Lodi, Arch Intern Med 2012, [6]Namazi, JID 2018,

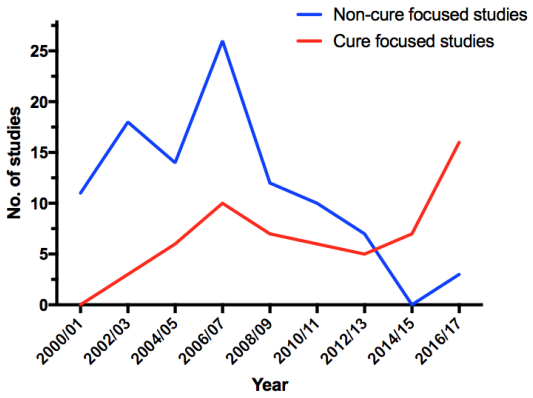
Analytical Treatment Interruptions

Gold standard test for an HIV cure intervention

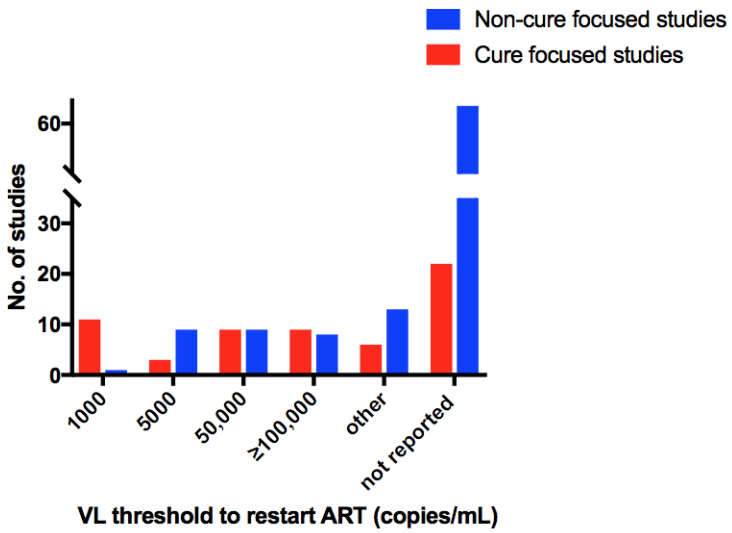
Temporary cessation of ART in a clinical trial with pre-set thresholds to restart therapy

Since 1999

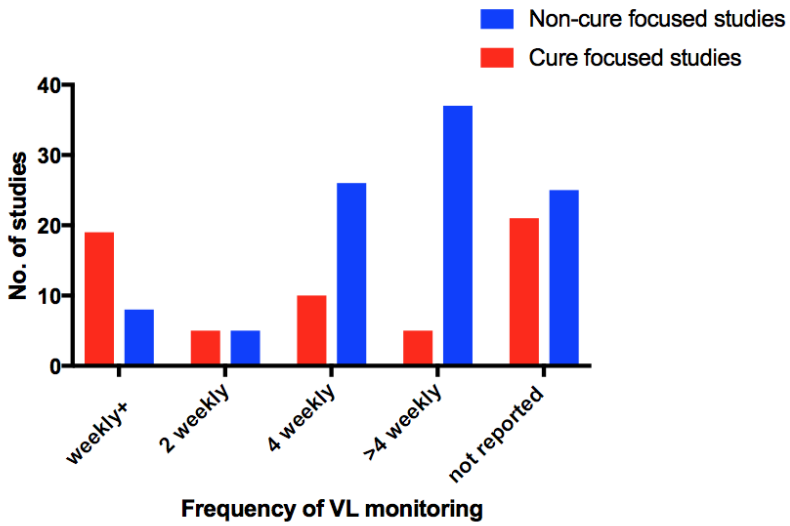
Evolved over time



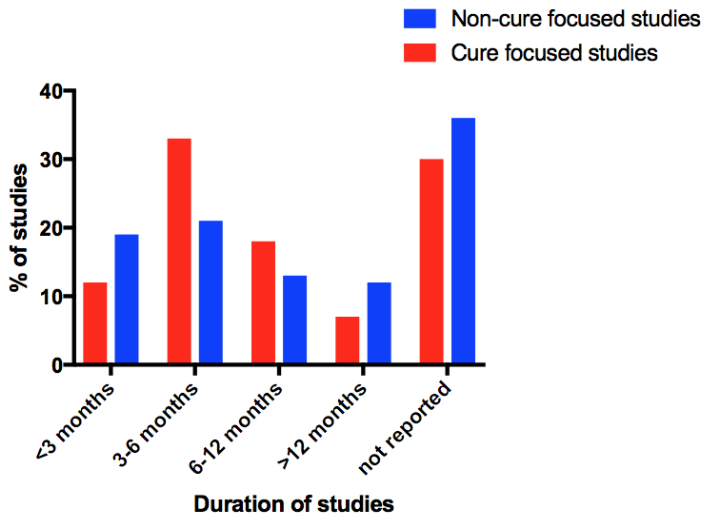
Lower VL threshold to restart ART in cure focused trials



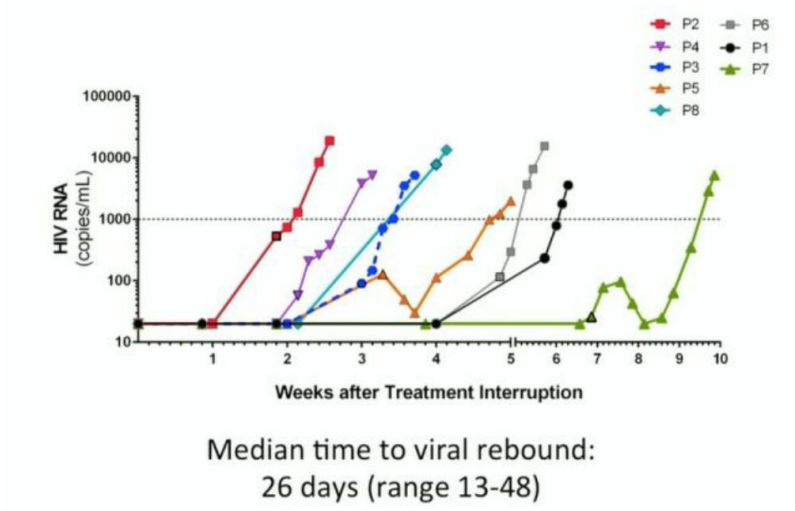
Cure focused studies monitor VL more frequently



Cure focused studies did not have shorter TI



Time to VL rebound

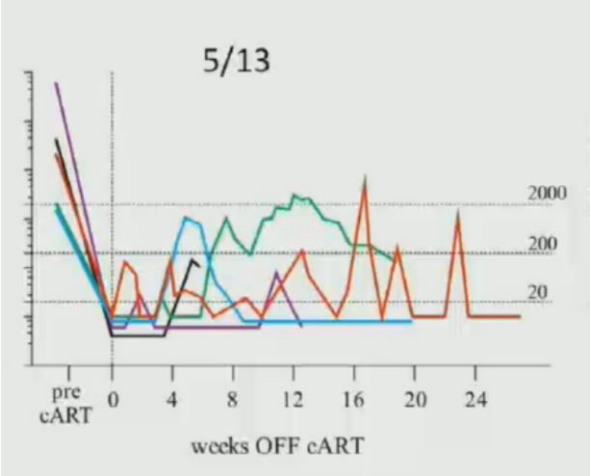


Median time to viral rebound:
26 days (range 13-48)

Colby, CROI, 2017 abstract no. 124, RV411 study

Set point

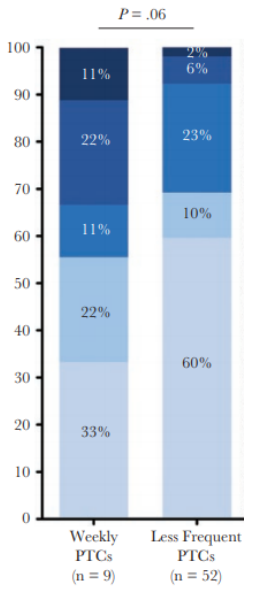
Therapeutic Vaccine and romidepsin in early treated HIV



Mothe, CROI, 2017 – abstract no. 119LB

CHAMP cohort

- 67 PTC from 14 ATI studies >700 participants
- PTC: VL ≤ 400c/mL for ≥24 weeks
- 45% had peak VL ≥ 1000c/mL
- 33% had peak VL ≥ 10,000c/mL



Namazi et al. JID 2018

ATI – The Debate

FOR

Steve Deeks, USCF, USA

- Can be safely performed
- Risks can be mitigated
- Informed consent can be obtained
- Needed to advance the science

AGAINST

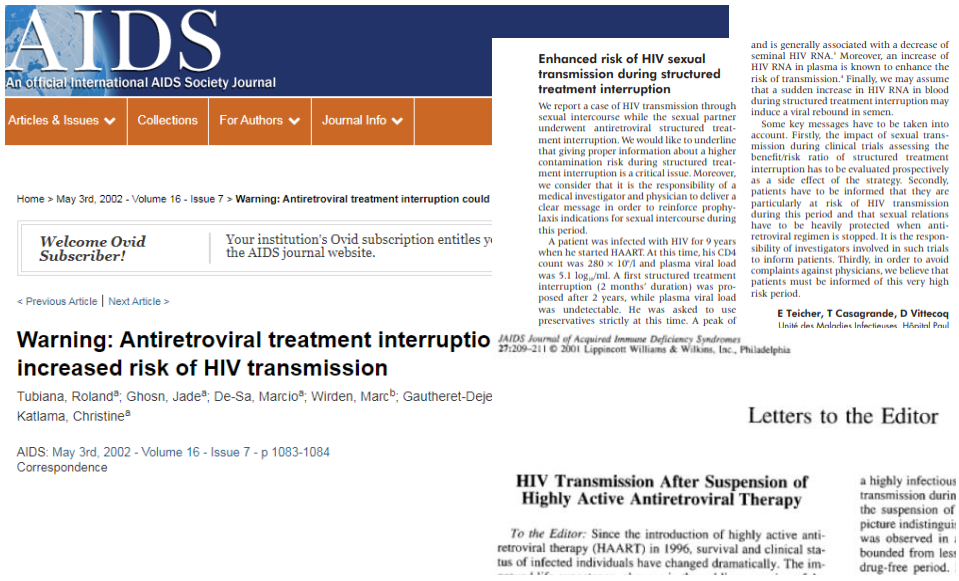
John Frater, Oxford, UK

- Can't guarantee they are safe
- No realistic cure interventions – no added value
- We don't know how to do a TI study properly
- May be useful one day, but not yet

Safety of TI

- Systematic review:
  - 31% non-cure focused studies reported AEs, compared to 25% cure focused studies
  - 1 death in cure focused studies
    - out of 2148 participants
    - Myocardial infarction 15 weeks into ATI

Transmission of HIV during TI



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Warning: Antiretroviral treatment interruptio increased risk of HIV transmission

Tubiana, Roland[a]; Ghosn, Jade[a]; De-Sa, Marcio[a]; Wirden, Marc[b]; Gautheret-Deje Katlama, Christine[a]

AIDS: May 3rd, 2002 - Volume 16 - Issue 7 - p 1083-1084
Correspondence

Enhanced risk of HIV sexual transmission during structured treatment interruption

We report a case of HIV transmission through sexual intercourse while the sexual partner underwent antiretroviral structured treatment interruption. We would like to underline that giving proper information about a higher contamination risk during structured treatment interruption is a critical issue. Moreover, we consider that it is the responsibility of a medical investigator and physician to deliver a clear message in order to reinforce prophylaxis indications for sexual intercourse during this period.

A patient was infected with HIV for 9 years when he started HAART. At this time, his CD4 count was 280 × 10⁶/l and plasma viral load was 5.1 $\log_{10}$/ml. A first structured treatment interruption (2 months' duration) was proposed after 2 years, while plasma viral load was undetectable. He was asked to use preservatives strictly at this time. A peak of

and is generally associated with a decrease of seminal HIV RNA.[3] Moreover, an increase of HIV RNA in plasma is known to enhance the risk of transmission.[4] Finally, we may assume that a sudden increase in HIV RNA in blood during structured treatment interruption may induce a viral rebound in semen.

Some key messages have to be taken into account. Firstly, the impact of sexual transmission during clinical trials assessing the benefit/risk ratio of structured treatment interruption has to be evaluated prospectively as a side effect of the strategy. Secondly, patients have to be informed that they are particularly at risk of HIV transmission during this period and that sexual relations have to be heavily protected when antiretroviral regimen is stopped. It is the responsibility of investigators involved in such trials to inform patients. Thirdly, in order to avoid complaints against physicians, we believe that patients must be informed of this very high risk period.

E Teicher, T Casagrande, D Vittecoq

JAIDS Journal of Acquired Immune Deficiency Syndromes
27:209–211 © 2001 Lippincott Williams & Wilkins, Inc., Philadelphia

Letters to the Editor

HIV Transmission After Suspension of Highly Active Antiretroviral Therapy

To the Editor: Since the introduction of highly active antiretroviral therapy (HAART) in 1996, survival and clinical status of infected individuals have changed dramatically. The im-

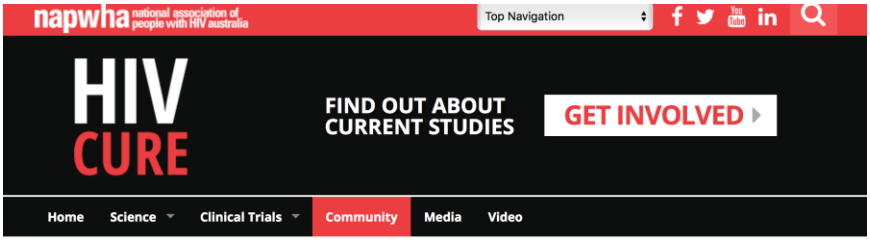
a highly infectious transmission durin the suspension of picture indistinguis was observed in bounded from less drug-free period.

Modern ATI is safe

- 7 trial cohorts, including BNAb study
- 31 participants
- No:
  - adverse events during TI
  - expansion of reservoir
  - new resistance mechanisms
  - long-term immunological abnormalities
  - virological failure ART resumption
  - transmissions of HIV

Clarridge, PLoS Pathog 2018, Bar (338), Strongin (335), Clarridge (334), CROI 2018

PLHIV and Provider Attitudes Towards ATI



PLHIV preferred monthly monitoring

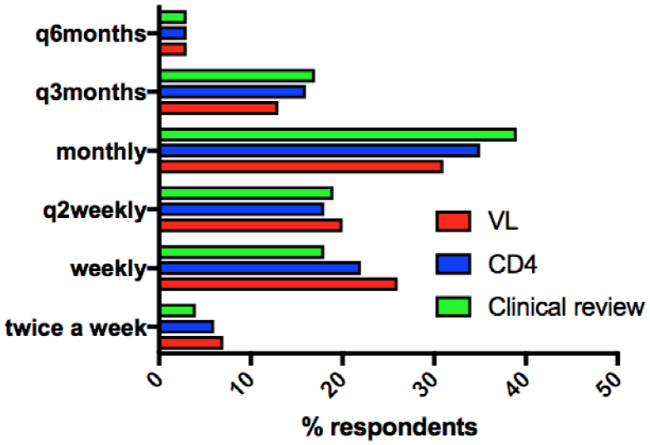


Fig.1: PLHIV preferred monthly monitoring

PLHIV less accepting of sustained viremia during ATI

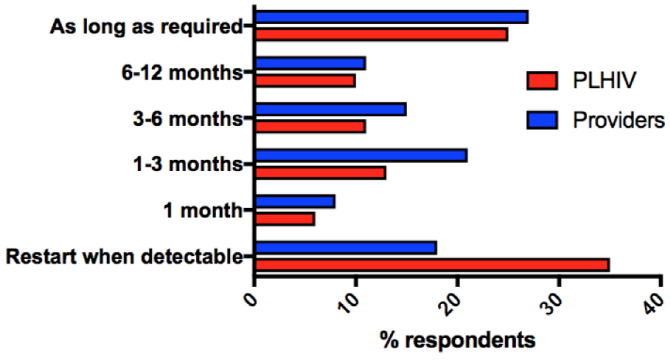
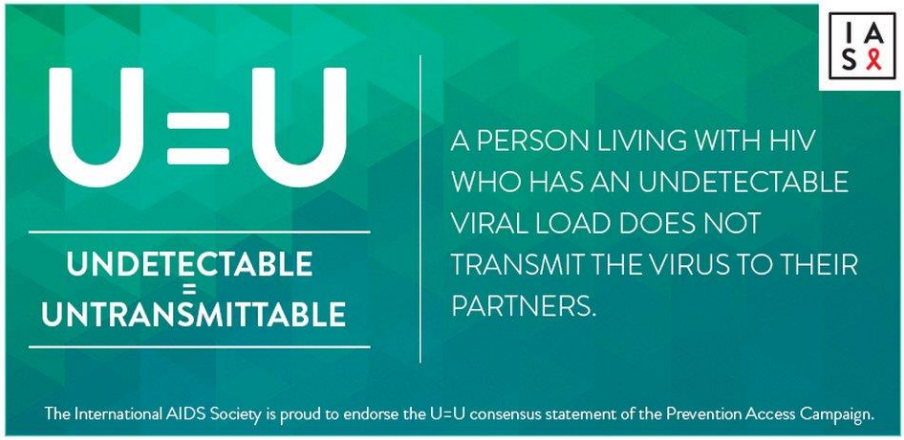
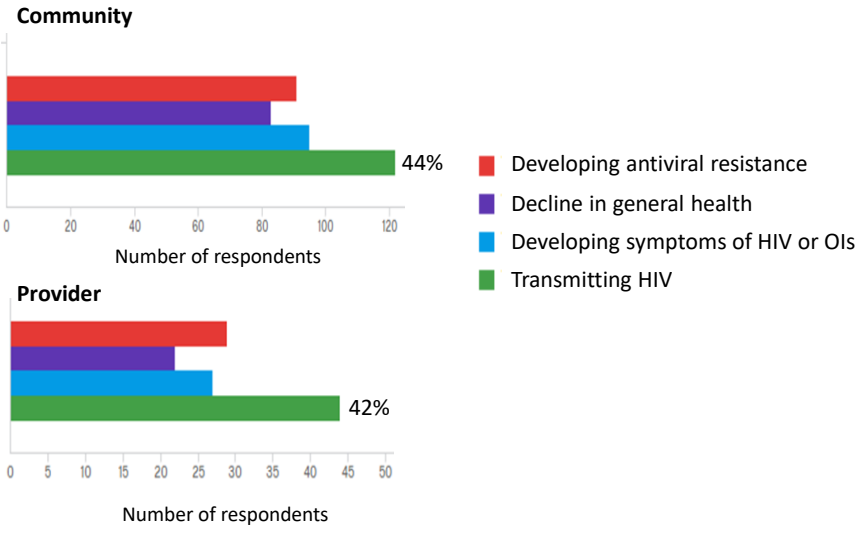


Fig. 2: Acceptable period of time off ART during ATI for PLHIV and Providers



PLHIV and their Providers were very concerned about transmission of HIV during ATI



Results

- 54% PLHIV more willing to participate if PrEP was offered for HIV negative partners
- PLHIV more optimistic of cure than Providers (55% vs 19% $p<0.001$)

Conclusions

- ATI increasingly being used to test HIV cure interventions
- Modern ATI is safe
- Disconnect between what PLHIV understand and expect from ATI and what is actually happening
- Education required
- PrEP and other strategies to reduce risk of transmission during ATI need to be embedded into trials

Acknowledgements

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