Should we treat acute HIV infection?

Cape Town South African clinicians meeting
September 2014

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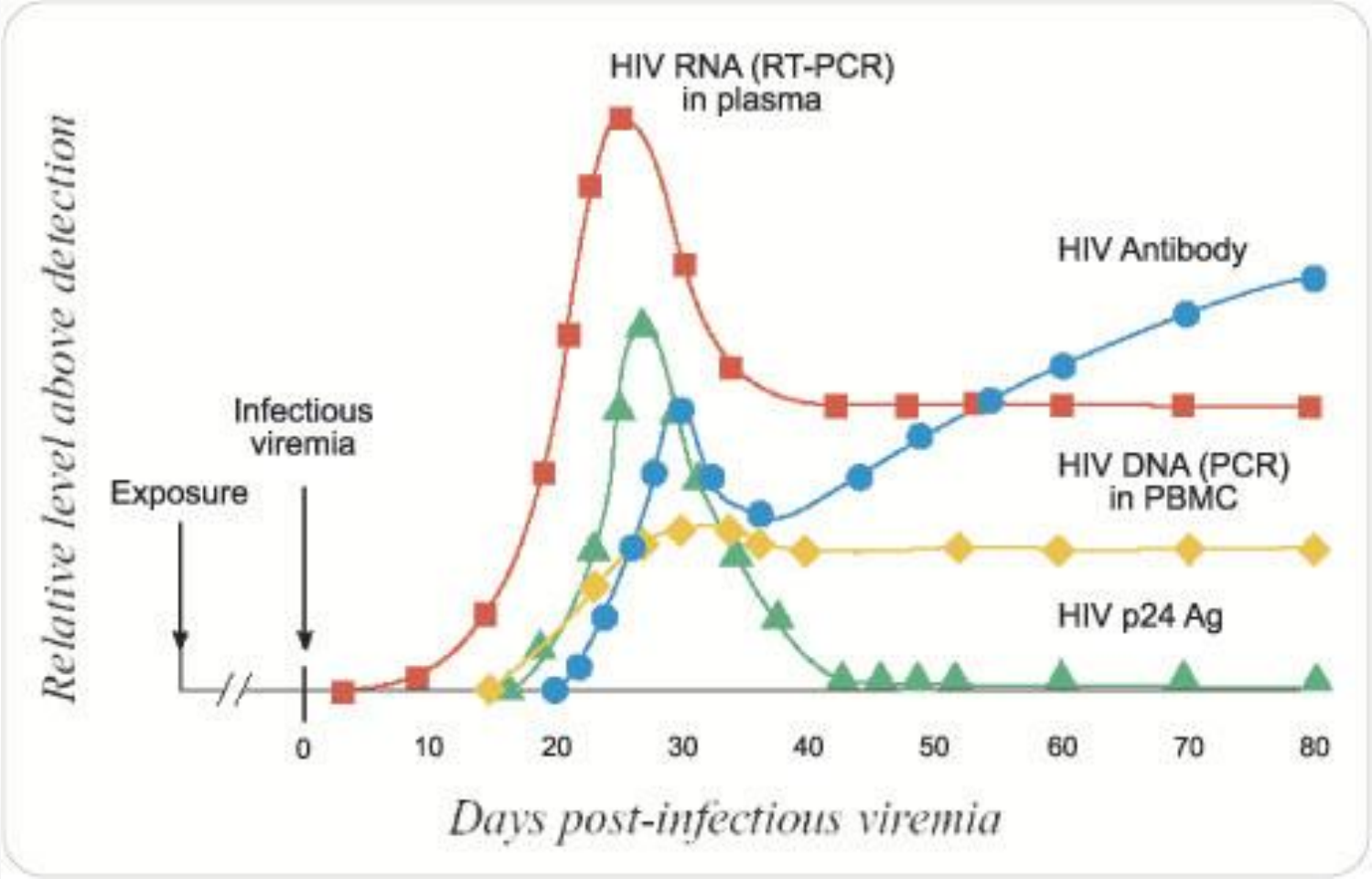
Days post-infection



Adapted from New York State Department of Health AIDS Institute. Available from http://www.hivguidelines.org/wp-content/uploads/2012/10/acute-hiv-infection-in-pregnancy-10-16-2012.pdf [accessed 26 Mar 2014].

How do we identify acute HIV?

- The presence of discordant rapid tests
- The presence of virus, RNA, DNA or p24 antigen with a negative rapid test
- Sick with signs of acute viral illness with previous or current negative POCT
- Various research “cross sectional incidence assays” in development based on an algorithm of viral load, CD4 count, antibody “avidity”

What should we consider when contemplating immediate ART?

- **Individual patient DO NO HARM** what is the evidence supports immediate intervention in PHI
  - Virologic rationale for ART in PHI
  - Immunological rationale for ART in PHI

- **Population level** reasons to treat acute HIV **DO NO HARM**

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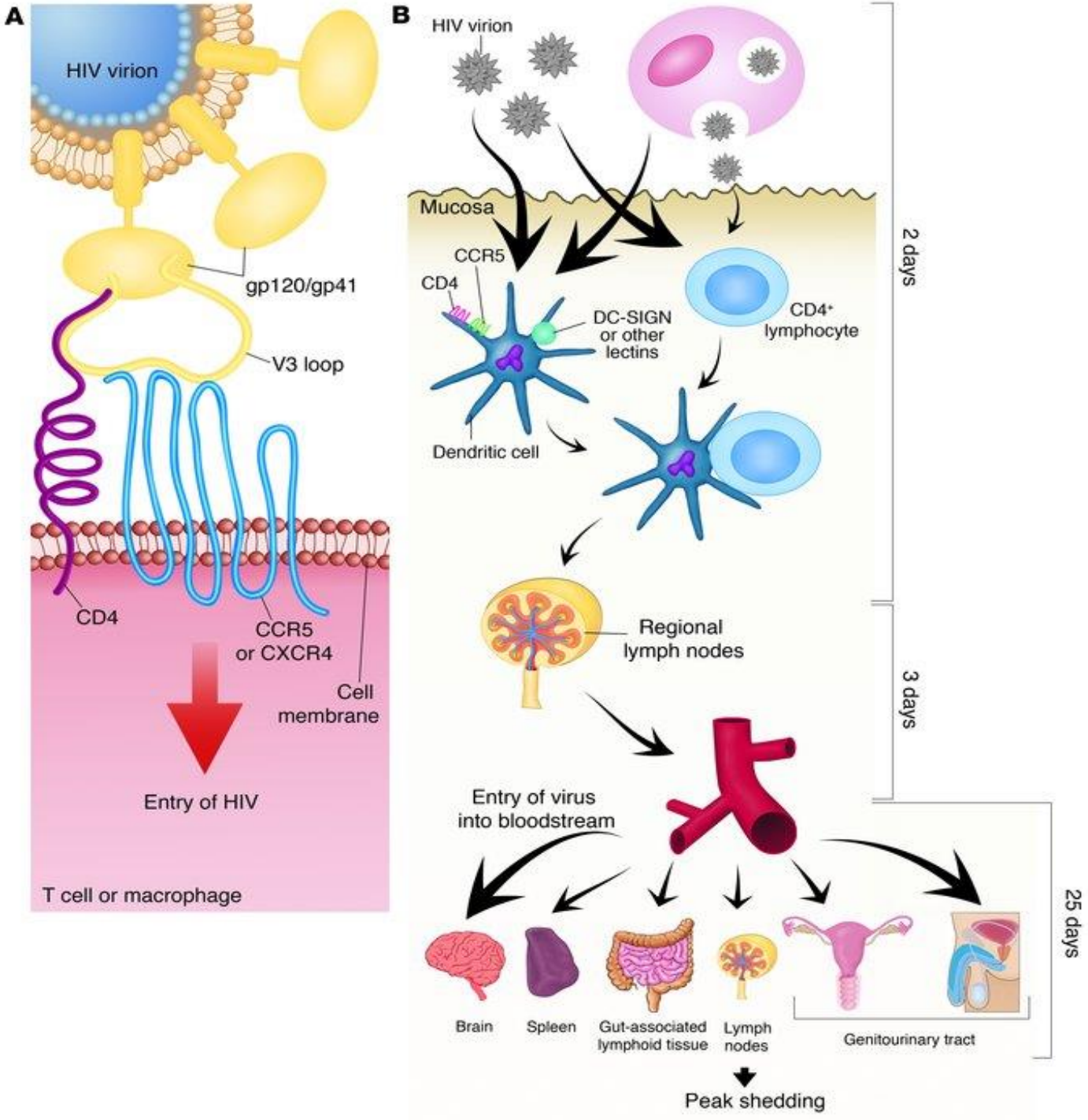
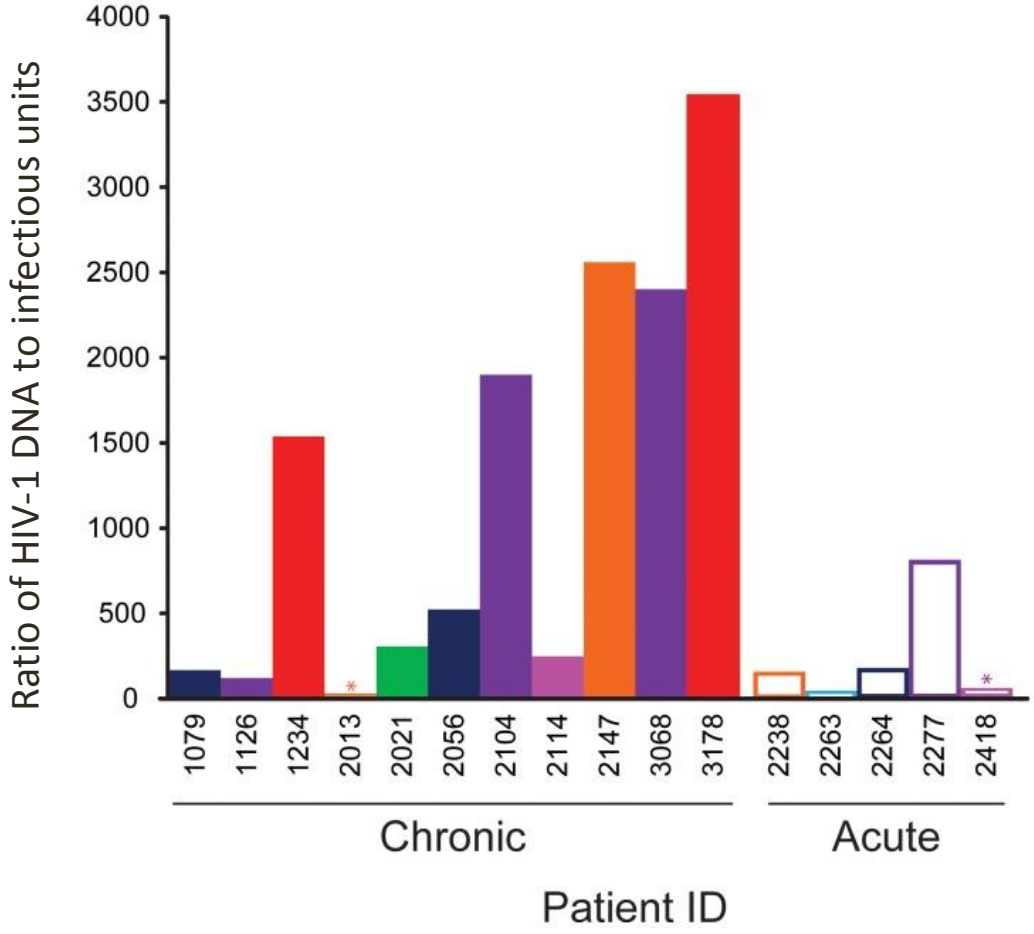
Evidence supporting immediate ART at seroconversion

Individual patient benefit vs risks

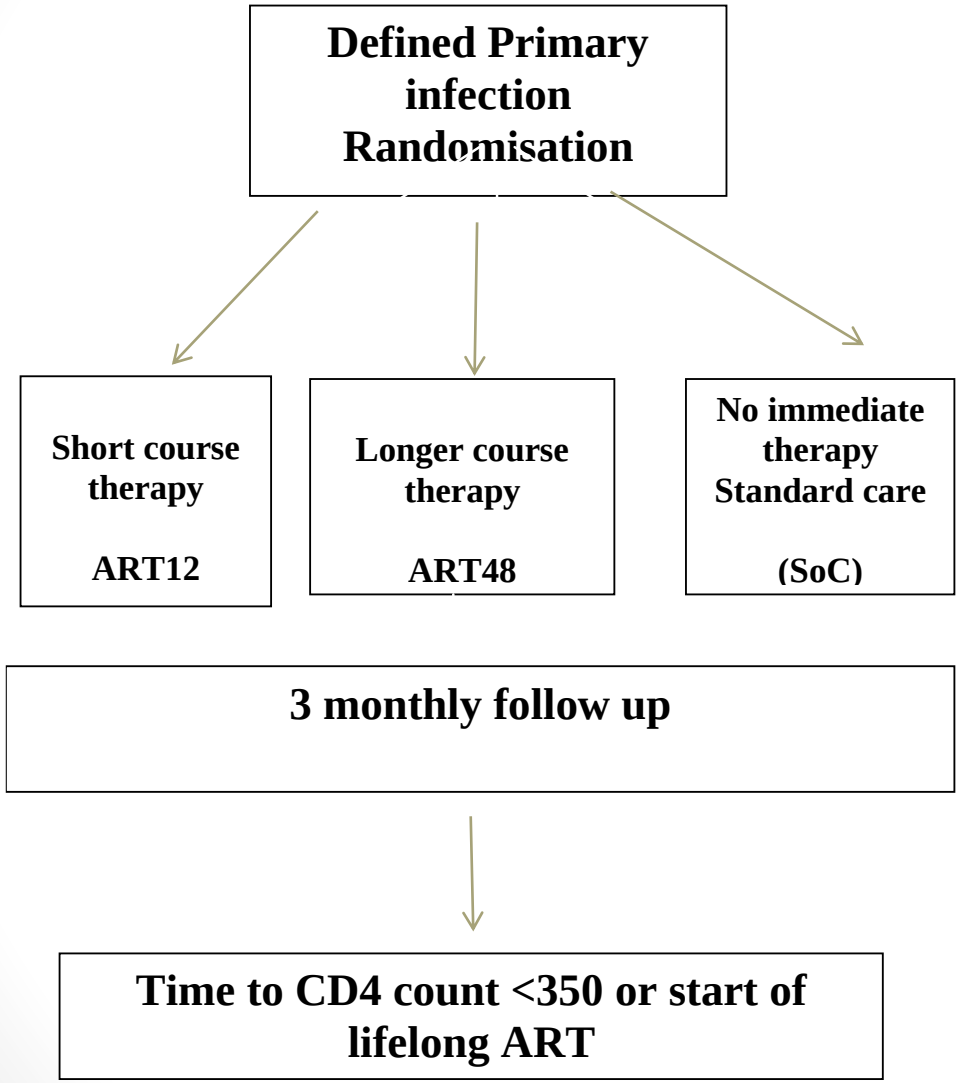

A
HIV virion
gp120/gp41
V3 loop
CD4
CCR5
or CXCR4
Cell
membrane
Entry of HIV
T cell or macrophage
B
HIV virion
Mucosa
CCR5
CD4
DC-SIGN
or other
lectins
CD4+
lymphocyte
Dendritic cell
2 days
Regional
lymph nodes
3 days
Entry of virus
into bloodstream
Brain
Spleen
Gut-associated
lymphoid tissue
Lymph
nodes
Genitourinary tract
25 days
Peak shedding

Reservoir of HIV is less in acutely infected individuals



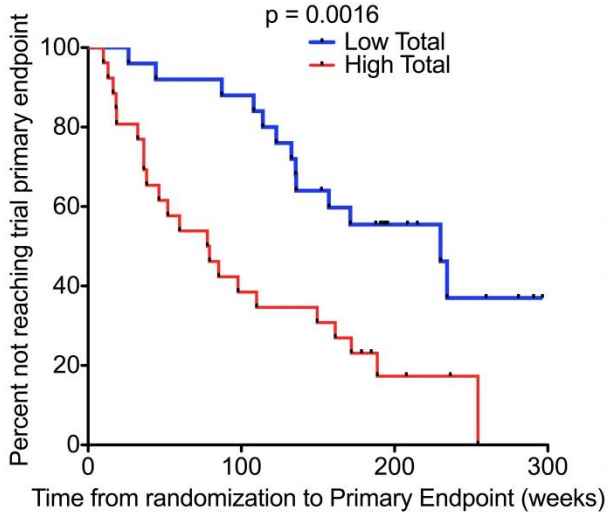
* Indicates maximum values in cases in which the HIV-1 DNA level was below the limit of detection (2 copies/ml).
Eriksson et al. PLoS Pathog 2013;9:e1003174.

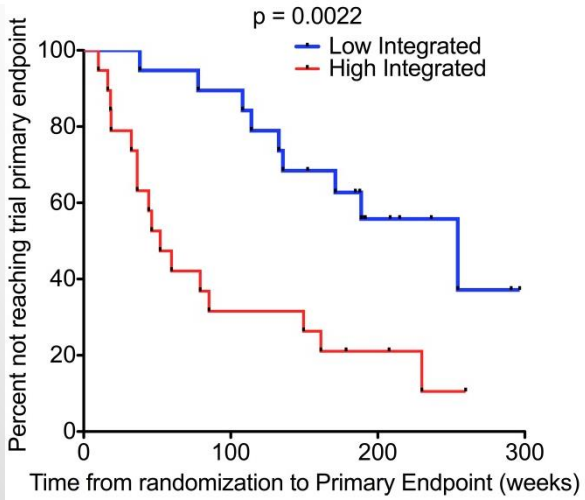
SPARTAC



PHI laboratory evidence of infection within 6 months of a previous negative test, <3 bands WB, RITA incident, antibody negative PCR+

HIV-1 DNA predicts TRIAL endpoint in untreated participants





Untreated individuals from PHI :
Cox Model:

Univariable predictors:

Total HIV-1 DNA HR 4.16 (CI 2.10-8.26); p <0.0001*

Int HIV-1 DNA HR 5.41 (CI 1.65-18.04); p = 0.006

Plasma VL HR 1.74 (CI 1.13-2.68); p = 0.011

Multivariable analyses

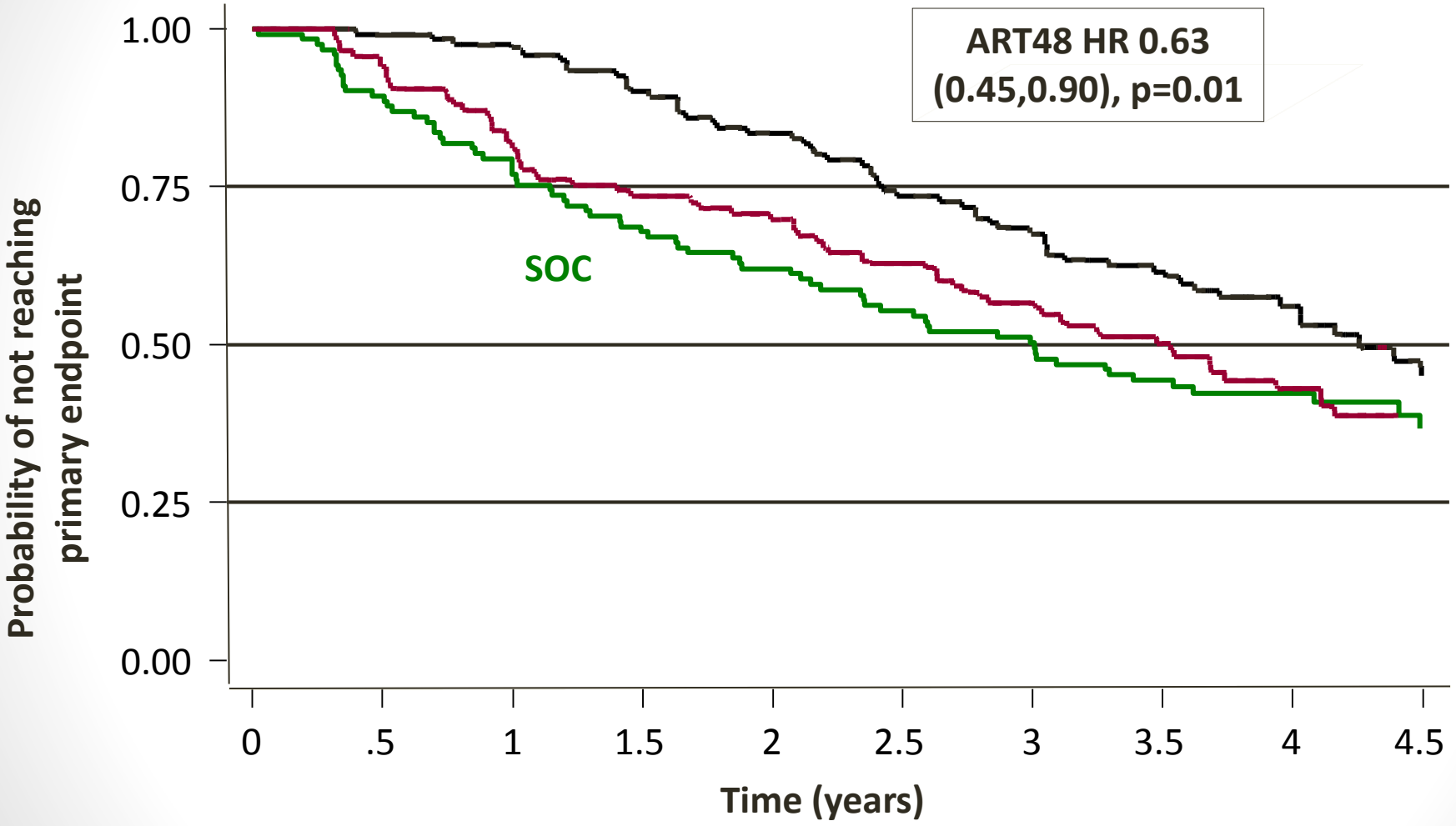
Total HIV-1 DNA HR=3.57 (1.58-8.08); p=0.002

CD4 count HR=0.67 (0.53-0.84); p<0.001

*HR = per $\log_{10}$ increase

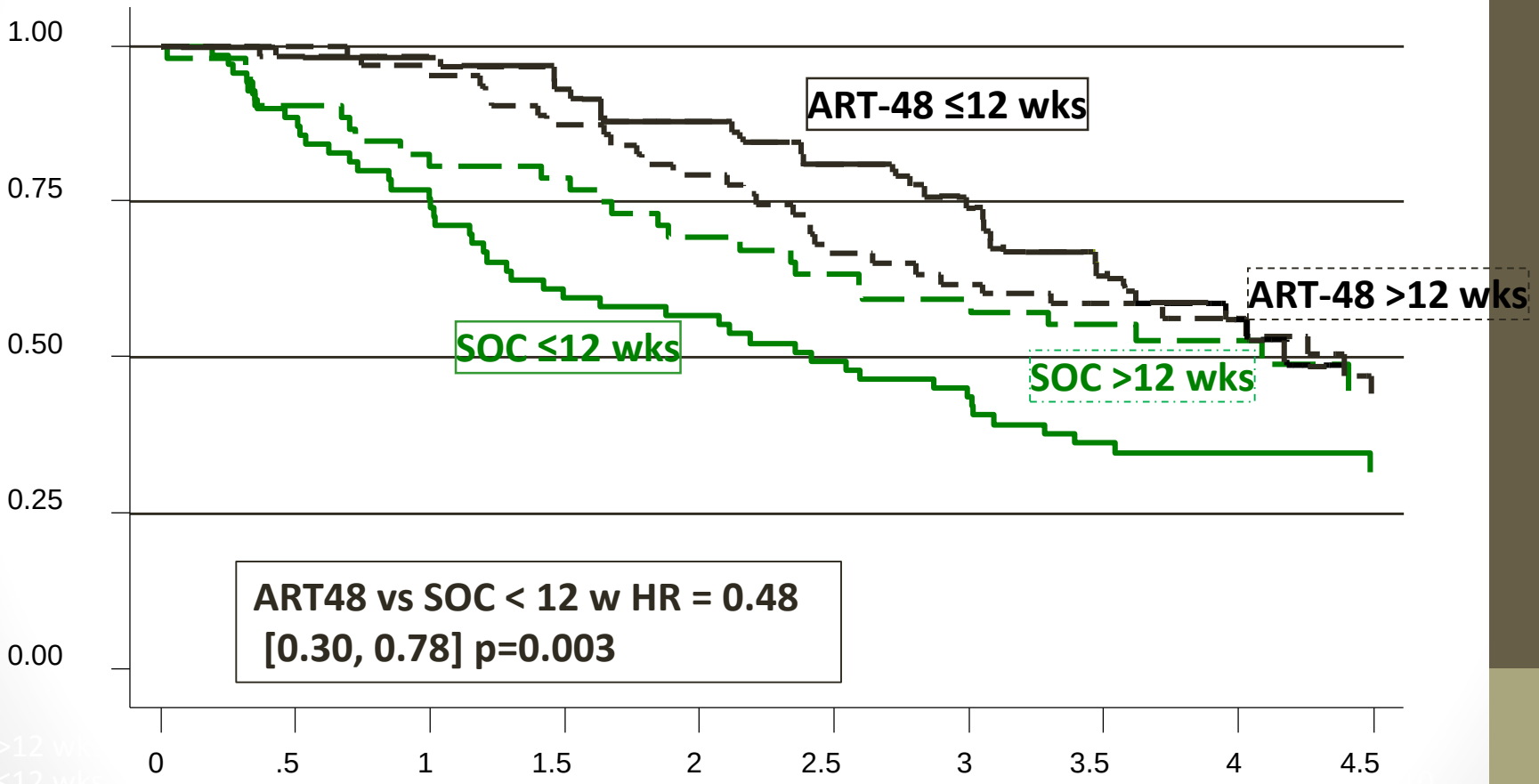
Not plasma viral load or Integrated DNA

Time to primary endpoint

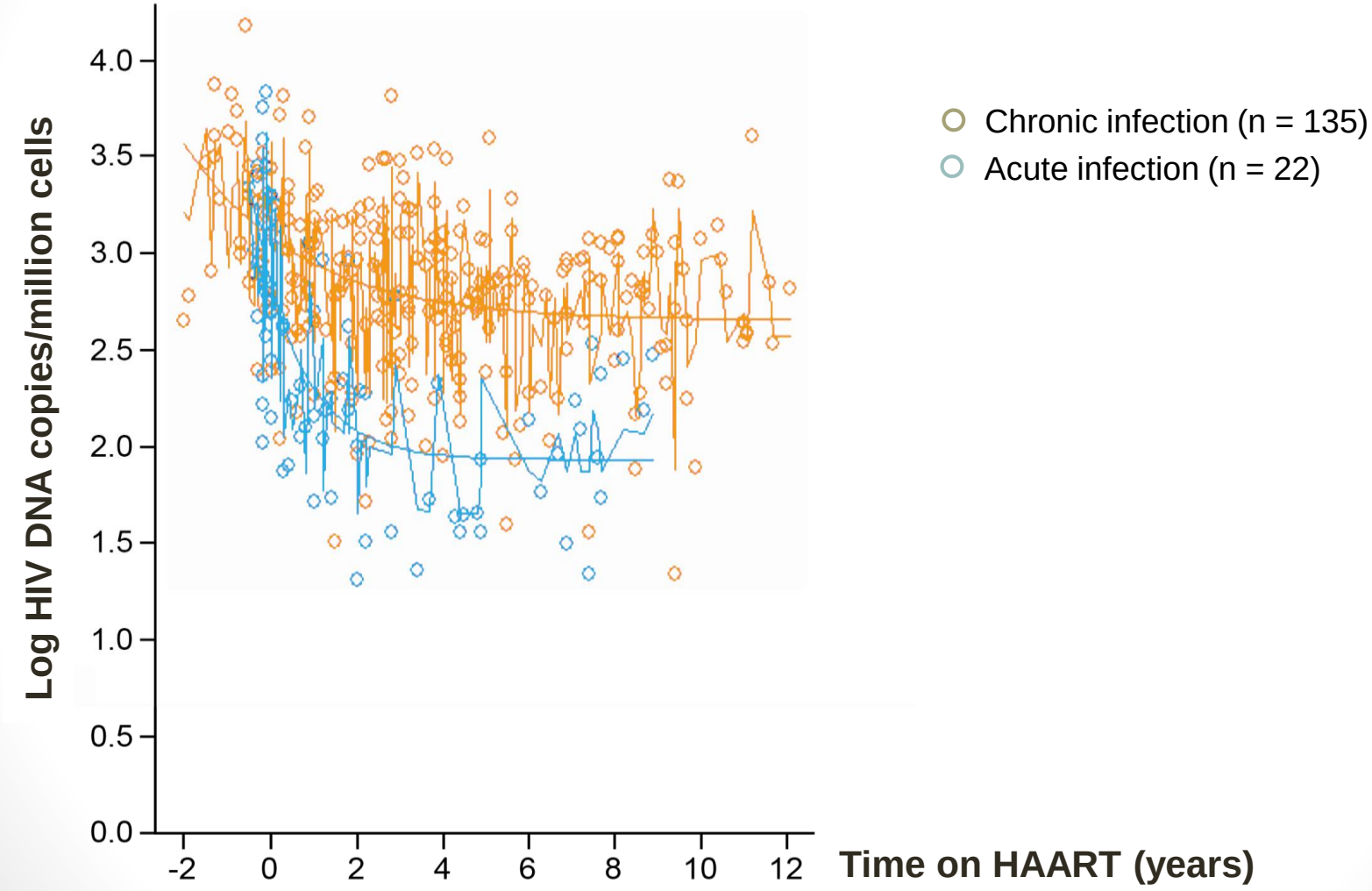


SOC	123	109	93	82	75	66	59	46	30	18
ART-12	120	110	95	84	79	71	63	49	32	21
ART-48	123	121	117	109	100	88	80	63	41	19

Duration of infection and time to Primary Endpoint



Reservoir reduced with early treatment



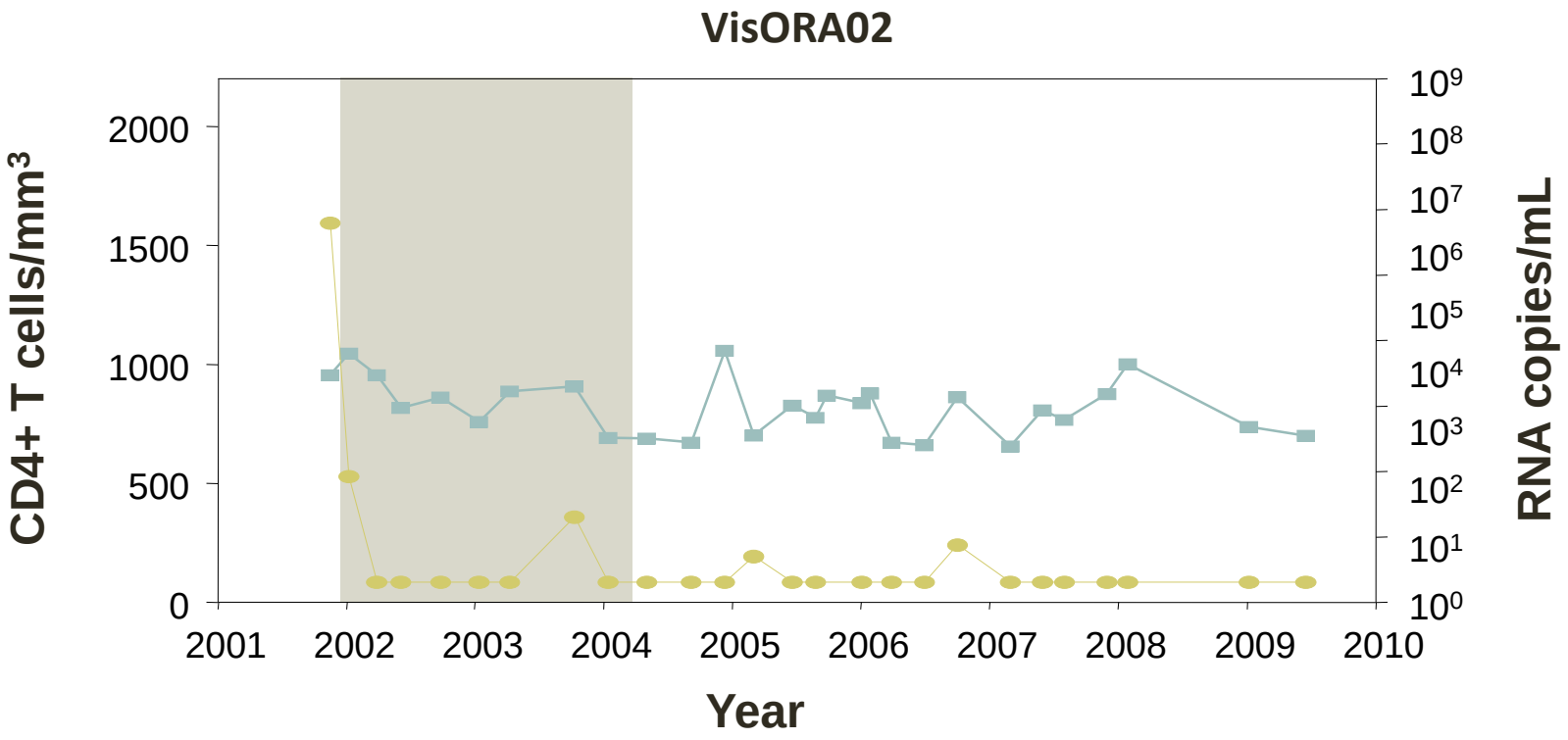
Adapted from Hocqueloux L, et al. J Antimicrob Chemother 2013;68(5):1169-78.

How low do we have to go?

- If ART in acute infection; can limit the size of the viral reservoir is there a critical threshold below which we could think about stopping treatment and not worry that virus will rebound?

- People treated close to the time of HIV infection seem to be in the best place to see if this could happen?

Functional cure: post-ART controllers

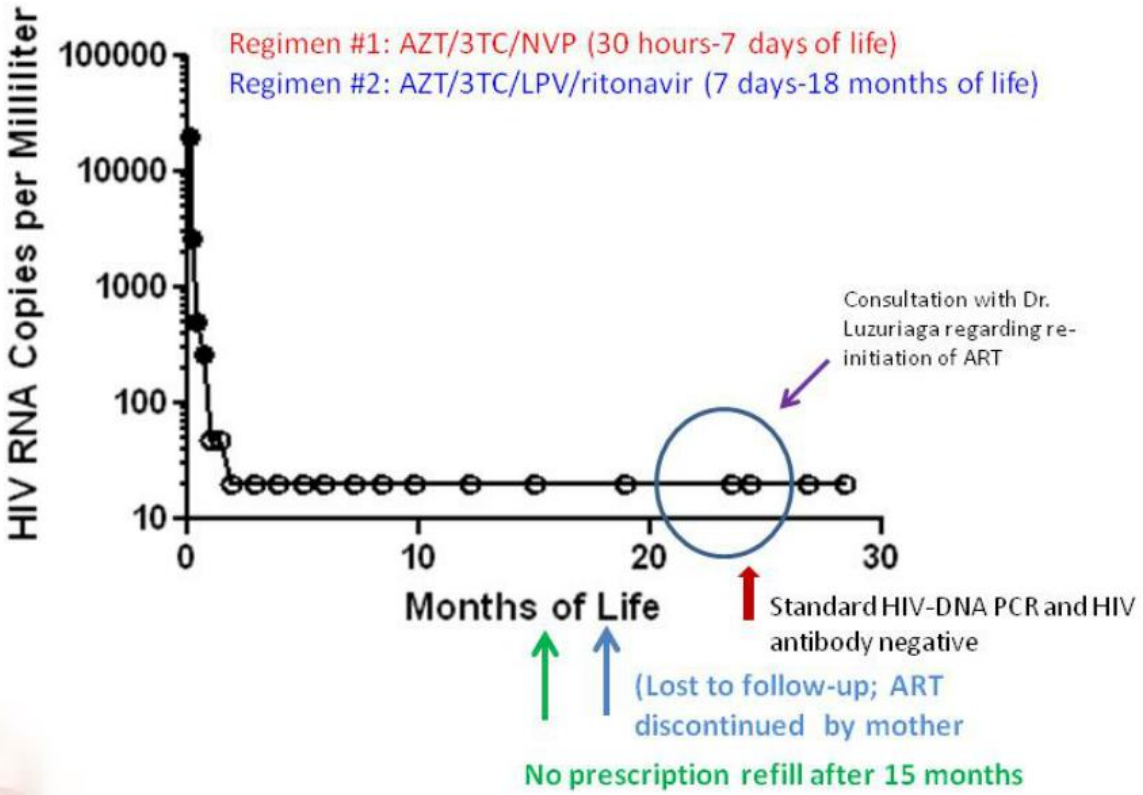


VISCONTI cohort; n = 12, treated in acute infection;
median times since treatment interruption at 72 months

Saez-Cirion et al. PLoS Pathog. 2013 Mar;9(3):e1003211

The "

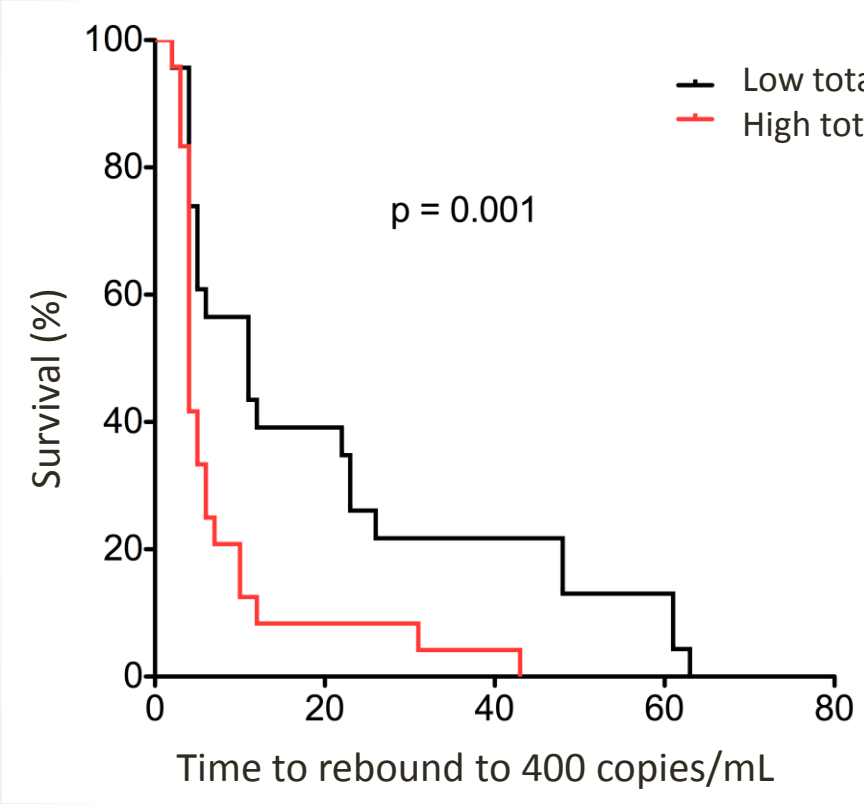
Maintenance of Undetectable Plasma Viral Load During and Following ART Discontinuation in the "Mississippi Child"



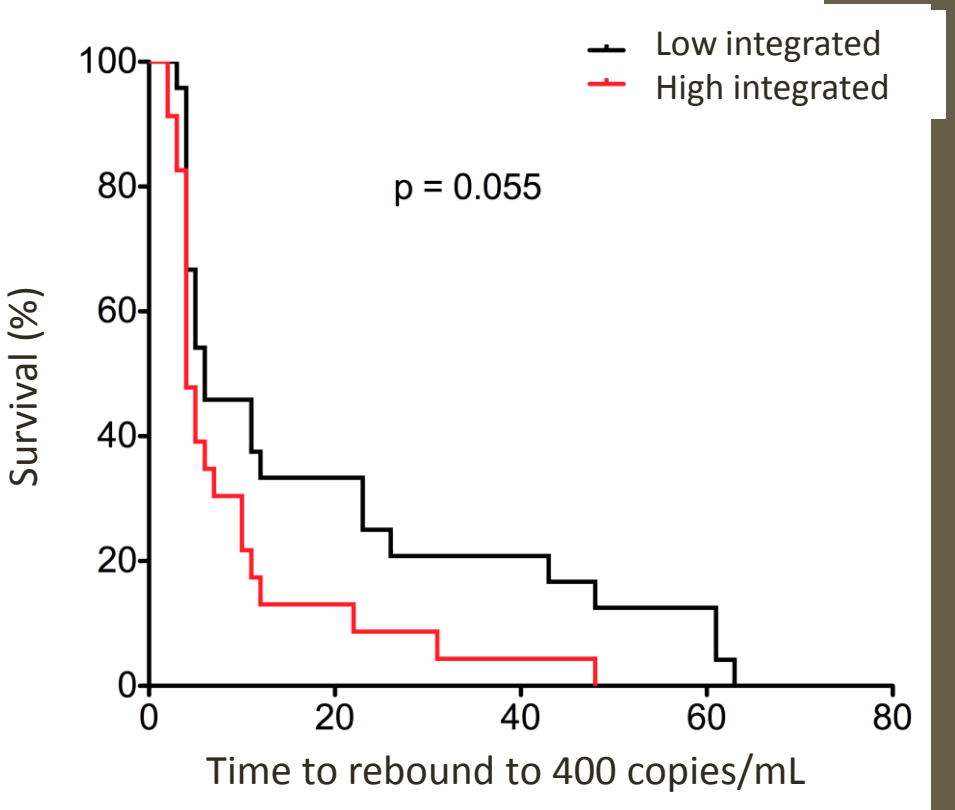
- How can we predict who might rebound after ART is stopped?

  Can we develop an “algorithm” to define who could safely stop ART?

SPARTAC: total and integrated DNA predict time to viral rebound after ART stop



Total DNA at ART stop vs time to viral rebound



Integrated DNA at ART stop baseline vs time to viral rebound

Hurst et al. HIV DNA in PHI Associates With T Cell Immunity and Predicts Disease Progression and Rebound Viraemia. CROI 2014 Abstract 403LB.

Summary of the impact of immediate ART in PHI on viral reservoir

- ART blocks viral replication and so prevents new virion formation but integrated virus underpins why ART alone cannot cure HIV
- Viral reservoirs are established early and persist through suppressive therapy.
- Viral reservoirs are smallest the closer to time of HIV acquisition.
- Immediate ART appears to reduce viral reservoir levels to lower levels than starting later
- The level of total and integrated DNA predict HIV disease progression and viral rebound.
- IF it is possible to achieve viral reservoir measures below an as yet unknown critical threshold by immediate ART, is post treatment control a possibililty?
- FOR better control we need immune recovery as well…..

What is the impact of immediate ART on the immune system?

- If we start ART immediately around the time of seroconversion do we have a better chance of normalisation of the immune system?
- We know that even for patients successfully treated with ART and good CD4 counts > 350, there remains an increased risk of all cause mortality compared with HIV negative age matched controls.

The NEW ENGLAND JOURNAL of MEDICINE

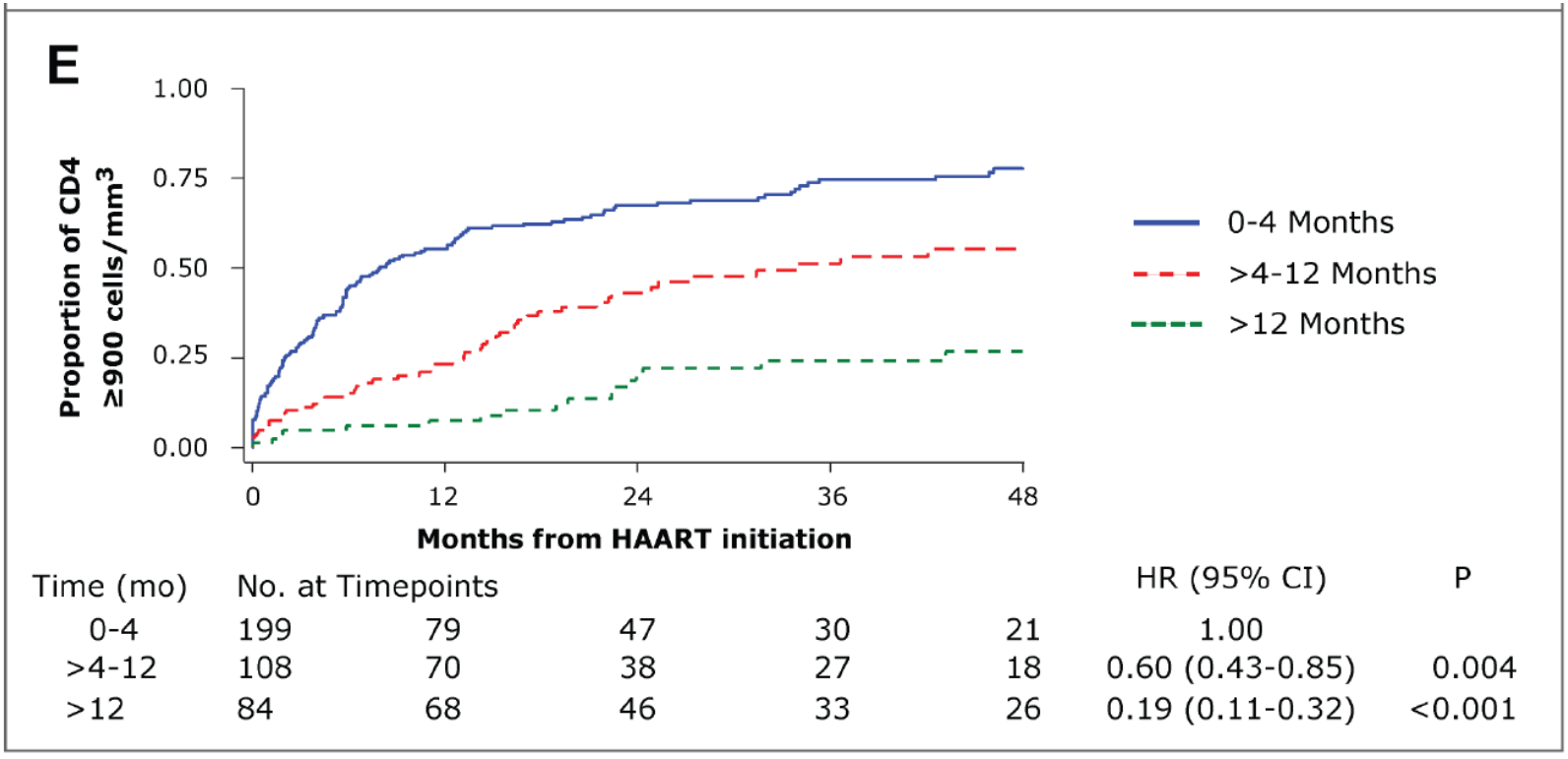
ORIGINAL ARTICLE

Enhanced CD4+ T-Cell Recovery with Earlier HIV-1 Antiretroviral Therapy

Tuan Le, M.D., Dr.P.H., Edwina J. Wright, M.D., Davey M. Smith, M.D., Weijing He, M.D., Gabriel Catano, M.D., Jason F. Okulicz, M.D., Jason A. Young, Ph.D., Robert A. Clark, M.D., Douglas D. Richman, M.D., Susan J. Little, M.D., and Sunil K. Ahuja, M.D.

Imperial College London

Probability of attaining post-ART 900 CD4 cell count depends on time from EDI to ART initiation



Time (mo)	No. at Timepoints					HR (95% CI)	P
0-4	199	79	47	30	21	1.00	
>4-12	108	70	38	27	18	0.60 (0.43-0.85)	0.004
>12	84	68	46	33	26	0.19 (0.11-0.32)	<0.001

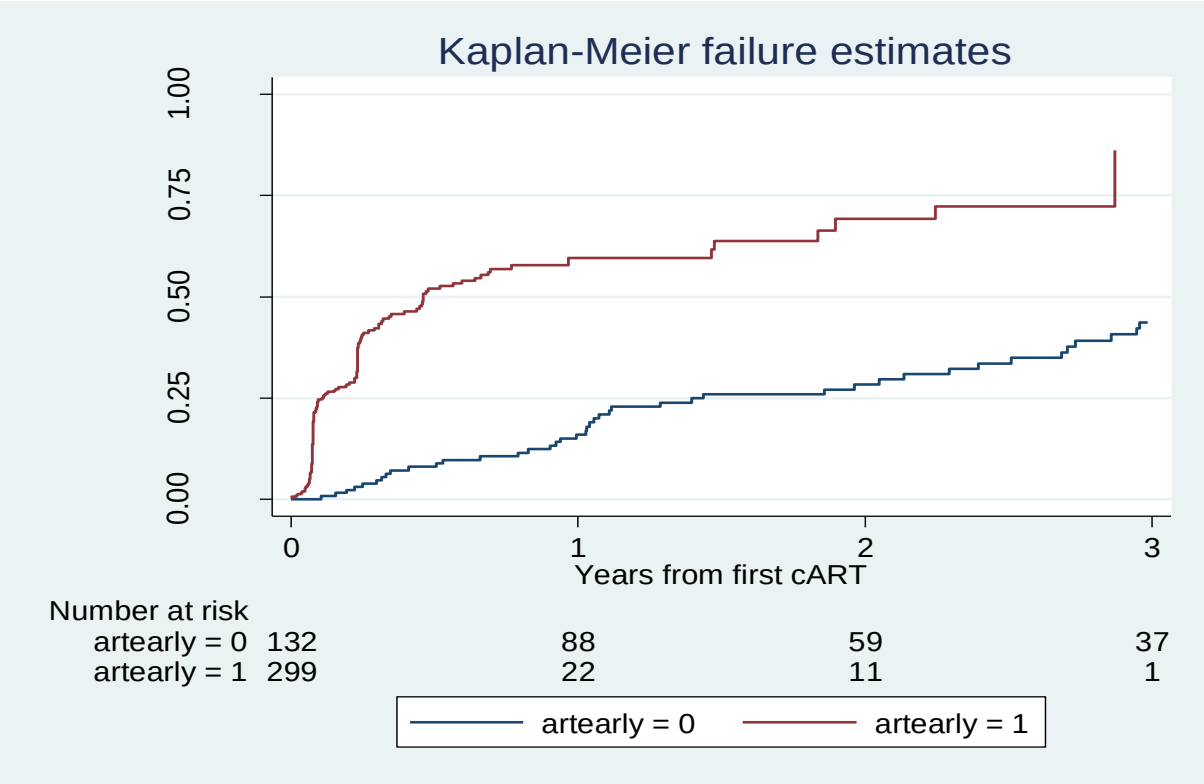
Inflammation and immune activation

- ART dramatically reduces most markers of immune activation and inflammation.
- However, many studies have shown that elevated markers of both inflammation and immune activation persist even for those on suppressive ART started in chronic stage infection.
- AIDS defining events do not plateau until CD4 > 750 [Mocroft CID 2013 57]
- VISCONTI PTC had low levels of CD8+ T-cell activation markers

- CD4:8 ratio is another marker of immune function that often fails to normalise when ART is initiated in chronic stage infection.

Probability of normalisation (> 1) CD4:8 ratio amongst ART treated seroconverters in UK

46.8% of ART early
13.5% of deferred achieved normal CD4:8 ratio after 1 year of ART



N = 431 individuals 299 initiated immediate ART (red) and 132 deferred ART (Blue)

Conclusions

- There is a critical time-window for CD4 recovery post-ART independent of the CD4 at ART initiation.
- The probability of attaining a CD4 >900 on ART was greatest for those who started ART within 4 months of EDI.
- **Each additional month delay in ART reduced probability of achieving a CD4 > 900 by approximately 10%.**
- Less than 25 % of the ART-naïve patients maintained CD4≥500 beyond 12 months
- Enhanced CD4:8 ratio was observed after immediate ART in acute infection
- 82% of individuals with CD4 > 500 at seroconversion had abnormal CD4:8 ratio (<1)

Projected population level impact of identifying and treating acute HIV infection

- Viral load is the most critical determinant of onward viral transmission (Rakai, HPTN052, PARTNER study)
- Acute infection is a time of very high viral load and often unknown altered HIV status of the individual
- The proportion of new infections driven by people with AHI is unknown but in focused epidemics is likely to be very high
- In generalised epidemic it is driven by rates and number of partner changes
- **As guidelines move to initiation of ART at higher CD4 thresholds acute infection may play a bigger role in onward transmission**

Overall Conclusion

- Identification of acute HIV infection is a challenge best made through repeat testing
- Consideration of immediate ART maybe important to help limit the epidemic, enhance individual biological surrogate markers of disease mortality and reduce the risk of transmission of virus to their children and partners
- Optimal immunological recovery is seen with immediate ART
- Optimal reduction in measures of viral reservoir are seen with immediate ART
- Future functional cure interventions will require full immunological recovery with limitation of viral replication and reservoir size to the lowest limits we can achieve
- Starting ART irrespective of CD4 count could have a huge impact on population level incidence

To treat or not to treat acute infection?

Yes

- Better chance of immune recovery
- Better chance of limitation of viral reservoir in preparation for cure interventions
- Reduce risk of onward transmission
- Reduce the years of on going immune activation

Not now

- Patients have years of future ART why expose them any longer than needed to drug toxicities?
- Ambivalent to treatment and too many other psychological issues at time of PHI
- Increased risk of poor adherence, drug resistance developing

Acknowledgements

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SPARTAC
Treating recent HIV infection

Imperial College London

British HIV Association BHIVA

MRC Medical Research Council

NHS National Institute for Health Research

OXFORDMARTIN SCHOOL

The Peter Medawar Building for Pathogen Research

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If we treat what with?

- Any standard ART regimen
- Raltegravir reduces high viral load quicker
- Transmitted DR makes bPI preferentially at v high VL
- Dolutegravir looks very interesting….
- No evidence that >3 ART agents is needed
- Often higher risk of rash, CNS side effects in acute infection compared with chronic disease potentially avoid Efavirenz and Nevirapine (high CD4) and Abacavir (High VL)

What is a Normal CD4 count ?

Summary Statistics for CD4+ counts				
Population	**No. of study groups (No. of subjects)**	**CD4+ T-Cell Counts (cells/mm^3)**		
		Weighted Mean (95% CI)	**Median (IQR)**	Range
European	17 (10937)	1012 (949-1074)	940 (834-1020)	796-1109
Mixed USA	6 (3175)	1014 (910-1118)	1015 (839-1036)	771-1075
African American	2 (1006)	1077 (1059-1095)	1078 (1055-1100)	1055-1100
Combo	25 (15118)	1017 (948-1085)	993 (839-1036)	771-1109

Le et al NEJM Jan 18, 2013