PEDIATRIC EXPERIENCE WITH ART INTERRUPTION

- SELF-SELECTED NONADHERENCE
- COST SAVING
- SELECTION OF WILD-TYPE VIRUS IN SOMEONE WITH HIGHLY RESISTANT STRAINS
- “DRUG HOLIDAY”
- AUTOLOGOUS VACCINATION STRATEGY

IS IT SAFE?

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RISKS ASSOCIATED WITH TREATMENT INTERRUPTION (ADULTS)

- SEVERE PRIMARY INFECTION-LIKE SYNDROME
- DECREASED CD4 T CELLS
- INCREASED RISK OF AIDS-RELATED EVENTS
- INCREASED RISK OF CARDIOVASCULAR EVENTS
- EMERGENCE OF DRUG RESISTANCE
- INCREASED RISK OF TRANSMISSION TO HIV NEGATIVE PARTNERS

RISKS ASSOCIATED WITH TREATMENT INTERRUPTION (Young Children)

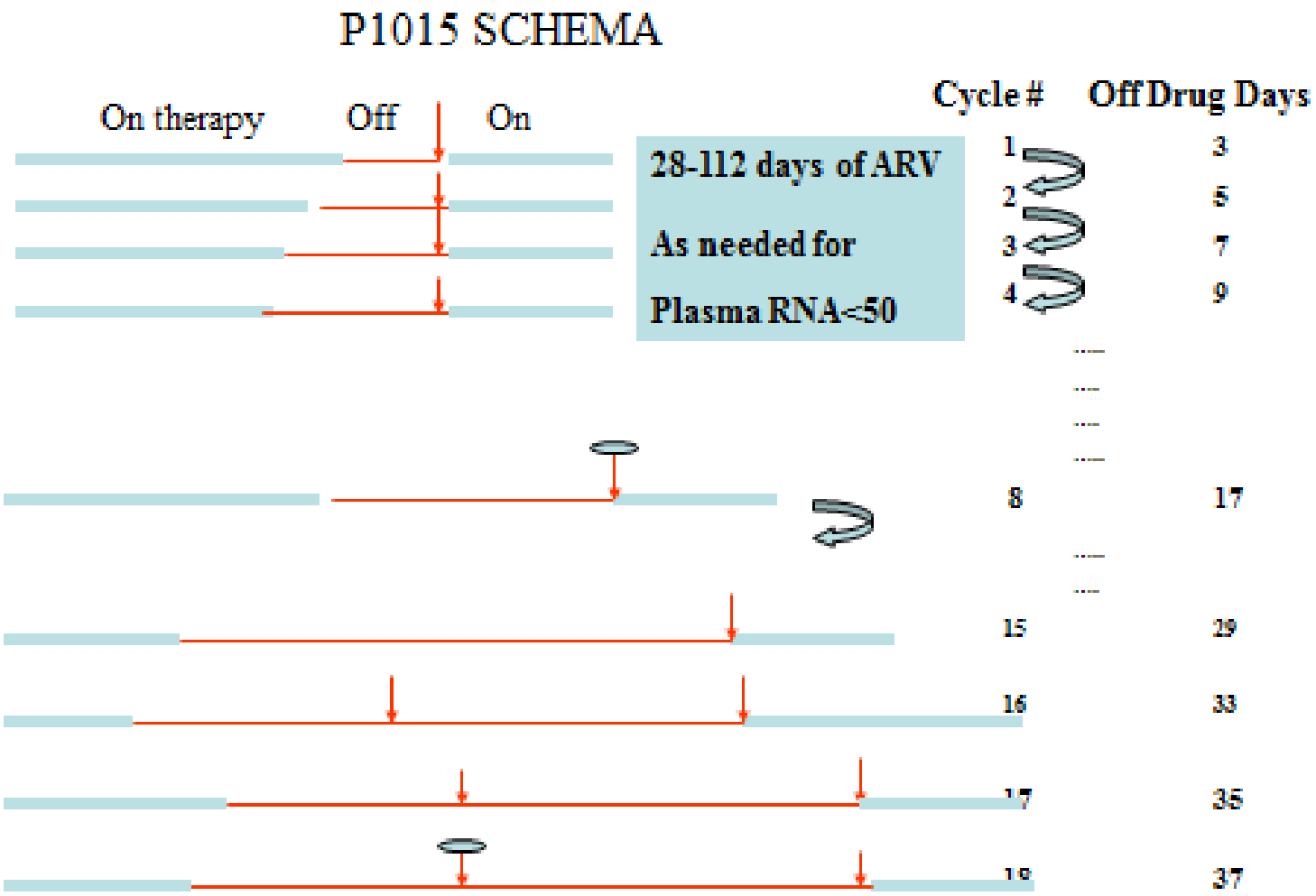
- SEVERE PRIMARY INFECTION-LIKE SYNDROME- not described
- DECREASED CD4 T CELLS- yes, but transient
- INCREASED RISK OF AIDS-RELATED EVENTS- not described
- INCREASED RISK OF CARDIOVASCULAR EVENTS- not described
- EMERGENCE OF DRUG RESISTANCE- possible, most frequently M184V
- INCREASED RISK OF TRANSMISSION TO HIV NEGATIVE PARTNERS- not described

- ✓ INCREASE IN LATENT HIV POPULATIONS- has been seen, possibly a transient phenomenon
- ✓ INCREASED NUMBER OF VISITS TO DETECT VIREMIA- ?weekly
- ✓ NEUROCOGNITIVE TOXICITY RESULTING FROM VIREMIA-not studied
- ✓ REMOVAL OF VIREMIC INDIVIDUALS FROM POOL AVAILABLE FOR OTHER INTERVENTIONS

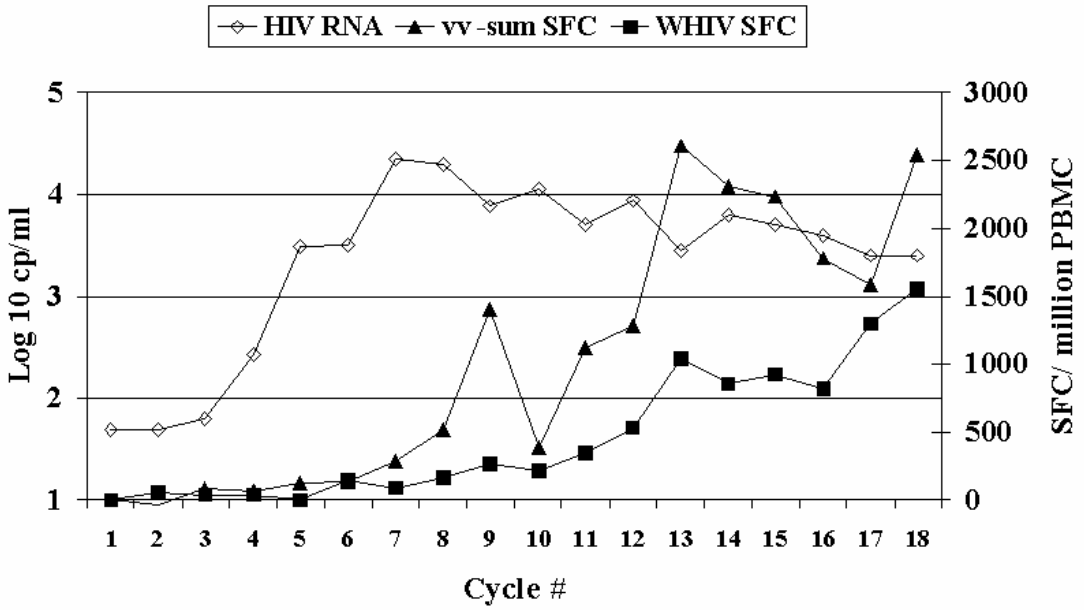
POTENTIAL BENEFITS OF TREATMENT INTERRUPTIONS (Young Children)

- ✓ CLOSEST ASSESSMENT OF LATENT DNA POOL SIZE (? GOLD STANDARD)
- ✓ INCREASE IN HIV-SPECIFIC CMI
- ✓ PURGING OF LATENT DNA VIA tat

Borkowsky et al. AIDS Res Hum Retrovirus (2008) 24:401-411

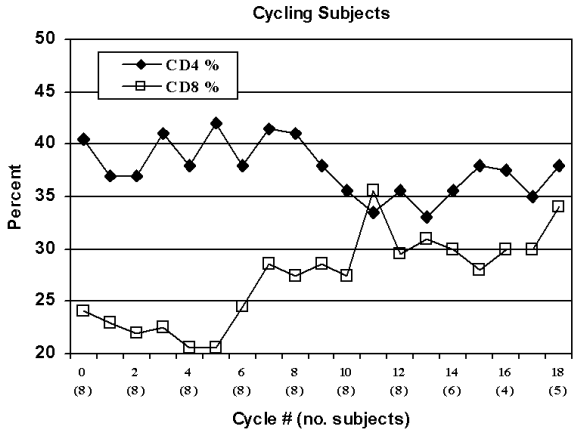


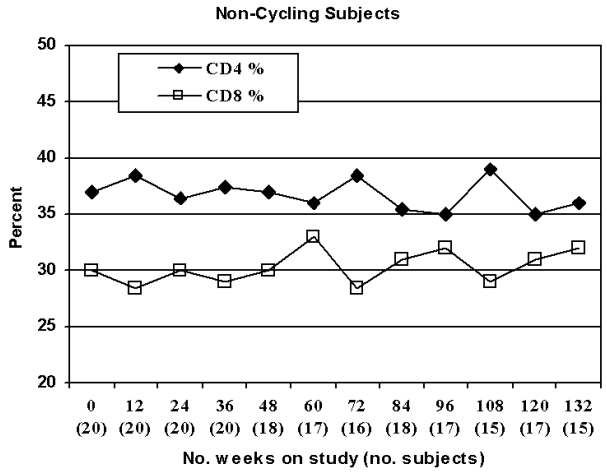
Intermittent Gradually Prolonging Treatment Interruptions Results in Increasing CMI and Decreasing HIV RNA



- 6-9 interruptions are required before HIV-specific CMI is demonstrated

Safety





CD4 percent change may reflect increase in CD8 percent. They are both percentages of CD3 T cells.

PENTA group **AIDS** 2010, **24**:231-241

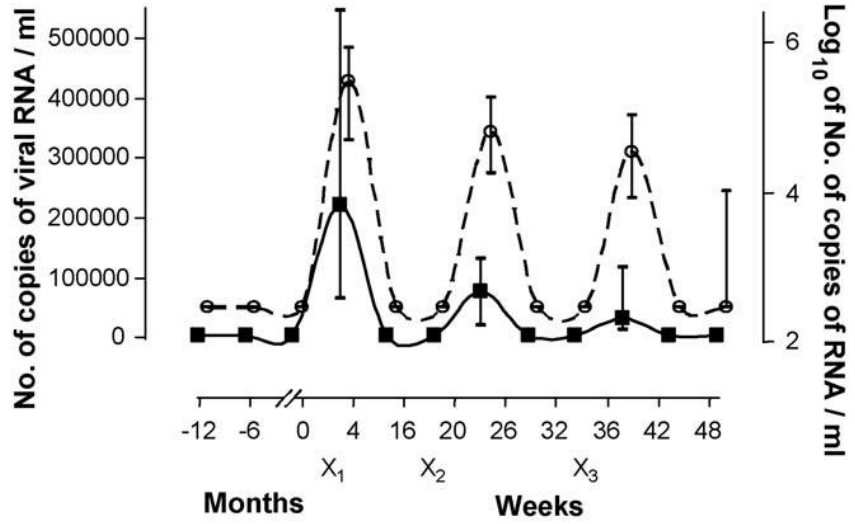
- 109 chronically infected children (2-15 yrs) with CD4% and # in 'nl' range
  - Median age 9
  - Median time on ART 6 yrs
  - Randomized to CART or TI; ART restarted if CD4<20% or at 48 wks

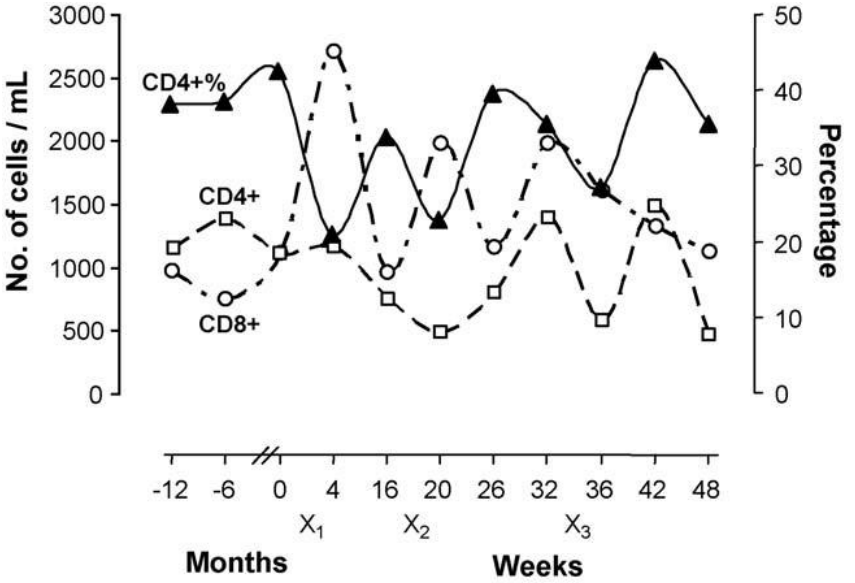
- 19/51 TI restarted based on CD4 criteria; 32/51 @48 wks
  - **Older age** starting ART predictive of early restart (3.3 vs 1.3 yrs, p=0.01)
  - **CD4 nadir predictive of early restart (13% vs 23%, p<0.001)**

While on ART, 10 CART and 9 TI children had viral load >100

- 5 CART and 5 TI had 1 or more resistance mutations (median of 5 in CART and 3 in TI group
- **NS differences in lab grade 2 abnormalities**
- Rate of Grade 2 or above clinical events more likely in TI group (50 vs 26)
  - 1/5 of TI events associated with lymphadenopathy/splenomegaly
  - 1/7 of TI events mild skin rash

Palacios GC et al. Int J Infect Dis (2010) **14: e34-e40**





4 Mexican children (6.5-11.2 yrs)

- <400 copies
- 4 wk TI/12 wk CART for 3 cycles

No AEs , nl growth

Wamalwa et al. AIDS 2016;30(15):2303-13. Nairobi cohort

- RCT trial with HIV-infected infants who complete **>2 yrs of ART** continue on ART (CART) or do TI and **followed for 18 months**
- **ART restart** based on **CD4%<25, a decrease in CD4# >1/3 peak**, more advanced WHO stage or weight loss to <5th%ile or cross of 2 weight for age %ile.

PreRandomization viral load >1,000		CD4% median	
CART 5/21	TI 5/21	CART 33 (30,40)	TI 34 (32,38)

18 month viral load >1,000		CD4% median	
CART 6/18	TI 5/21	CART 35 (27,42)	TI 35 (33,37)

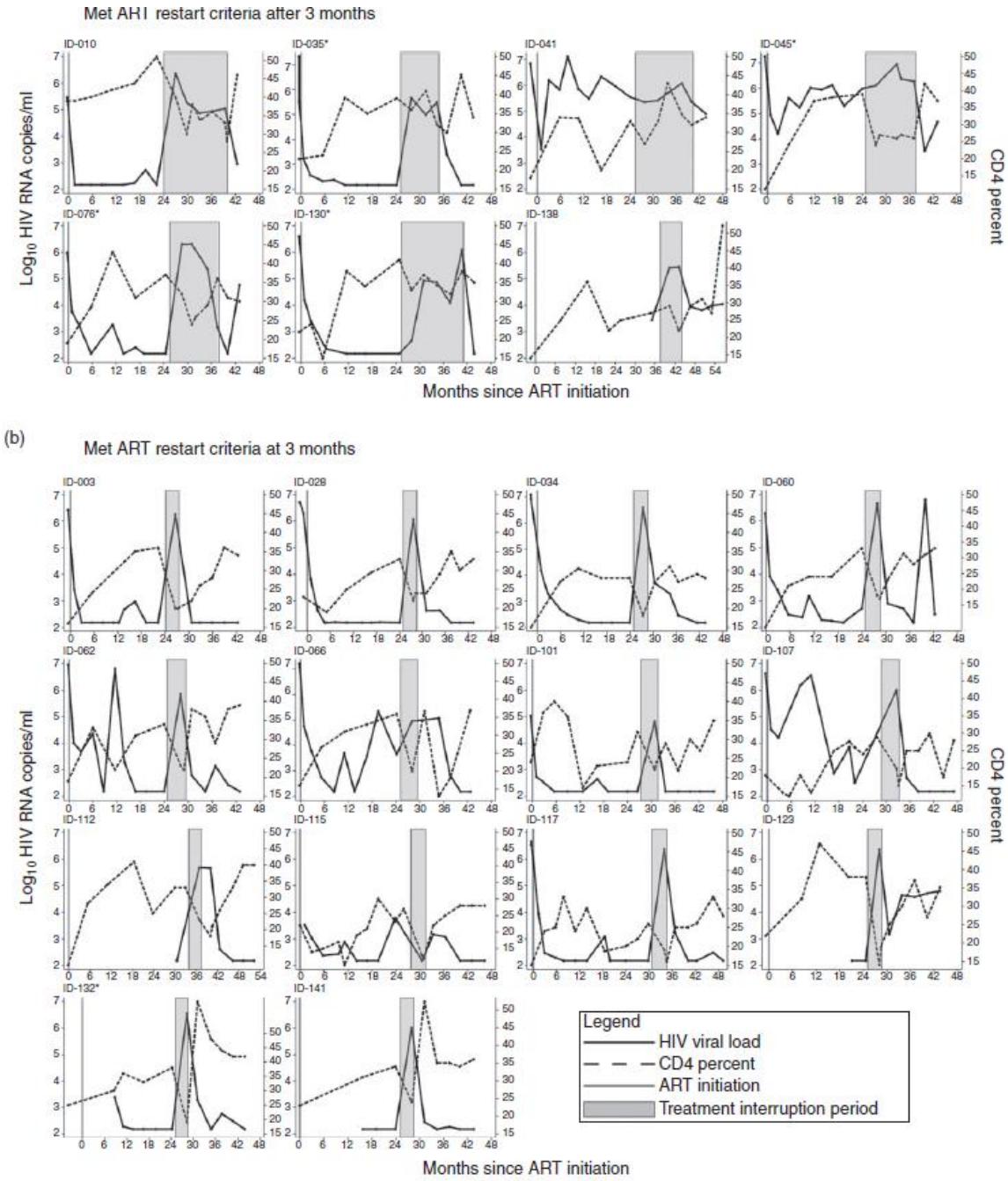
Morbidity and adverse events per 100 child years

SAEs, URI, Rash, Anemia, Diarrhea, Pneumonia, Lymphadenopathy, Death

- All NS

High Cholesterol

- Increased in CART (p=0.03)


Met ART restart criteria after 3 months
ID-010
ID-035*
ID-041
ID-045*
ID-076*
ID-130*
ID-138
Log10 HIV RNA copies/ml
CD4 percent
Months since ART initiation
(b)
Met ART restart criteria at 3 months
ID-003
ID-028
ID-034
ID-060
ID-062
ID-066
ID-101
ID-107
ID-112
ID-115
ID-117
ID-123
ID-132*
ID-141
Log10 HIV RNA copies/ml
CD4 percent
Months since ART initiation
Legend
HIV viral load
CD4 percent
ART initiation
Treatment interruption period

Neurocognitive effects of treatment interruption in stable HIV-positive patients in an observational cohort (A5170) in Neurology 2010

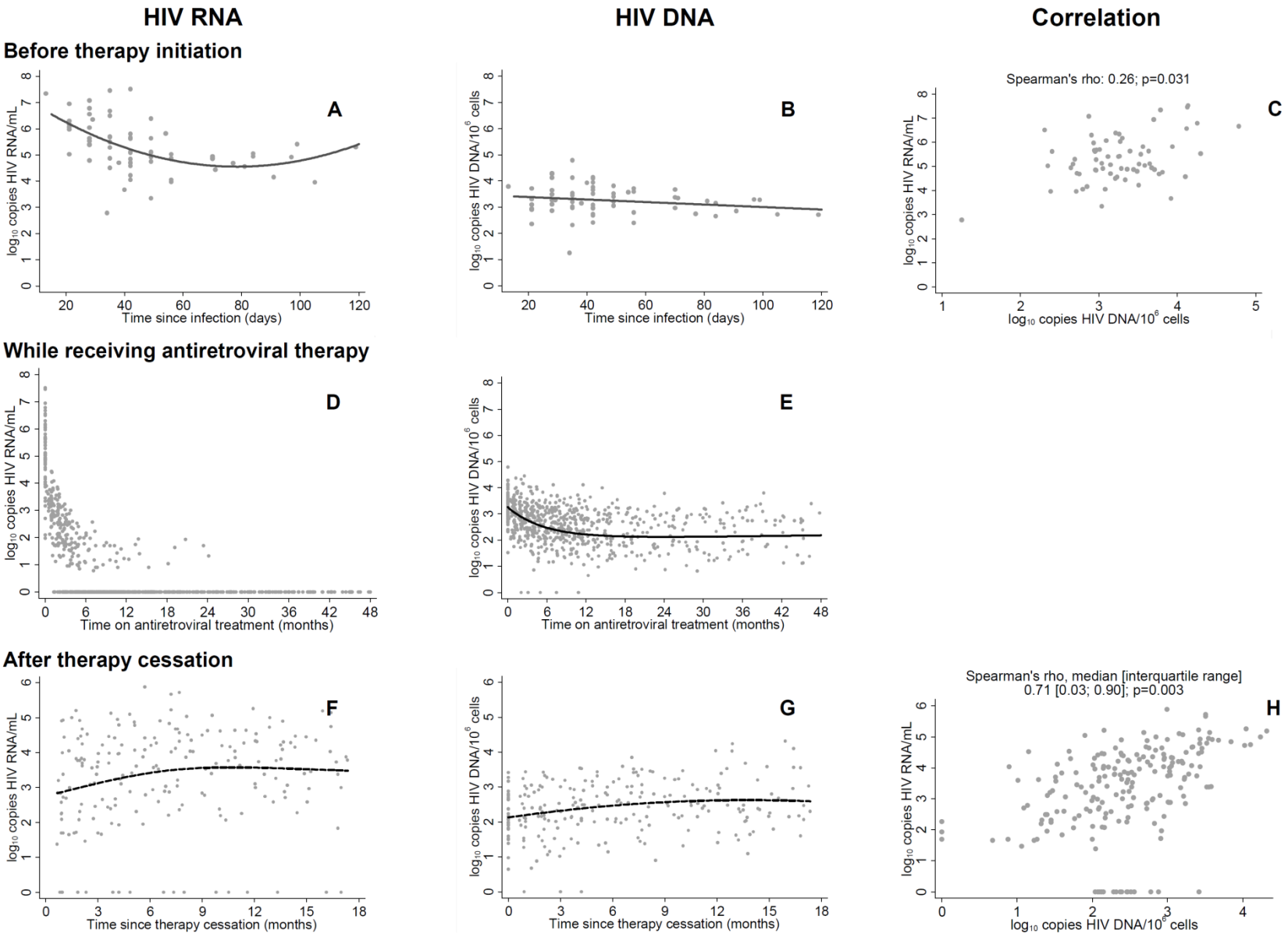
Objective: Prior studies have shown improved neurocognition with initiation of antiretroviral treatment (ART) in HIV. We hypothesized that stopping ART would be associated with poorer neurocognitive function.

Methods: Neurocognitive function was assessed as part of ACTG 5170, a multicenter, prospective observational study of HIV-infected subjects who elected to discontinue ART. Eligible subjects had CD4 count >350 cells/mm^3, had HIV RNA viral load <55,000 cp/mL, and were on ART (≥2 drugs) for ≥6 months. **Subjects stopped ART at study entry and were followed for 96 weeks with a neurocognitive examination**.

Results: A total of 167 subjects enrolled with a median nadir CD4 of 436 cells/mm^3 and 4.5 median years on ART. **Significant improvements in mean neuropsychological scores of 0.22, 0.39, 0.53, and 0.74 were found at weeks 24, 48, 72, and 96 (all $p < 0.001$**). In the 46 subjects who restarted ART prior to week 96, no significant changes in neurocognitive function were observed.

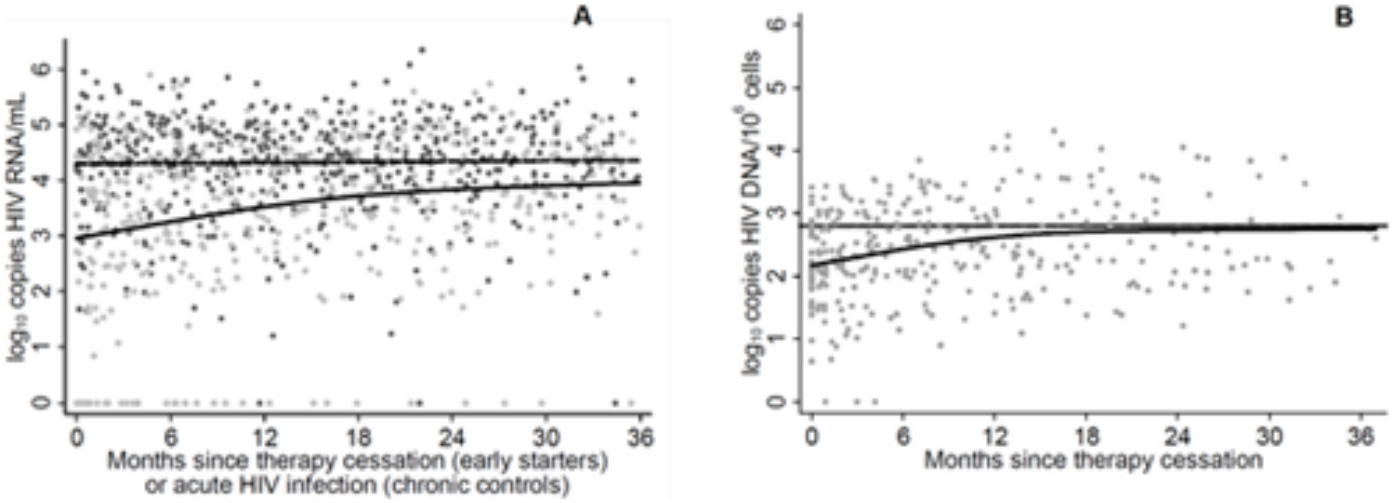
Conclusion: Subjects with preserved immune function found that neurocognition improved significantly following antiretroviral treatment (ART) discontinuation. The balance between the neurocognitive cost of untreated HIV viremia and the possible toxicities of ART require consideration.

Classification of evidence: This study provides Class III evidence that discontinuing ART is associated with an improvement in 2 neuropsychological tests (Trail-Making Test A & B and the Wechsler Adult Intelligence Scale–Revised Digit Symbol subtest) for up to 96 weeks. Resuming ART was not associated with a decline in these scores for up to 45 weeks.

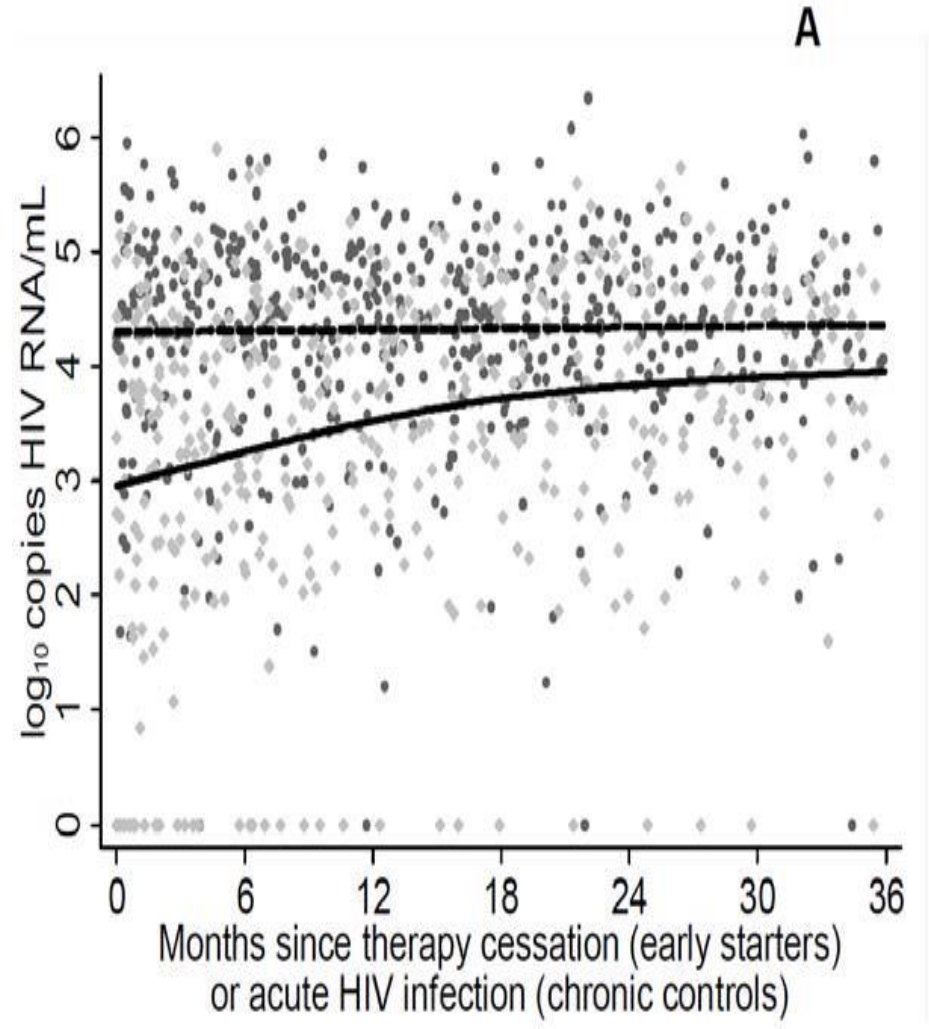


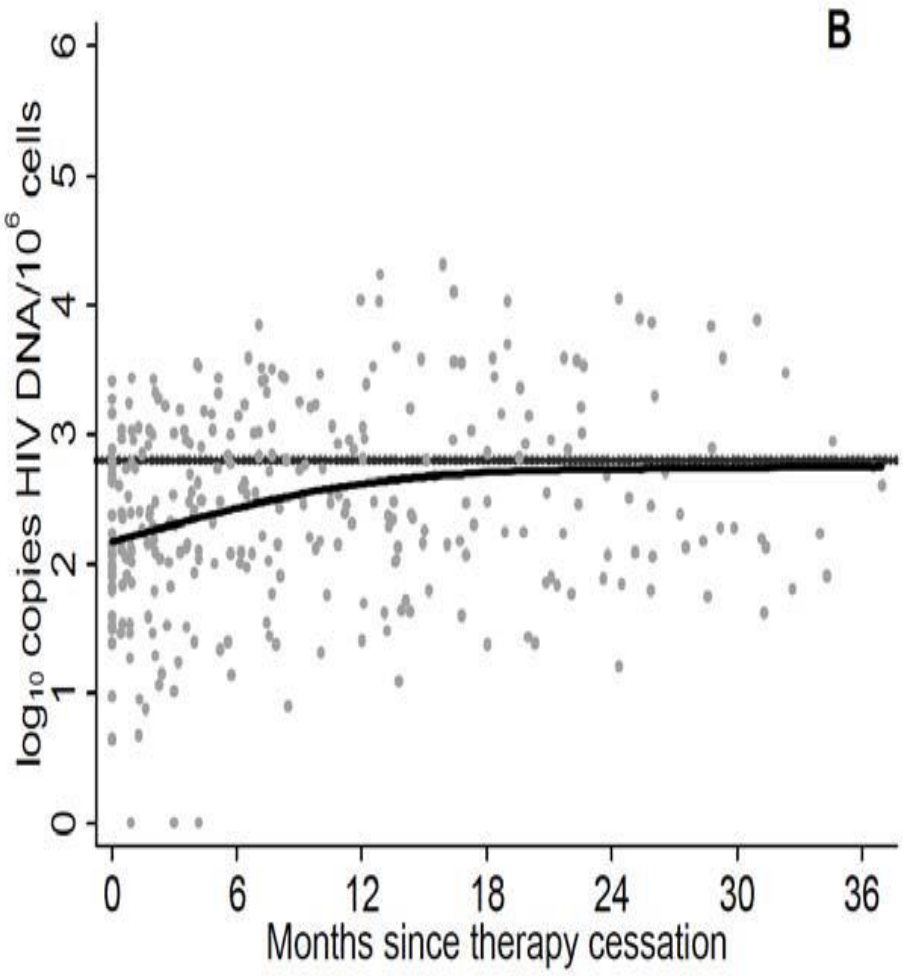
Wyl, Viktor von, et al. "Early Antiretroviral Therapy during Primary HIV-1 Infection Results in a Transient Reduction of the Viral Setpoint upon Treatment Interruption." PLoS One 6.11 (2011)ProQuest. Web. 24 May 2017

Figure 3. Long-termevolution of viral markers.

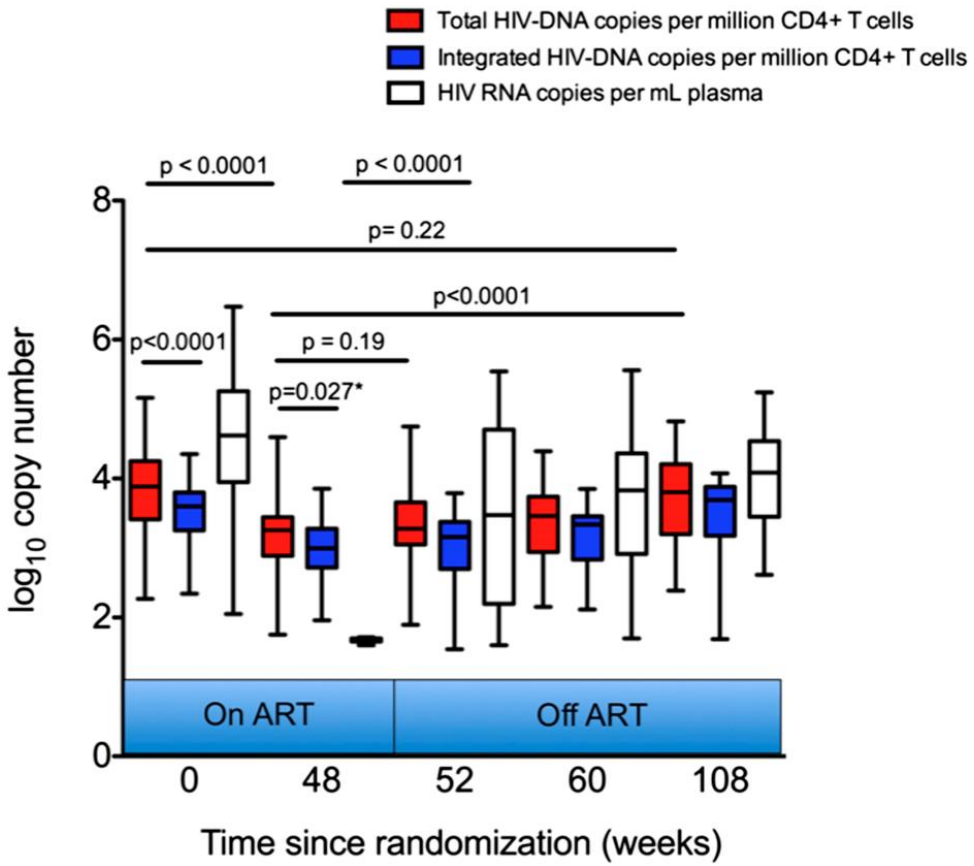


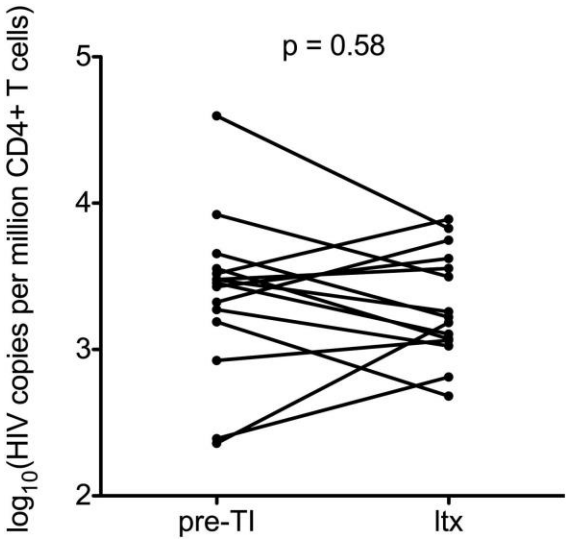
von Wyl V, Gianella S, Fischer M, Niederoest B, Kuster H, et al. (2011) Early Antiretroviral Therapy During Primary HIV-1 Infection Results In a Transient Reduction of the Viral Setpoint upon Treatment Interruption. PLOS ONE 6(11): e27463.
https://doi.org/10.1371/journal.pone.0027463
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0027463


A
log10 copies HIV RNA/mL
0
1
2
3
4
5
6
0
6
12
18
24
30
36
Months since therapy cessation (early starters)
or acute HIV infection (chronic controls)


B
log10 copies HIV DNA/10^6 cells
0
1
2
3
4
5
6
0
6
12
18
24
30
36
Months since therapy cessation

Williams et al. HIV-1 DNA predicts disease progression and post-treatment virological control. eLife 2014;3:e03821





Numbers analysed at each time-point					
Total DNA	154	47	46	32	48
Integrated DNA	111	47	39	27	31
Plasma VL	154	47	47	45	42

PROBLEMS ASSOCIATED WITH USING PBMC SURROGATE MARKERS

WHICH TISSUE? BLOOD? LYMPH NODE? BRAIN? GI TRACT? SEMEN?

Wong and Yuki. Tissue reservoirs of HIV.
Curr Opin HIV AIDS 2016:11;362-70

WHICH BLOOD CELL? Tcm? Tfh? MACROPHAGE? FDC?

HOW MANY BLOOD CELLS?

Tfh rare in peripheral blood

Ueno. J Clin Immunol 2016;36(suppl 1);34-9

DNA? RNA? SPLICED? UNSPLICED?

Table 1. Advantages and Limitations of Strategies to Quantify and Characterize the Human Immunodeficiency Virus Reservoir

Approach	Advantages	Limitations
Total and integrated HIV DNA by quantitative PCR (eg, real-time, digital PCR)	Highly sensitive, able to be performed on tissues and cells; inexpensive; high throughput	The majority of HIV DNA is defective and does not constitute replication-competent virus; variation in measurements across assays and laboratories; PCR inhibitors exist in various biofluids
Cell-associated HIV RNA by quantitative PCR	Highly sensitive, can be used to detect the entire spectrum of HIV transcript species within cells; inexpensive; high throughput	Usually measured from bulk cell extracts; sensitive to time of sampling and time from sampling to processing; variation in measurements across assays and laboratories; PCR inhibitors exist in various biofluids
Ultrasensitive measurement of residual plasma HIV RNA	Highly sensitive, may reflect the "active" HIV reservoir	Remains to be determined if replication-competent virus is exclusively characterized
qVOA	Provides measurement of replication-competent HIV reservoir	Expensive; time consuming; requires large numbers of cells; variation in results across assays and laboratories; primarily used on cells obtained from peripheral blood; challenging to obtain sufficient viable cells from tissues; some genetically intact viruses may not grow in culture
Inducible measures of HIV reactivation (eg, TILDA)	Provides measure of the percentage or number of cells in which HIV reactivates upon maximal stimulation; relatively high throughput; requires fewer cells than traditional qVOA	Does not provide measures of replication competence as RNA can be generated from defective viral genomes; challenges with downstream isolation and characterization of genomic DNA or mRNA from individual cells
Viral protein quantification (eg, HIV p24)	Measures virus with sufficient genetic integrity to drive transcription, translation, and downstream processing	May overestimate viral reservoir size as replication-incompetent viruses may still generate protein
PET-based imaging/nuclear medicine	Has the potential to survey the whole-body HIV reservoir in various tissues and anatomical locations	In development; requires expression of viral protein and may lack sensitivity required to detect latently infected cells or low levels of viral transcriptional and translational activity in antiretroviral-treated individuals; potential for low signal to noise ratios; expensive; involves in vivo radiation exposure
Single-cell HIV reservoir characterization	Potential to lead to a greater understanding of the genomic and transcriptional differences between actively infected, latently infected and uninfected cells	Commercially available platforms are expensive and lack the throughput to characterize millions of cells that may be required given low frequency of latently infected CD4 T cells in individuals on ART; higher throughput assays still in development
Measurement of anti-HIV immune responses (indirect marker)	Titer and avidity of HIV antibodies may represent whole-body, tissue-based HIV persistence and be useful in predicting HIV recrudescence following ATI	Heterogeneous responses; larger longitudinal and cross-sectional studies required to rigorously associate immune responses with reservoir size and HIV rebound dynamics

Abbreviations: ART, antiretroviral therapy; ATI, analytical treatment interruptions; HIV, human immunodeficiency virus; mRNA, messenger RNA; PCR, polymerase chain reaction; PET, positron emission tomography; qVOA, quantitative viral outgrowth assay; TILDA, Tat/Rev-induced limiting dilution assay.

Measuring the Size of the Latent Human Immunodeficiency Virus Reservoir: The Present and Future of Evaluating Eradication Strategies

Timothy J. Henrich,[1] Steven G. Deeks,[2] and Satish K. Pillai[3]

Heinrich, Deeks and Pilla

Measuring the size of the latent Human Immunodeficiency virus reservoir: the present and future of evaluating eradication strategies.

JID 2017:215 (suppl 3) S134-41

“Currently, interrupting ART for a certain duration is the only definitive approach to determining the efficacy of a particular HIV cure strategy”

Brandon S. Razooky, Anand Pai, ...,
Igor M. Rouzine, Leor S. Weinberger