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GIORNATE INFETTIVOLOGICHE "LUIGI SACCO" 2017
Milano, 25-26 Maggio 2017
Ospedale Luigi Sacco-Polo Universitario, ASST Fatebenfratelli Sacco
Aula Magna Polo LITA

HIV tra cura funzionale ed eradicazione: quali prospettive.

Prof. Adriano Lazzarin
Dipartimento di Malattie Infettive
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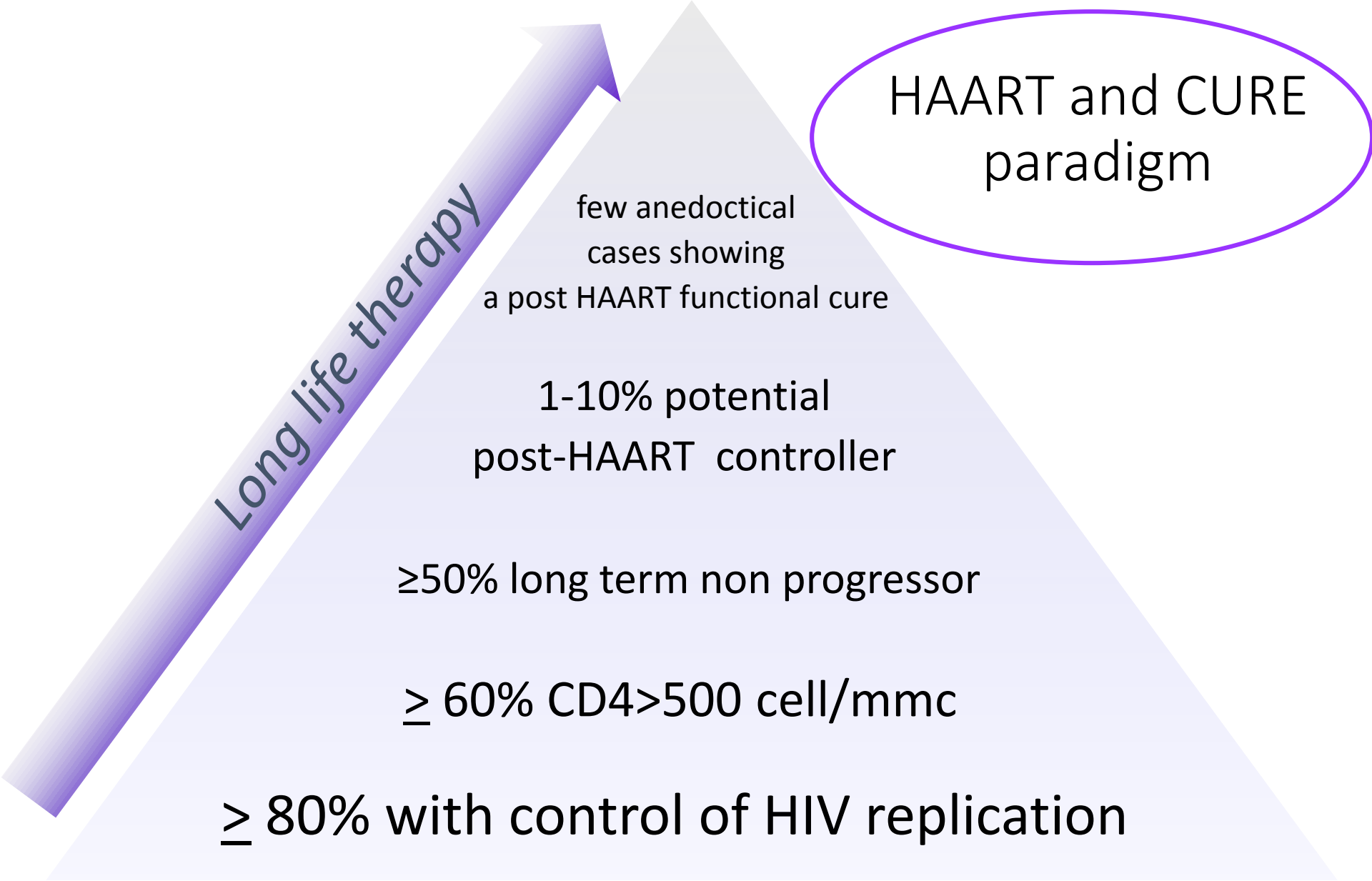
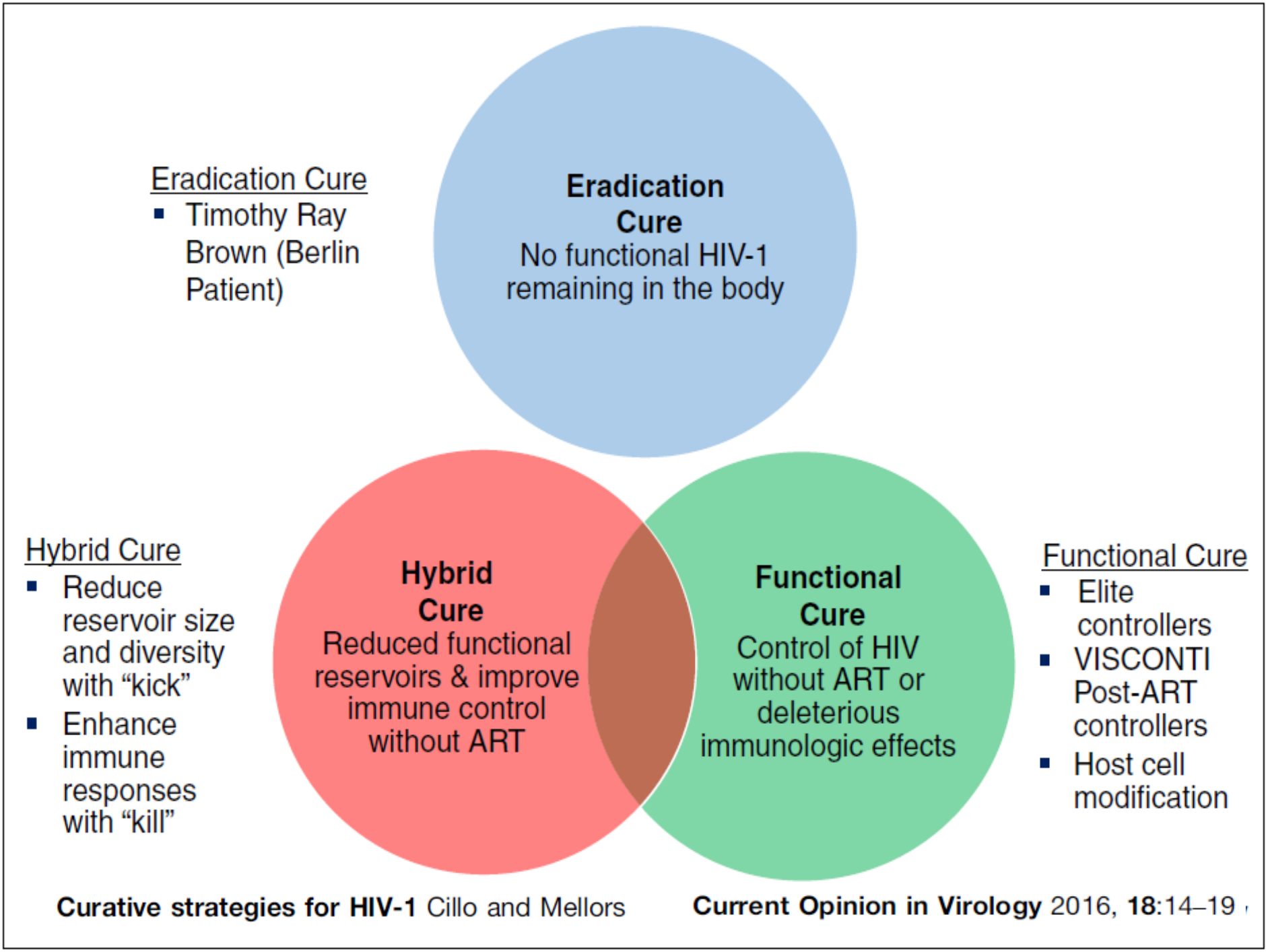


20.000.000 of PLW HIV under cART


Eradication Cure
Timothy Ray Brown (Berlin Patient)
Eradication Cure
No functional HIV-1 remaining in the body
Hybrid Cure
Reduce reservoir size and diversity with "kick"
Enhance immune responses with "kill"
Hybrid Cure
Reduced functional reservoirs & improve immune control without ART
Functional Cure
Control of HIV without ART or deleterious immunologic effects
Functional Cure
Elite controllers
VISCONTI Post-ART controllers
Host cell modification
Curative strategies for HIV-1 Cillo and Mellors
Current Opinion in Virology 2016, 18:14–19

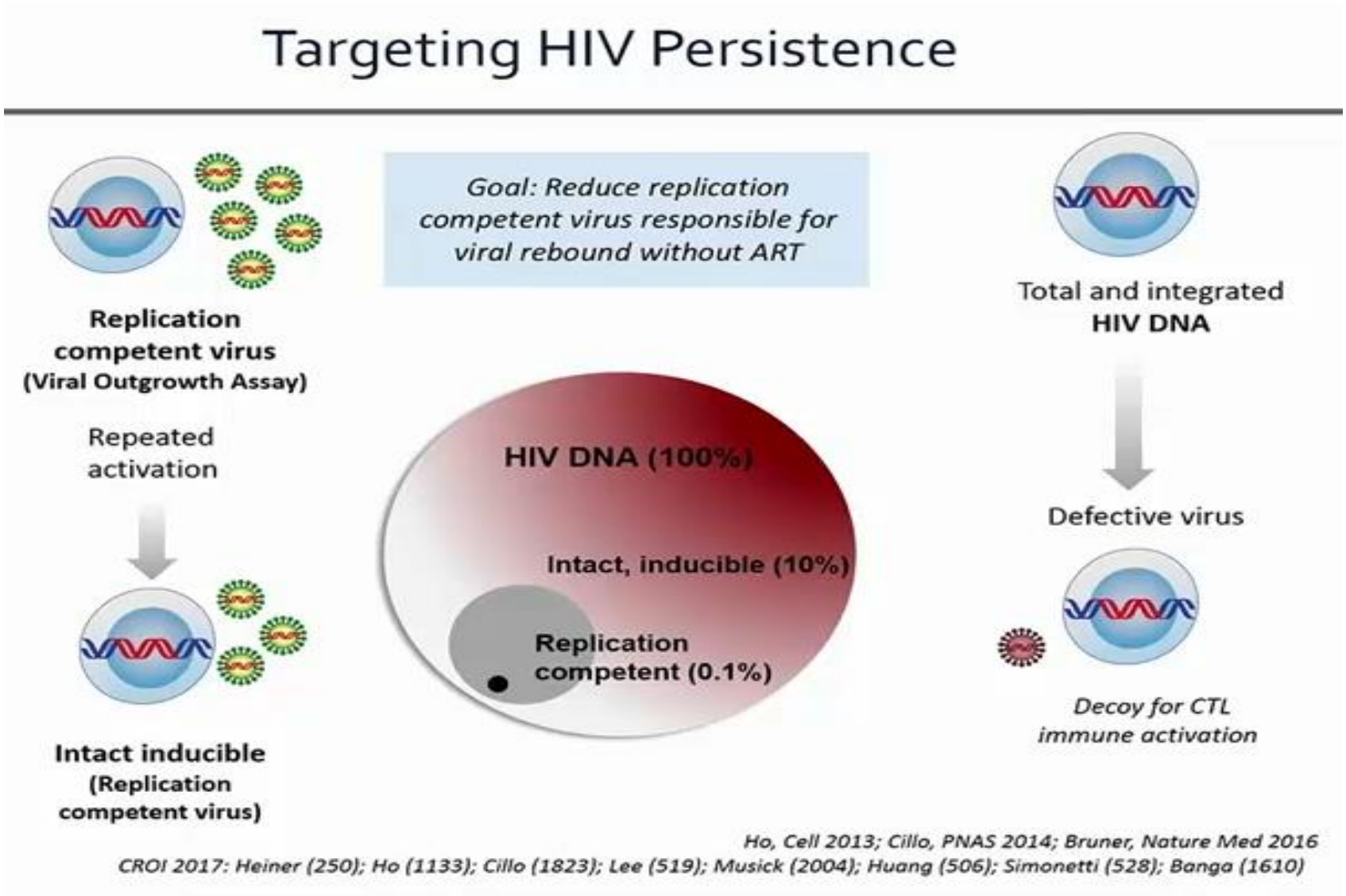
cART – EXIT

Treatment interruption (TI) is ultimately the only way to determine if a patient is cured.

There are precautions and ethical issues to consider when using the time of remmission lenght as a measurement of latent reservoir (LT) size and pros/cons of analitical treatment interruption (ATI) strategy.

Proof of concepts:

1. PHI therapy
2. Post Treatment Control
3. Flushing out HIV
4. Gene Editing Strategy



VOA: resting Cd4+ T cells are subjected to a single round of activation with a mitogen and the resulting amount of produced virus is measured

The size of the expressed HIV reservoir predicts timing of viral rebound after treatment interruption

Jonathan Z. Li[a], Behzad Etemad[a], Hayat Ahmed[a], Evgenia Aga[b], Ronald J. Bosch[b], John W. Mellors[c], Daniel R. Kuritzkes[a], Michael M. Lederman[d], Michael Para[e] and Rajesh T. Gandhi[f]

Conclusion: Higher levels of HIV expression while on ART are associated with shorter time to HIV rebound after treatment interruption. Quantification of the active HIV reservoir may provide a biomarker of efficacy for therapies that aim to achieve ART-free HIV remission.

AIDS 2016, **30**:343–353

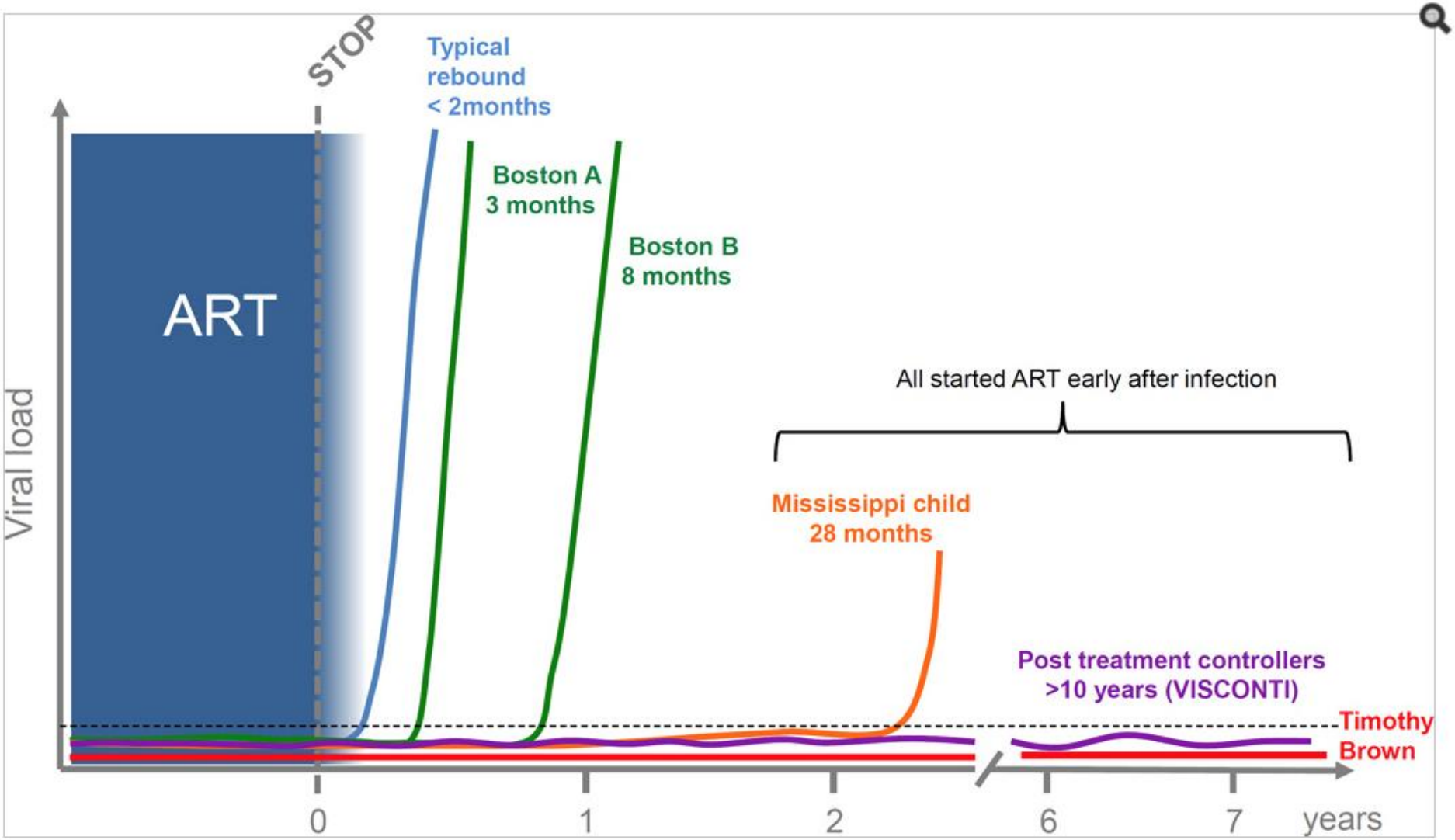
A low HIV-DNA level in peripheral blood mononuclear cells at antiretroviral treatment interruption predicts a higher probability of maintaining viral control

Lambert Assoumou[a,b], Laurence Weiss[c,d], Christophe Piketty[c], Marianne Burgard[e], Adeline Melard[f], Pierre-Marie Girard[g], Christine Rouzioux[d,e], Dominique Costagliola[a,b], the ANRS 116 SALTO study group

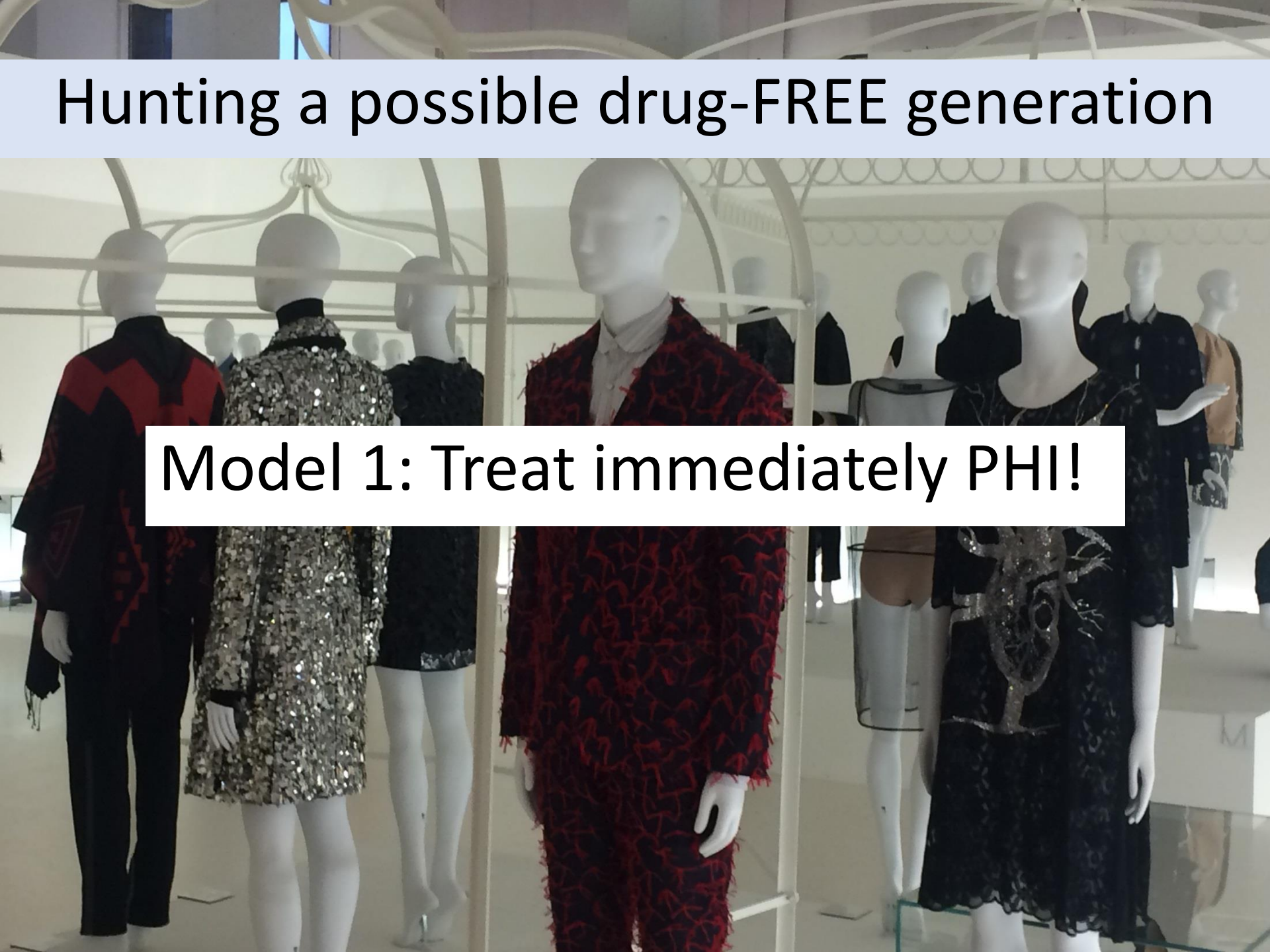
Conclusion: Patients who have low HIV-DNA levels at antiretroviral treatment interruption are more likely to maintain viral control for long periods.

AIDS 2015, **29**:2003–2007

Remission lenght is related to DNA burden extent.



Hunting a possible drug-FREE generation



Model 1: Treat immediately PHI!

PHI conclusions: Two types of viral remission

We must consider

HARD EVIDENCE

Transient Remission

- SPARTAC
  - Stohr W, et al. PLoS ONE 2013
- Cascade
  - Lodi S, et al. Arch Intern Med 2012
- Primo
  - Goujard C, et al. Antivir Ther. 2012

Rebound occurs,
but with significant delay
significant delay

Post Treatment Control

- VISCONTI Case Series
  - Hocqueloux L, et al. AIDS 2010
  - Saez-Cirión A, et al. PLoS Pathog 2013
- French Teenager
  - Frange, et al. Lancet HIV 2016
- UK Adult
  - Kinloch, et al. OFID 2015

No sign of rebound
No sign of rebound

ATI new SOC: NIAID attempt

Rebound of plasma viremia following cessation of antiretroviral therapy despite profoundly low levels of HIV reservoir: implications for eradication

Tae-Wook Chun[a], J. Shawn Justement[a], Danielle Murray[a], Claire W. Hallahan[a], Janine Maenza[b], Ann C. Collier[b], Prameet M. Sheth[c], Rupert Kaul[c], Mario Ostrowski[c], Susan Moir[a], Colin Kovacs[c] and Anthony S. Fauci[a]

Conclusions: Our data suggest that a significant reduction in the size of viral reservoirs may be achievable in selected individuals who initiate standard ART early in infection. However, given re-emergence of plasma viremia in an individual with an extraordinarily low viral burden, therapeutic strategies aimed at specifically targeting these extremely rare HIV-infected cells with novel interventions may be necessary in order to achieve eradication of virus.

AIDS 2010, **24**:2803–2808

Tab. 1 - **Immunologic and virologic profiles of selected HIV-infected individuals in whom sigmoid colon biopsies were performed.**

Participant	Plasma HIV RNA at time of study (copies/ml)[b]	Level of HIV DNA in blood (copies/10^6 cells)	Level of infectious HIV in blood (/10^6 cells)	Level of HIV DNA in sigmoid colon (copies/10^6 cells)
1	<50	<2.56	0.05750	89.0
2	<50	<2.56[c]	0.00064	<2.56

AIDS 2010, Vol 24 No 18

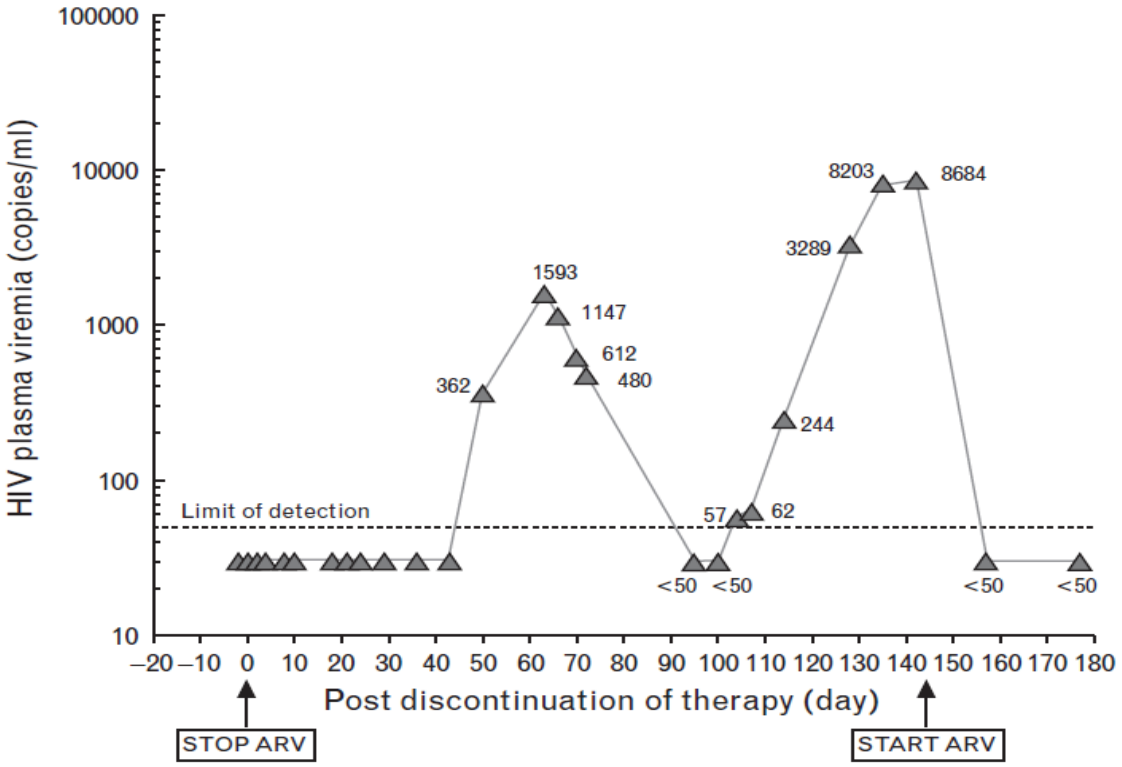
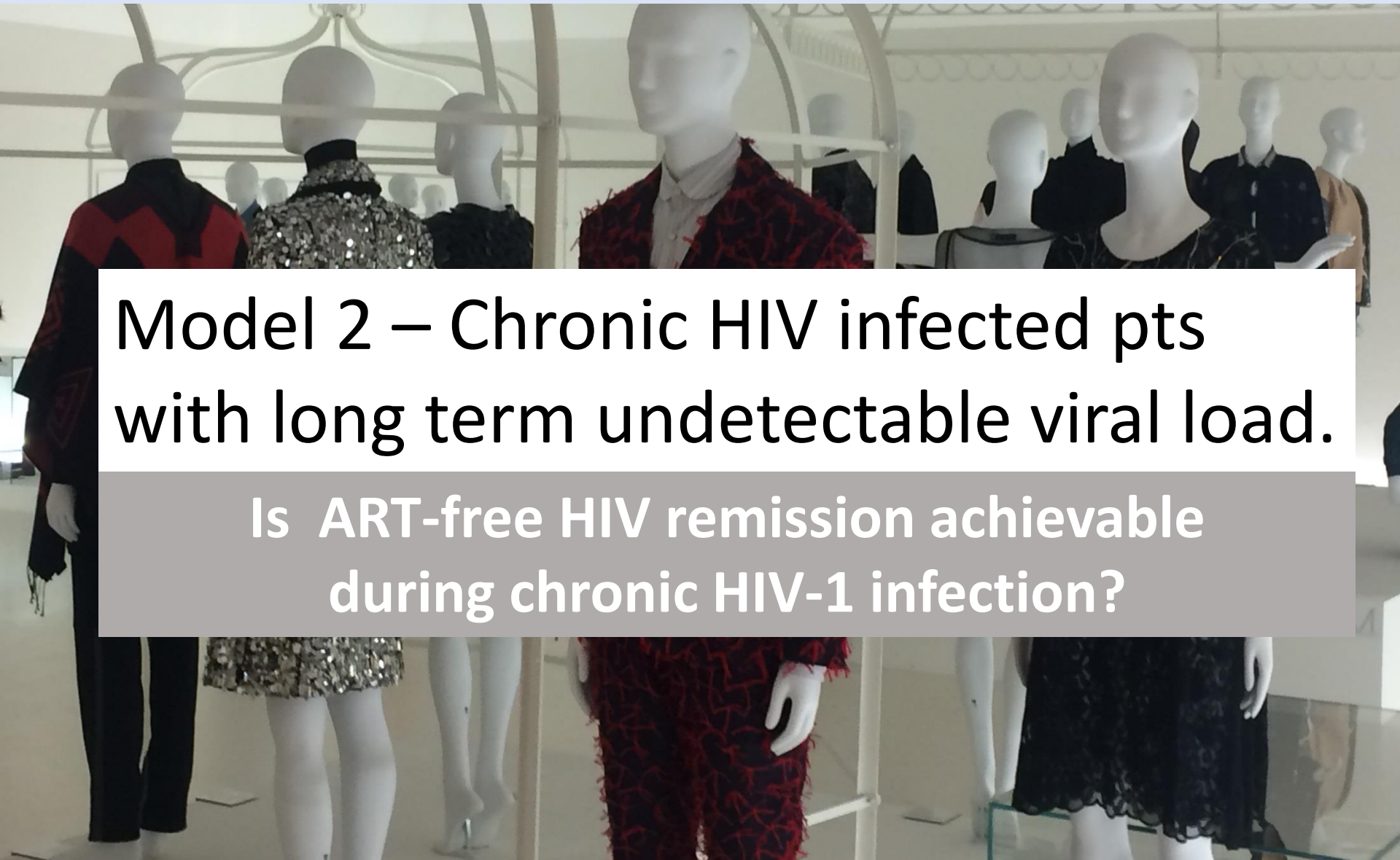


Fig. 2. Levels of plasma viremia following discontinuation and re-initiation of ART. Plasma viremia was determined by a branched DNA assay with the detection limit of 50 copies of HIV RNA per ml of plasma. ARV, antiretroviral.

Hunting a possible drug-FREE generation



Model 2 – Chronic HIV infected pts with long term undetectable viral load.

Is ART-free HIV remission achievable during chronic HIV-1 infection?

Subjects with chronic HIV-1 infection favourable to stop therapy

Biomarker Panel

Biomarker 'Class'	Biomarker
Clinical	CD4 Cell Count
	Plasma Viral Load
	CD4/CD8 Ratio
Viral nucleic acid	HIV-1 DNA (Total)
	HIV-1 DNA (Integrated)
	Cell-Associated Unspliced HIV-1 RNA
HIV-1 T cell immunity	CD8 ELISpot
	CD4 ELISpot
T cell activation	HLA-DR
	CD38
	CD25
	CD69
T cell exhaustion/ 'immune checkpoint'	PD-1
	LAG-3
	TIM-3
Soluble markers	IL-6
	D-dimer

J. Frater, ICAR 2016

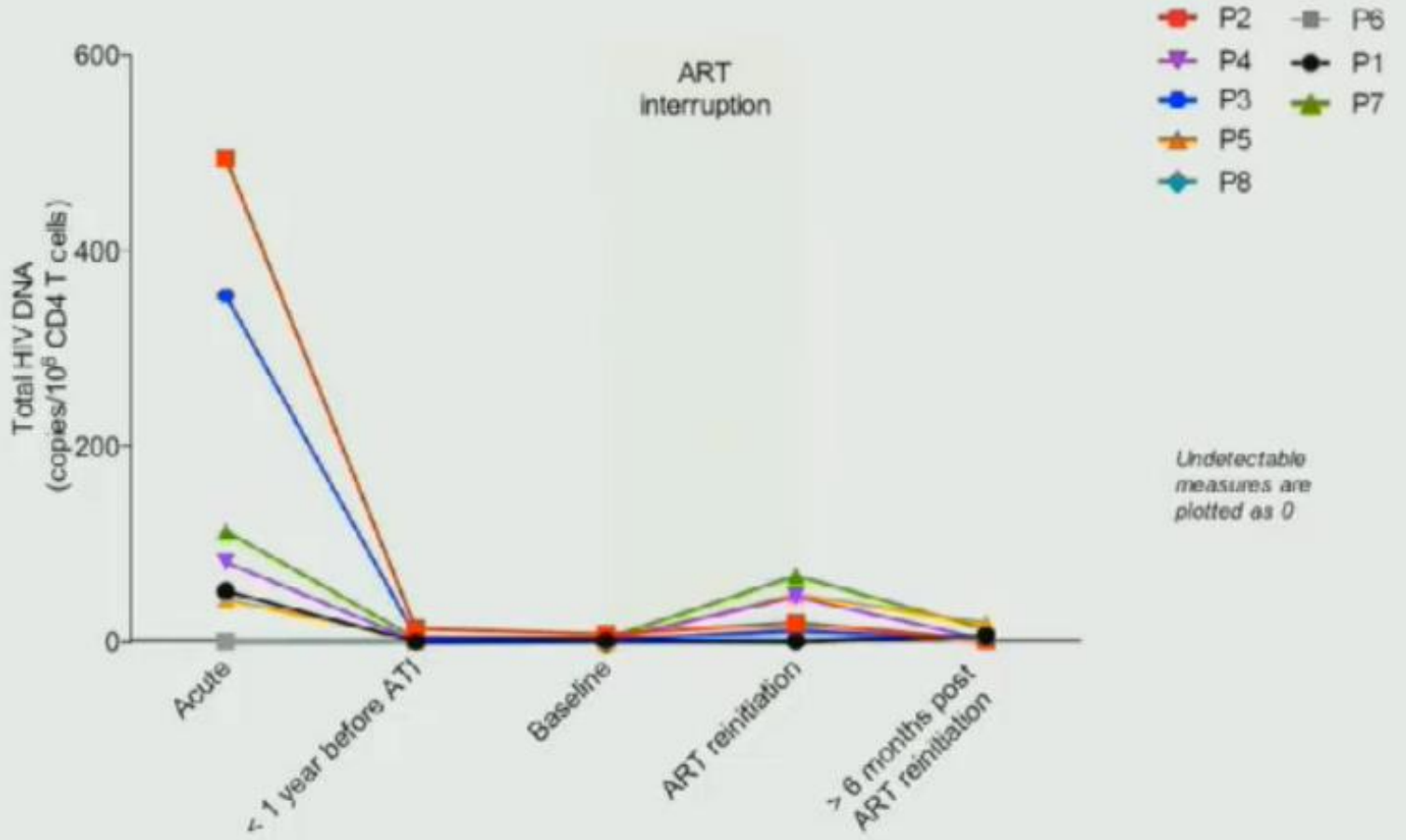
Treatment interruption in chronically HIV-infected patients with an ultralow HIV reservoir

Ruxandra Calin[a,b,e], Chiraz Hamimi[c,*], Sidonie Lambert-Niclot[b,d,*], Guislaine Carcelain[c], Jonathan Bellet[b], Lambert Assoumou[b], Roland Tubiana[a,b], Vincent Calvez[b,d], Yasmine Dudoit[a,b], Dominique Costagliola[b,e,‡], Brigitte Autran[c,e,‡], Christine Katlama[a,b,e], the ULTRASTOP Study Group[†]

Conclusion: In a highly selected population of 10 patients with chronic HIV infection, an excellent immune status, durable virological suppression and ultralow reservoir, the success rate of ATI was 10% (95% confidence interval 0.3–44.5%) and nine of 10 patients had prompt rebound of plasma viremia. Resumption of ART led to return to baseline cell-associated total DNA.

AIDS 2016, **30**:761–769

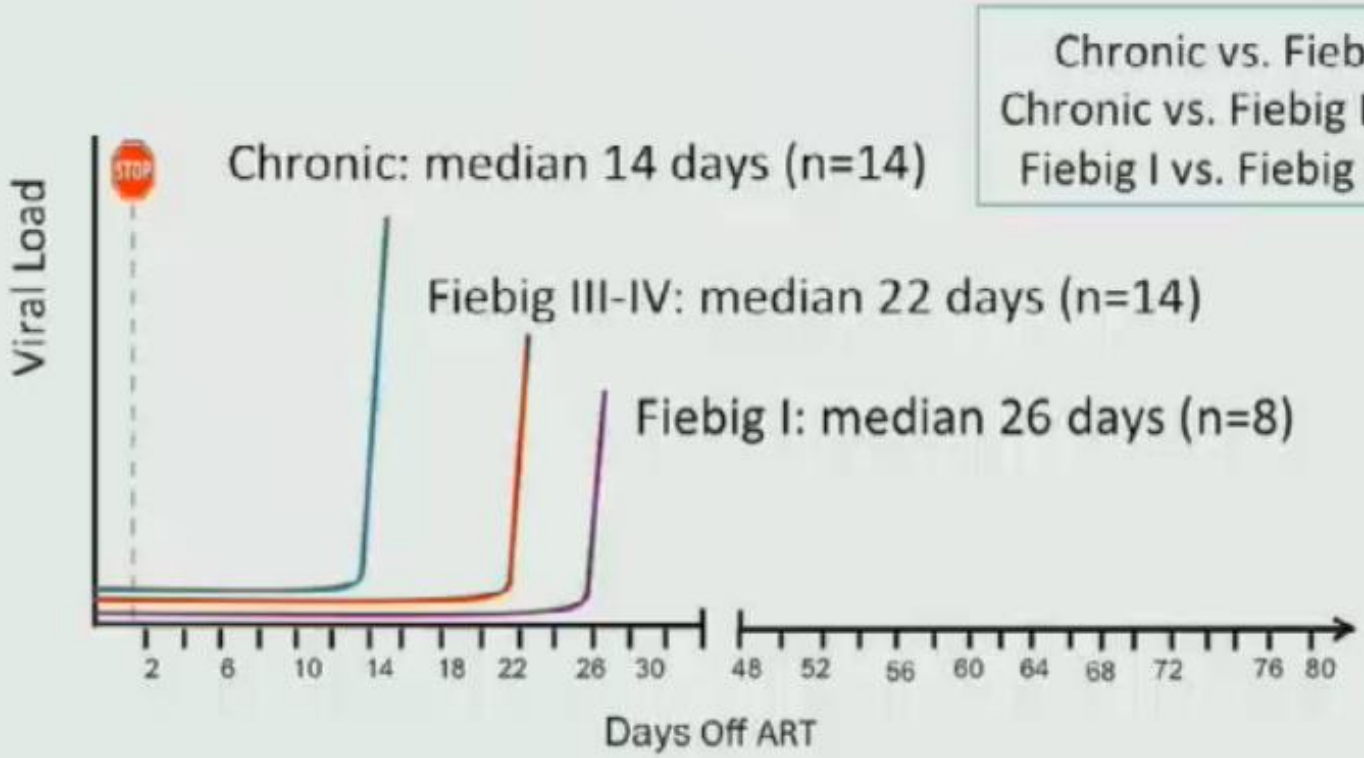
HIV Reservoir Size Increased during ATI and Declined to Pre-ATI Levels after ART Resumption



TILDA ≤ 1.4 tat/rev RNA+ cells/10^6 CD4 prior to ATI in all participants

Louise Leyre, Nicolas Chomont (U Montreal)

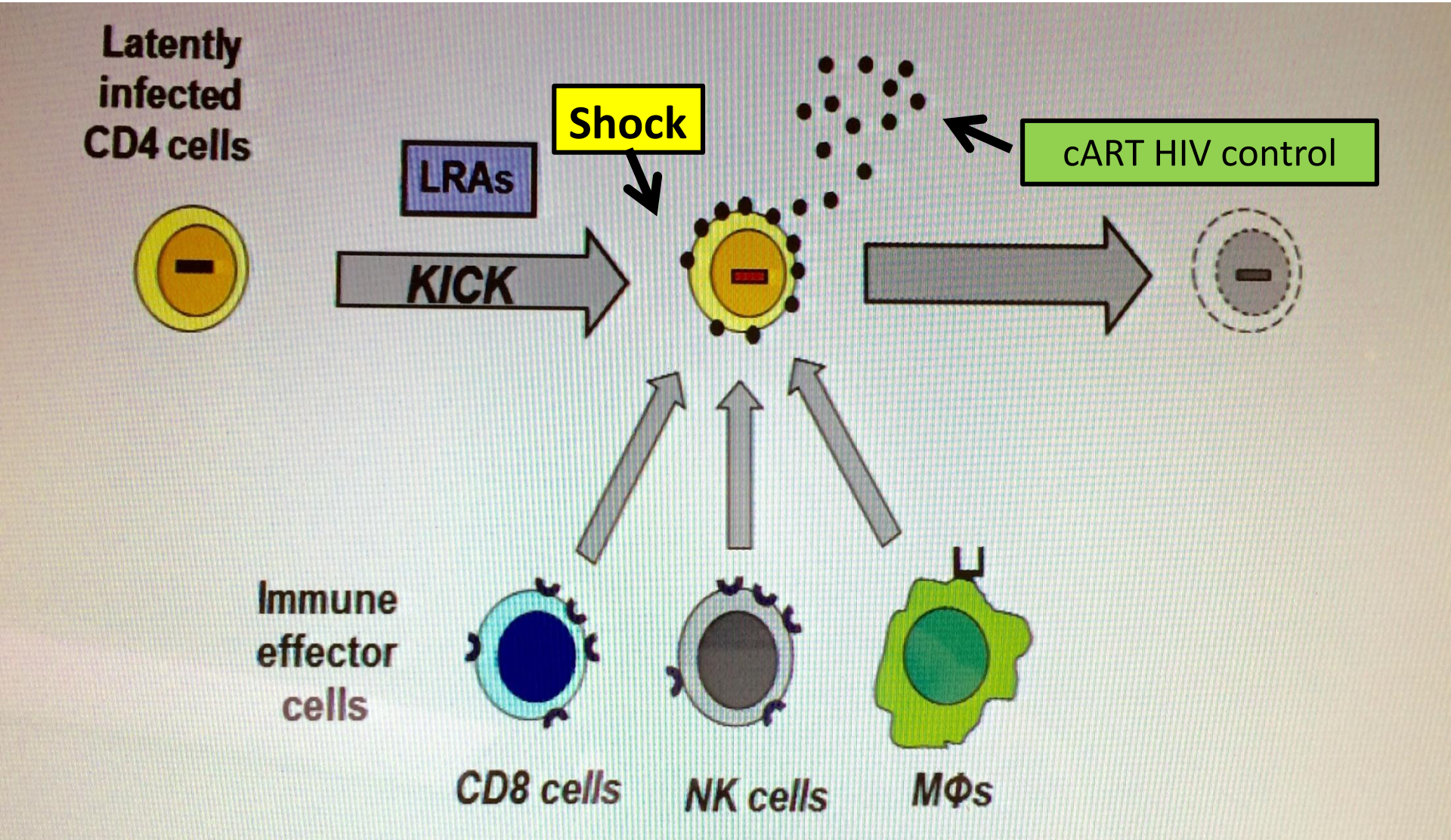
Longer Time to VL Rebound in Thai Acute vs. US Chronic Cohorts



Chronic US: Rothenberger, Schacker, PNAS 2015
Fiebig III/IV Thai: Kroon, de Souza, IAS 2016

Model 3A: kick/shock and kill strategy to flushing out HIV

Towards Remission/Cure



CURRENT OPINION

Shocking HIV out of hiding: where are we with clinical trials of latency reversing agents?

Thomas A. Rasmussen[a,b] *and Sharon R. Lewin*[a,c]

Summary

More effective latency-reversing interventions and additional strategies to eliminate virus-expressing cells are needed. Key challenges include testing combinations of LRAs and/or LRAs with immune modulation to optimize potency in the absence of adverse events. A better understanding of the mechanisms of action of LRAs as well as strategies to enhance potency and penetration in tissue are key challenges for future studies.

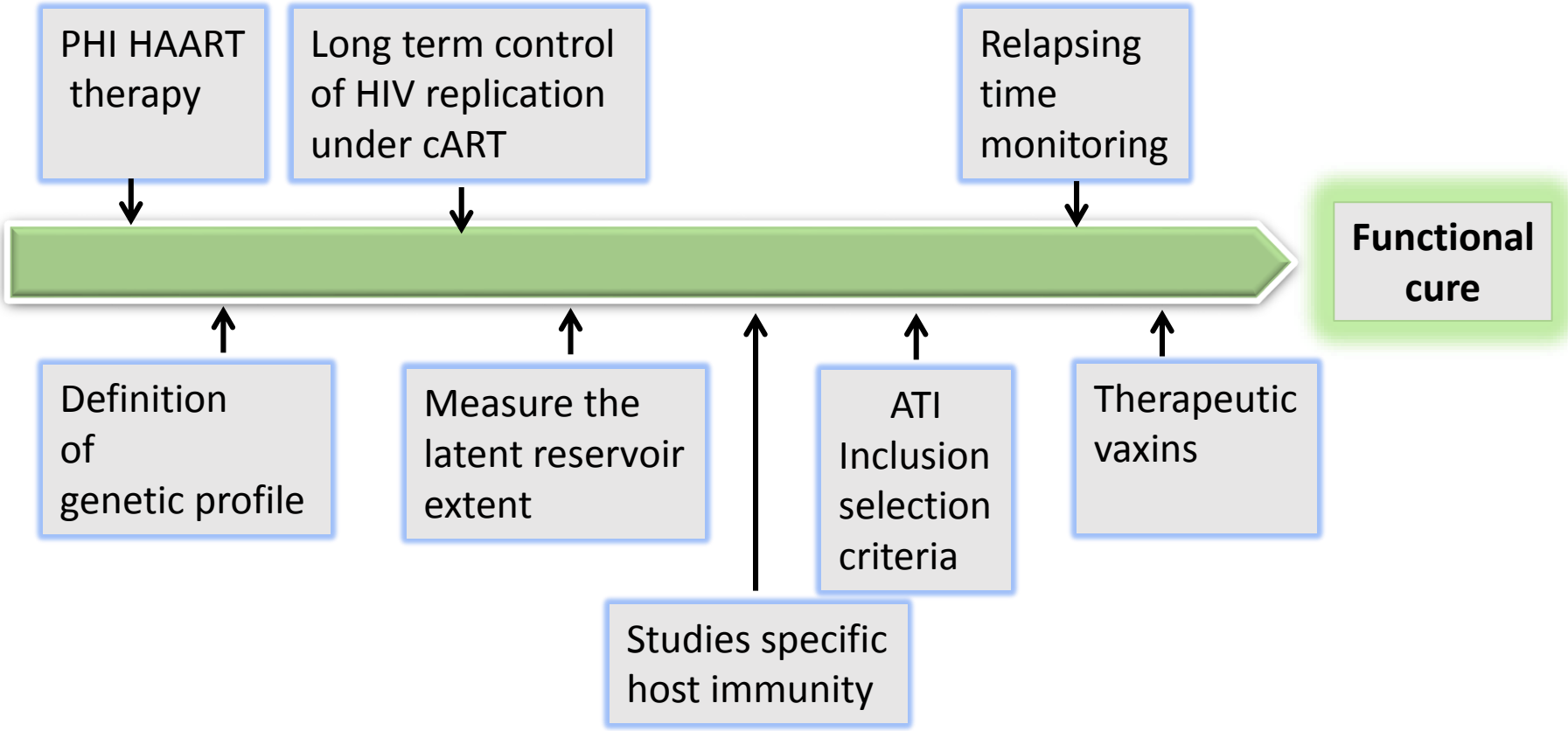
Treatment intensification followed by interleukin-7 reactivates HIV without reducing total HIV DNA: a randomized trial

Christine Katlama[a,b,c], Sidonie Lambert-Niclot[b,c,d], Lambert Assoumou[b,c], Laura Papagno[b,e,f], François Lecardonnel[e], Rima Zoorob[b,f], Giuseppe Tambussi[g], Bonaventura Clotet[h], Mike Youle[i], Chad J. Achenbach[j], Robert L. Murphy[j], Vincent Calvez[b,c,d], Dominique Costagliola[b,c], Brigitte Autran[f,k], on behalf of the EraMune-01 study team

Conclusion: IL-7 administration and dual ART intensification induced, despite a mild HIV reactivation, an amplification of the HIV reservoir, as a result of central-memory $CD4^+$ T-cell expansion, thus limiting this IL-7 based strategy.

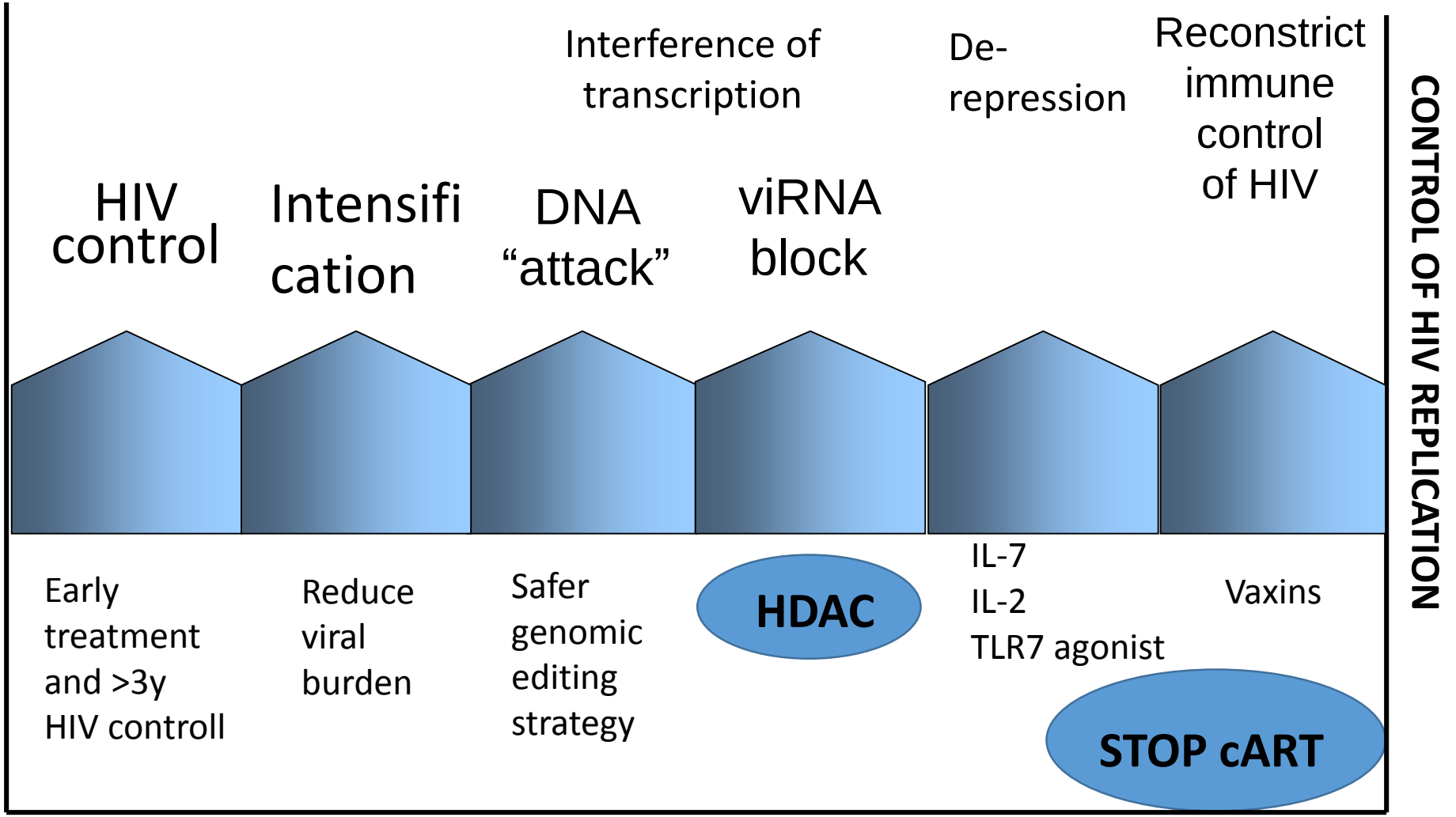
AIDS 2016, **30**:221–230

Model 3B – host specific immunity improvement strategy



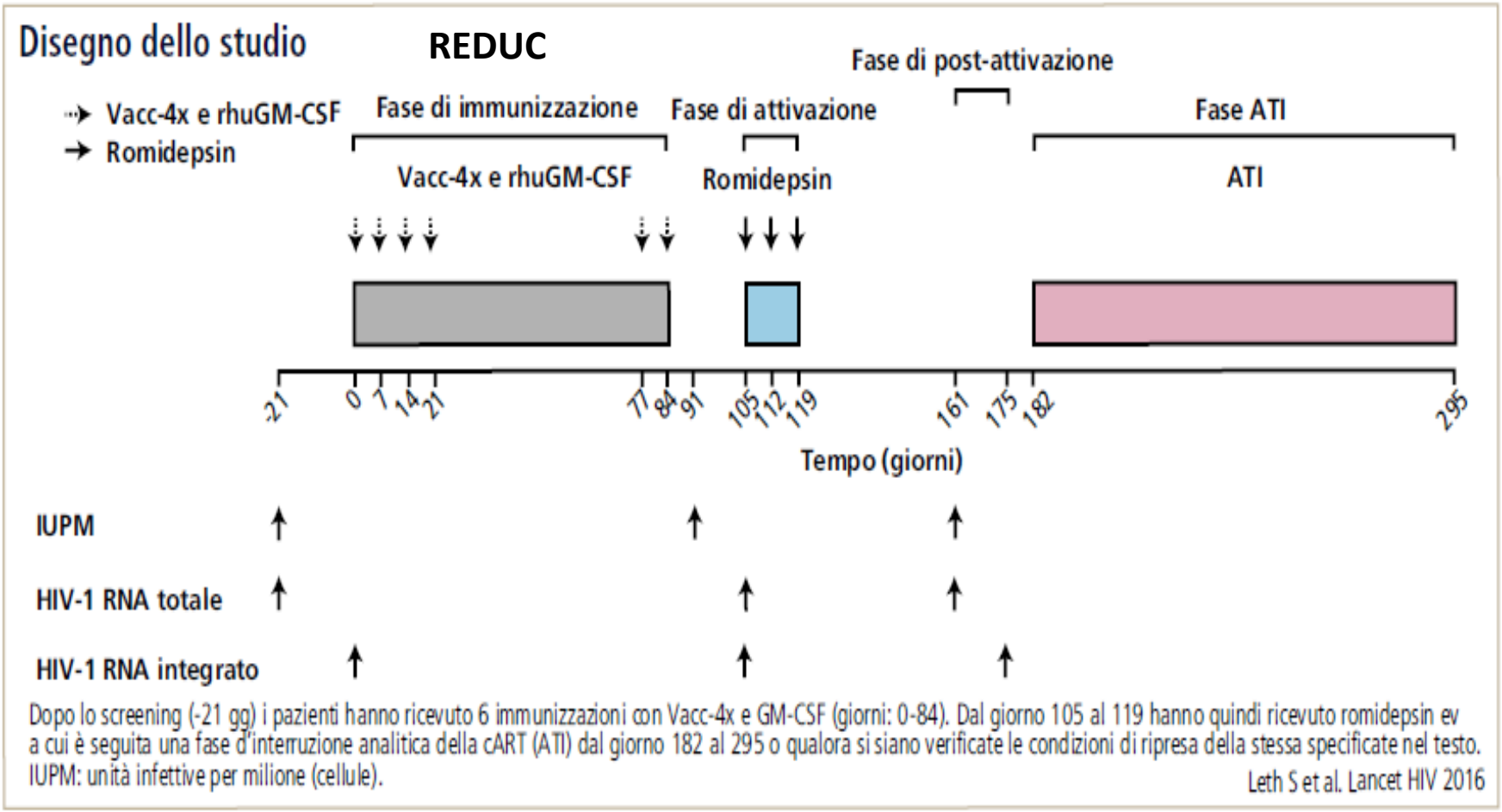
Model 3A+3B: Hunting late rebounders

The multi-step HIV flush-out and therapeutic vaxin



Elisa Vicenzi
Unità di Patogeni Virali e Biosicurezza, Ospedale San Raffaele, Milano

Figura 1

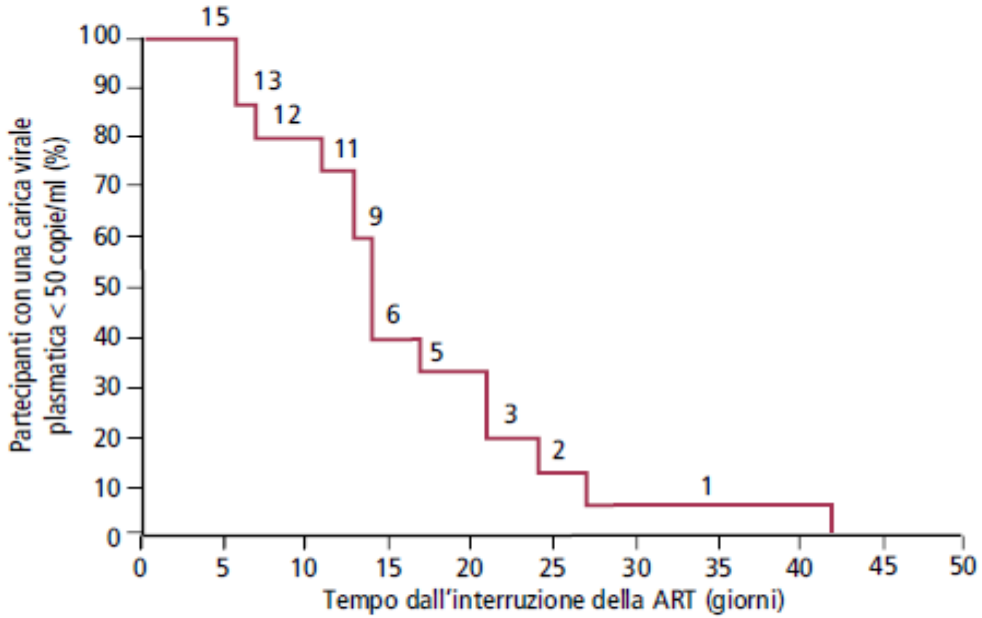


Dopo lo screening (-21 gg) i pazienti hanno ricevuto 6 immunizzazioni con Vacc-4x e GM-CSF (giorni: 0-84). Dal giorno 105 al 119 hanno quindi ricevuto romidepsin ev a cui è seguita una fase d'interruzione analitica della cART (ATI) dal giorno 182 al 295 o qualora si siano verificate le condizioni di ripresa della stessa specificate nel testo.
IUPM: unità infettive per milione (cellule).

Leth S et al. Lancet HIV 2016

Figura 2

Controllo spontaneo della viremia (<50 copie di RNA/ml) dopo sospensione della cART



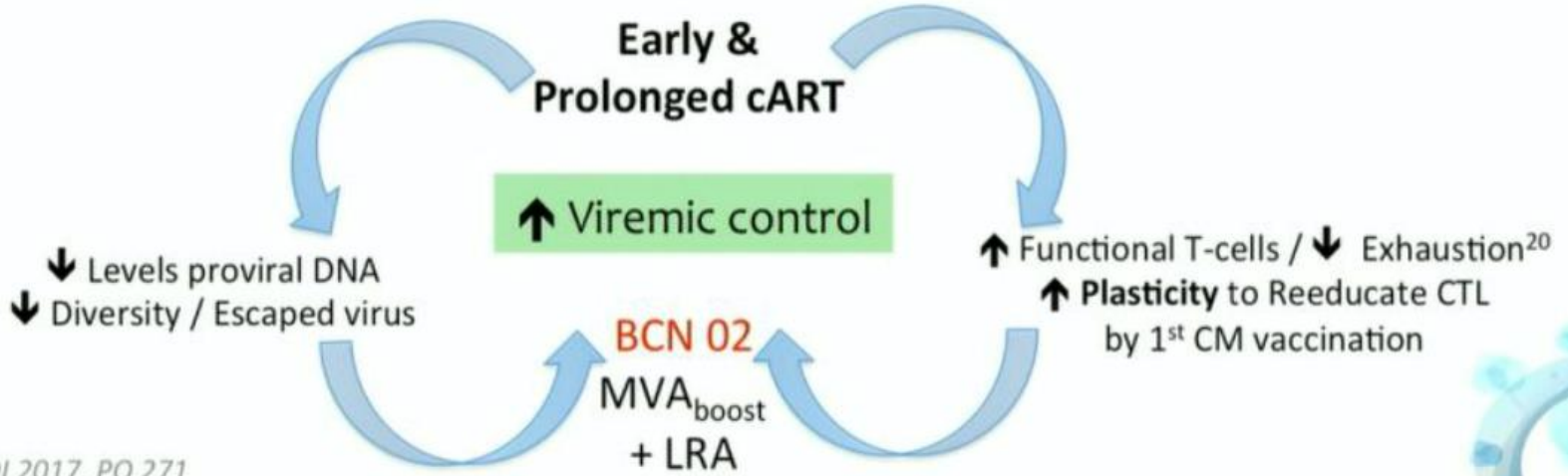
Modificato da Leth S, et al. Lancet HIV 2016

“ Benchè i risultati dello studio REDUC mostrino la riduzione dell'ampiezza del reservoir, in assenza di cART non si è ottenuto un significativo prolungamento della fase aviremica ”

Elisa Vicenzi
Unità di Patogeni Virali e Biosicurezza, Ospedale San Raffaele, Milano

Conclusions

- This is the first therapeutic vaccine trial reporting a durable control of HIV-1 after cART cessation in a substantial proportion of patients (≈35-38%, so far >12-24wks).
- BCN 02 data suggest that viral control can be achieved by an effective redirection of CTL towards conserved regions in the context of a limited viral reservoir.



[20]Rosas, CROI 2017, PO 271

Mothe B. et al, BCN 02

Next model: Gene Editing Strategy

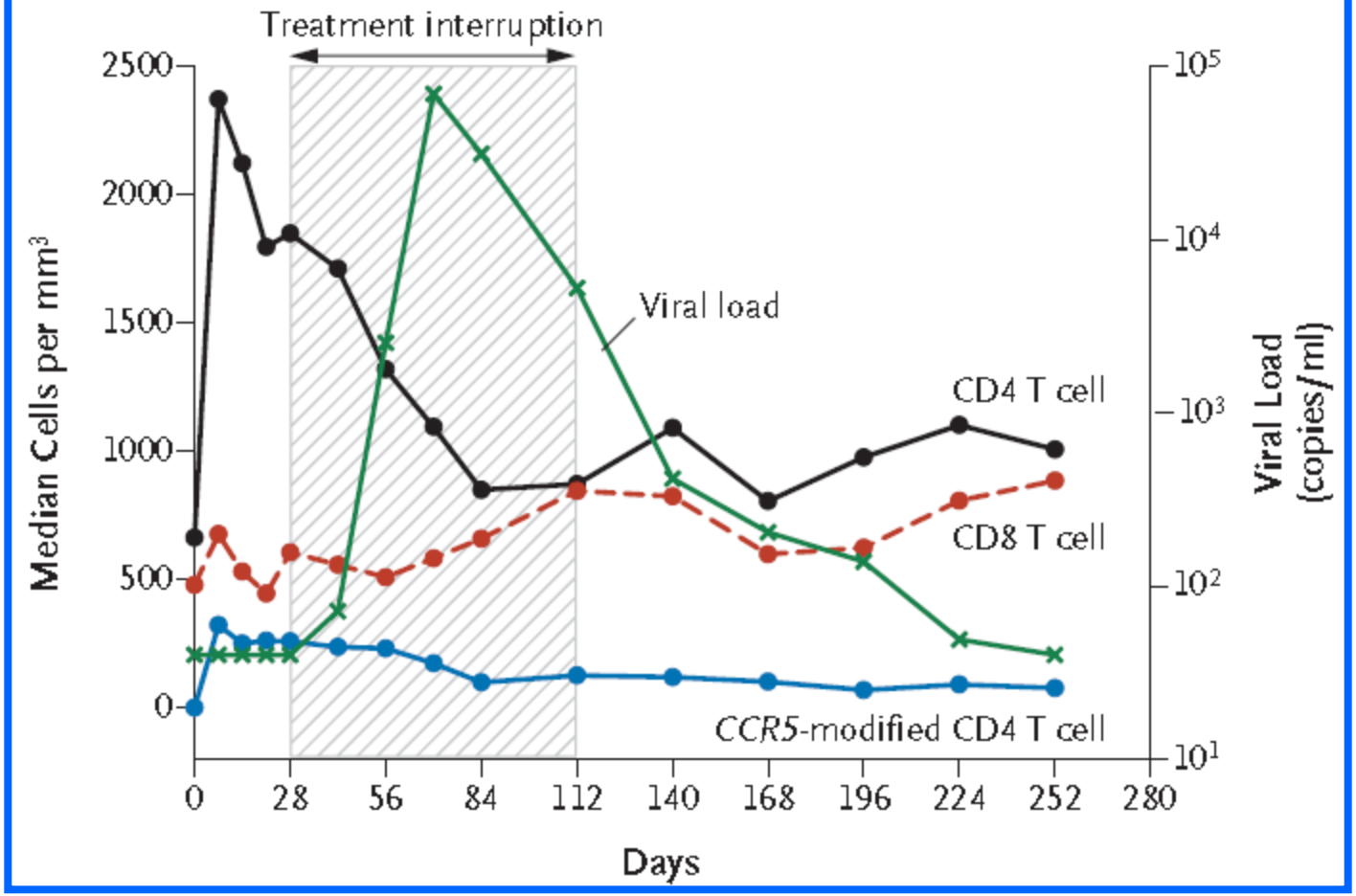
HIV: la tecnica “taglia e cuci” del DNA fa sperare nell’eradicazione

HIV ott 07,2016 0 Comments

ESTABLISHED IN 1812 MARCH 6, 2014 VOL. 370 NO. 10

Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.



A Proof of Concept (Berlin Patient)

Long-Term Control of HIV by CCR5 Delta32/ Delta32 Stem-Cell Transplantation

G Hutter, E Thiel et al.

New England Journal of Medicine, 360:692, 2009

Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation

K Ellers, T Schenider et al.

Blood, 117:2791, 2011

- An encouraging proof of concept that a "functional cure" may be possible
- No immediate, practical application as HIV therapy due to risk, expense, and the difficulty in finding suitable donors

J. Neurovirol. (2015) 21:310–321
DOI 10.1007/s13365-014-0308-9

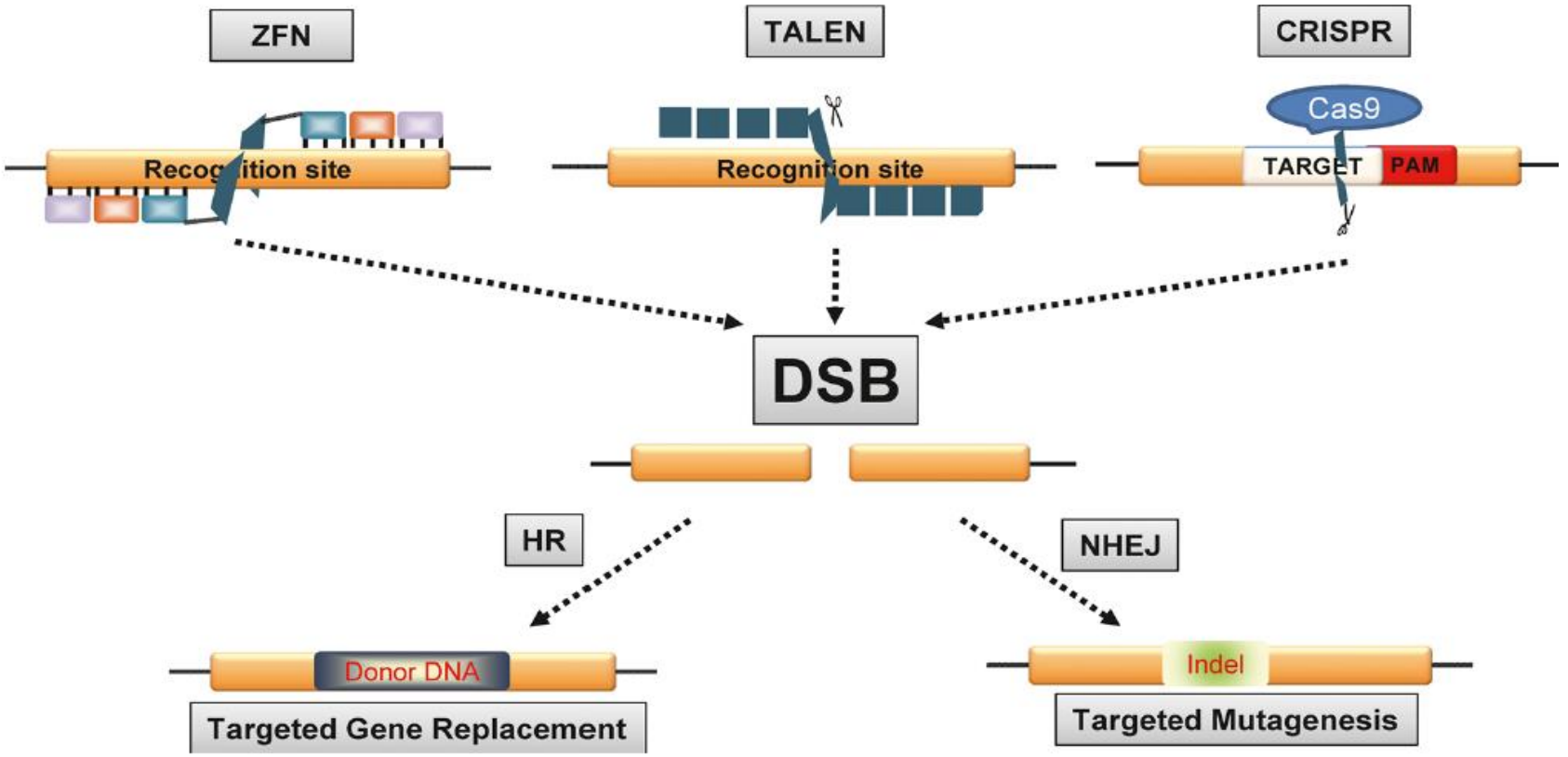
REVIEW

Genome editing strategies: potential tools for eradicating HIV-1/AIDS

Kamel Khalili · Rafal Kaminski · Jennifer Gordon · Laura Cosentino · Wenhui Hu

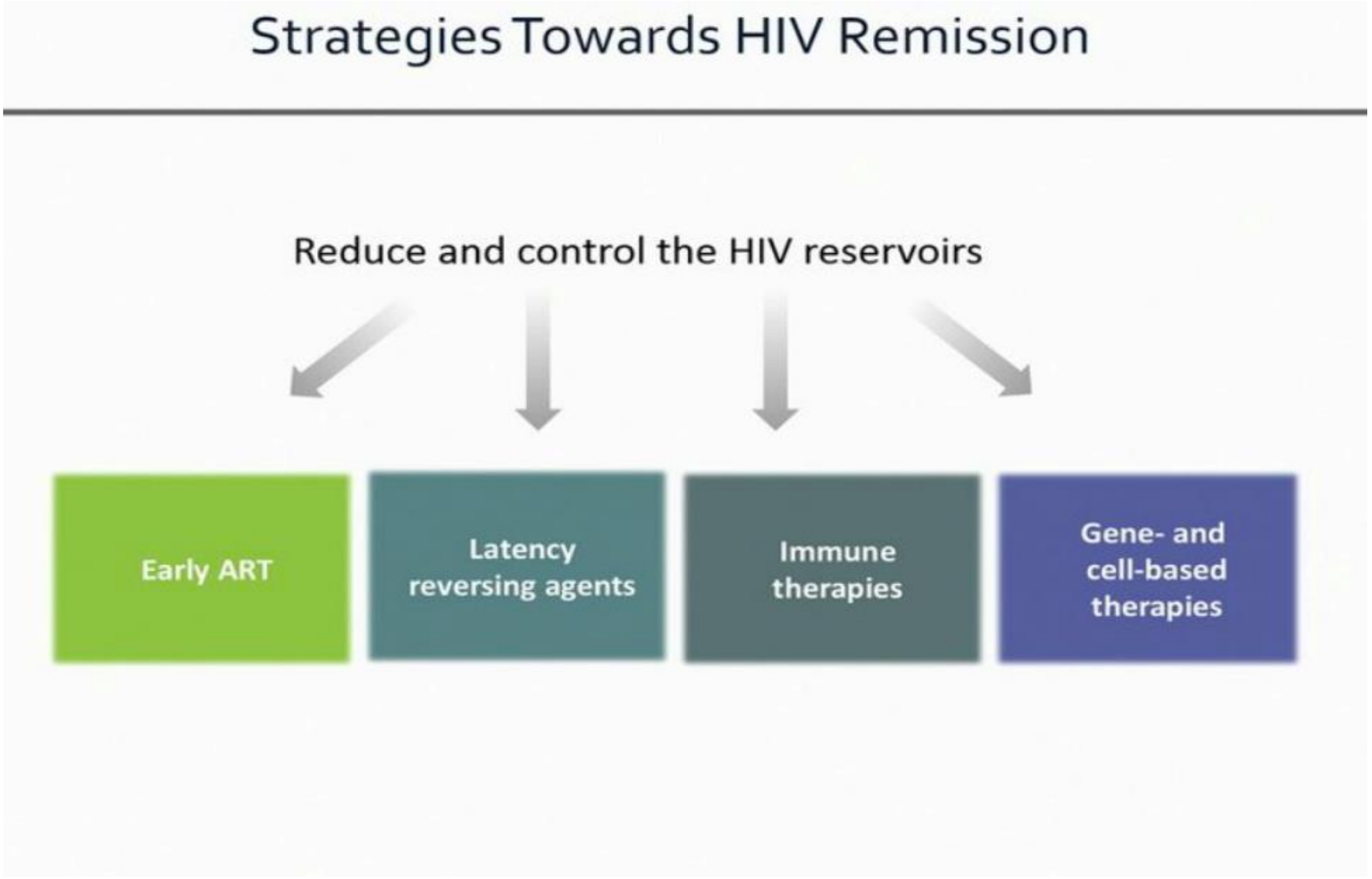
however, such a cure could be achieved by excision of the integrated viral genome from the host DNA utilizing one of several genome editing strategies, which are still in the early stages of development (Hu et al. 2014; Manjunath et al. 2013; Stone et al. 2013).

Nuclease-inducted double strand breaks (DSBs)



J. Neurovirol. (2015) 21:310–321

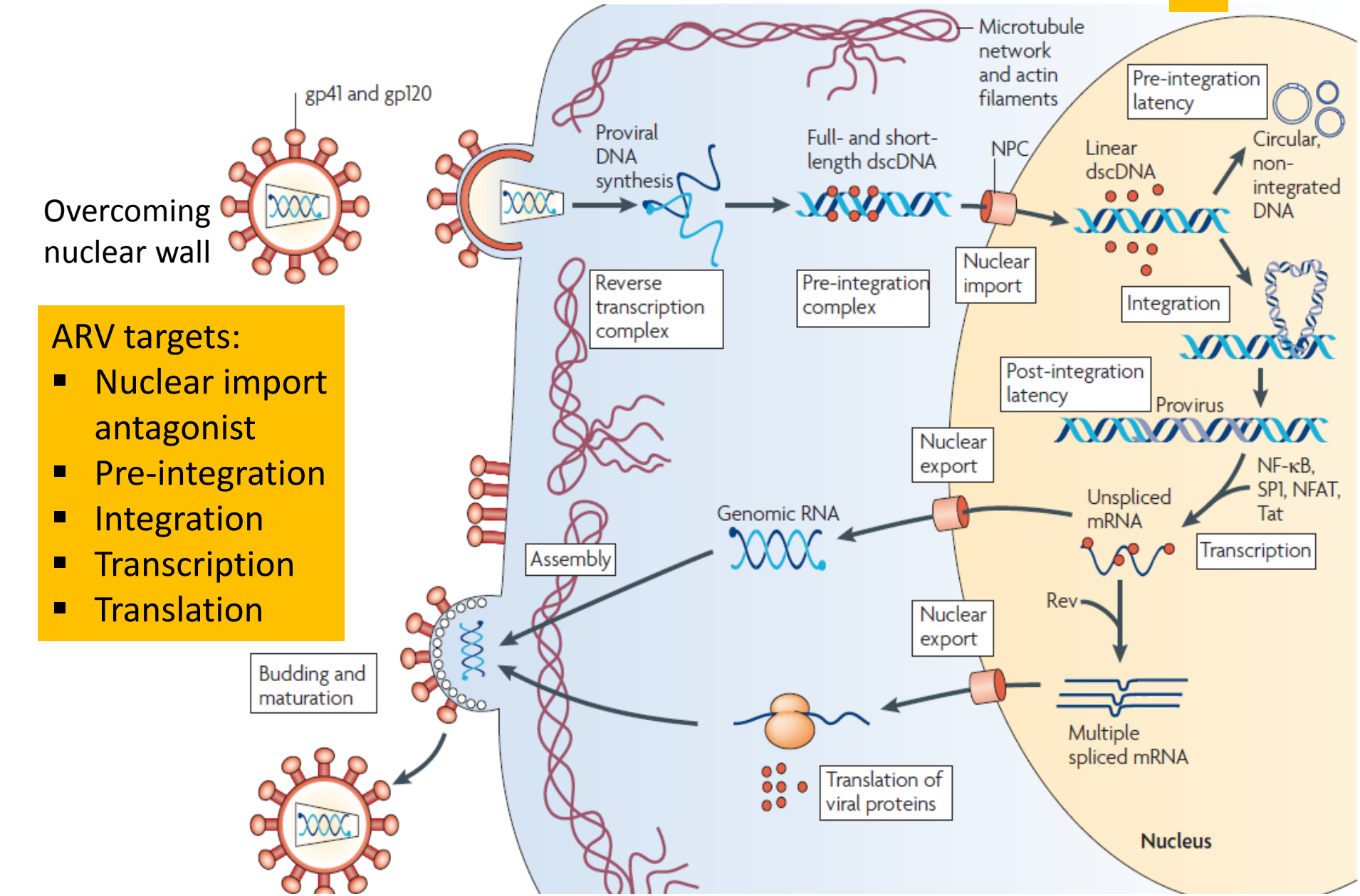
Conclusions:




ON THE ROAD
Reduce reservoir extent
Keep a persistent immune surveillance
Select best candidates to ATI
Get a durable remission
Hope in eradication

HIV-1 life cycle and viral latency.

1



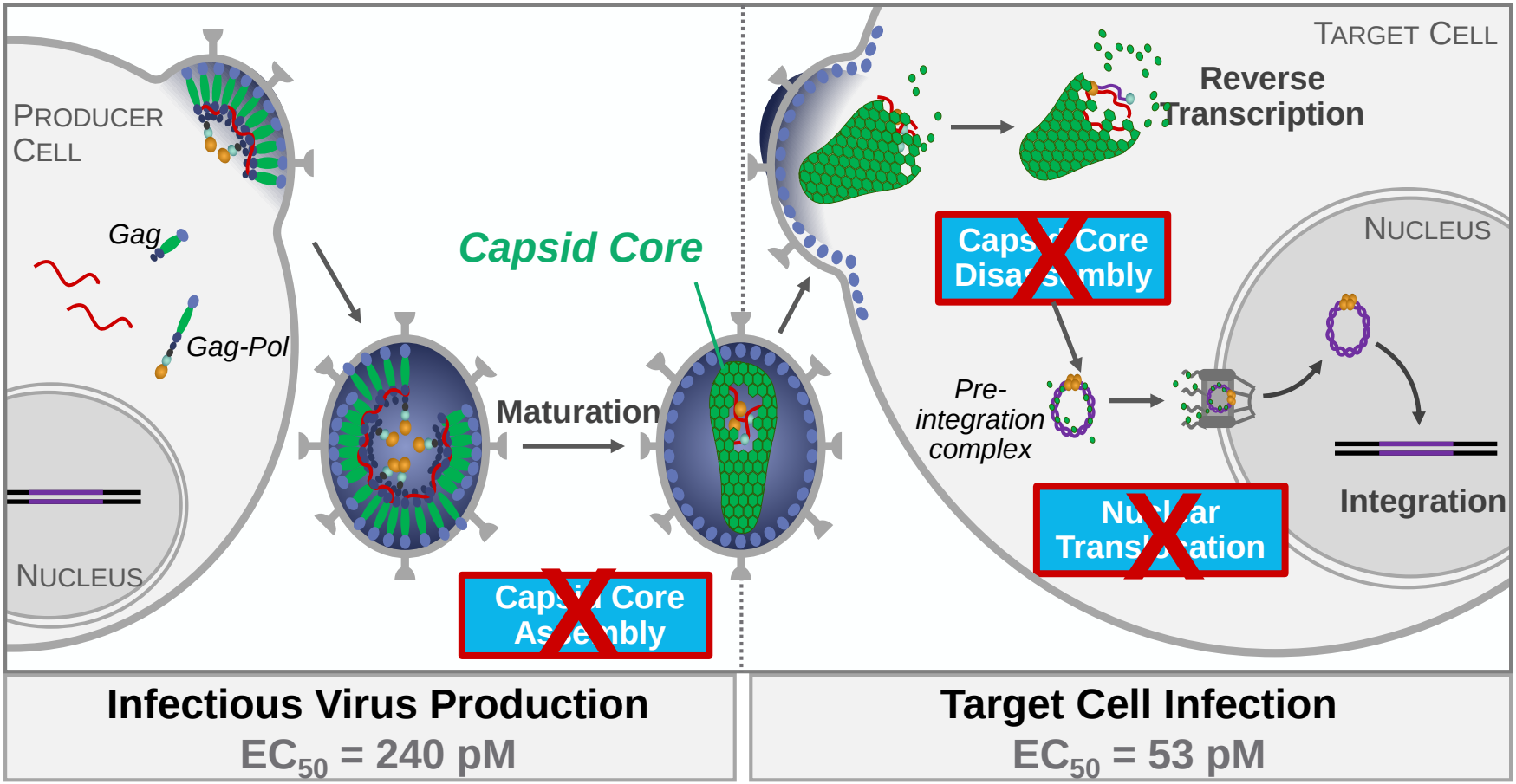
ARV targets:

- Nuclear import antagonist
- Pre-integration
- Integration
- Transcription
- Translation

HIV Capsid Acts at Multiple Stages in the Viral Life Cycle

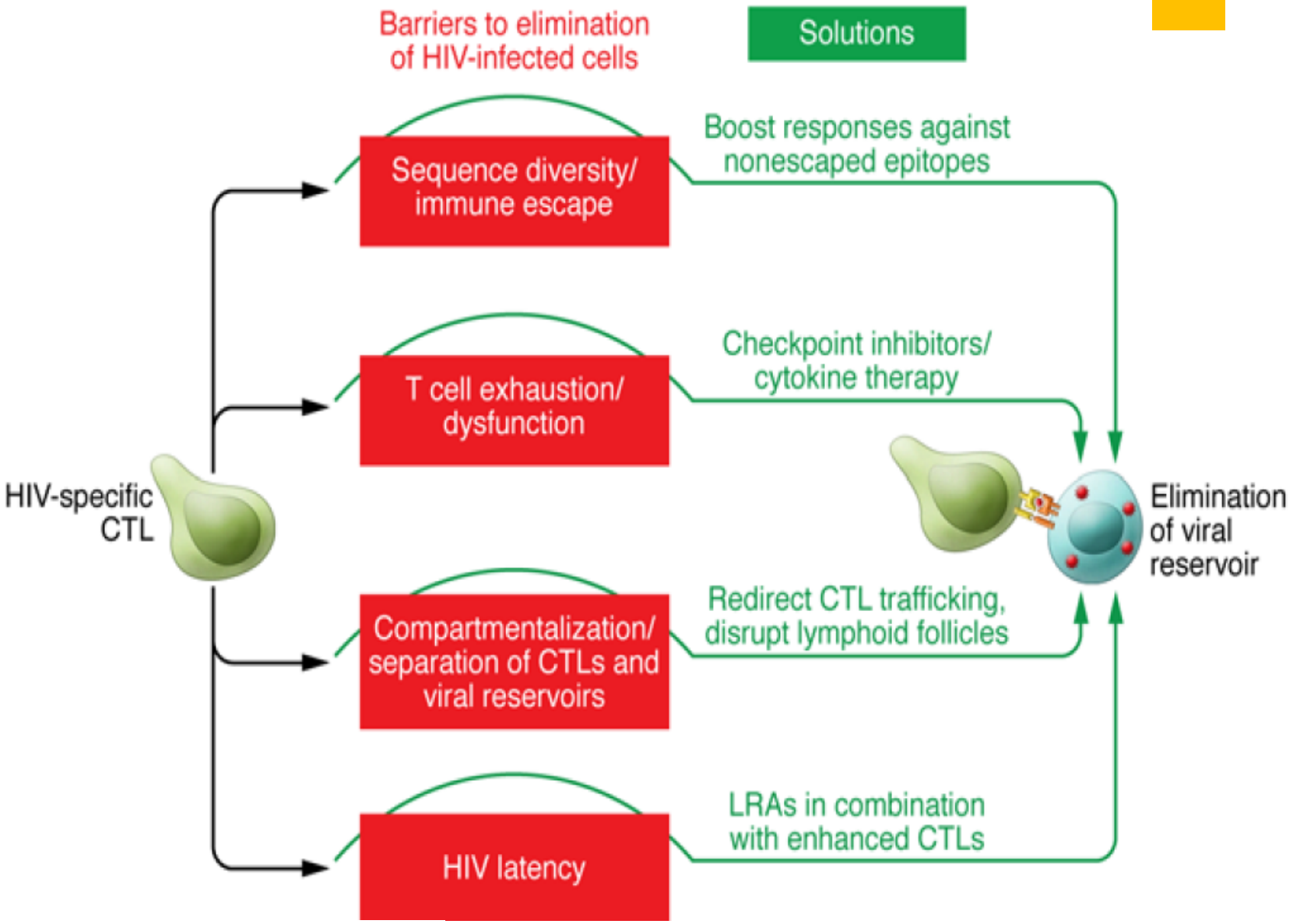
1

- GS-CA1 inhibits HIV capsid function, resulting in aberrant core assembly/disassembly via multiple steps in HIV replication cycle



- For a full single round of replication the EC_{50} is 85 pM

Tse W, et al. CROI 2017. Seattle, WA. Oral #38.


Barriers to elimination of HIV-infected cells
Solutions
Sequence diversity/ immune escape
Boost responses against nonescaped epitopes
T cell exhaustion/ dysfunction
Checkpoint inhibitors/ cytokine therapy
HIV-specific CTL
Elimination of viral reservoir
Compartmentalization/ separation of CTLs and viral reservoirs
Redirect CTL trafficking, disrupt lymphoid follicles
HIV latency
LRAs in combination with enhanced CTLs

The International HIV Controllers Study *(ii)*

- Investigations of HIV-1 controllers that have been carried out since then have confirmed that there is an over-representation of certain 'protective' HLA class I alleles in this group — including HLA-B*57, HLA-B*27, HLA-B*13 and HLA-B*58:01 — compared with HIV-1 progressors.

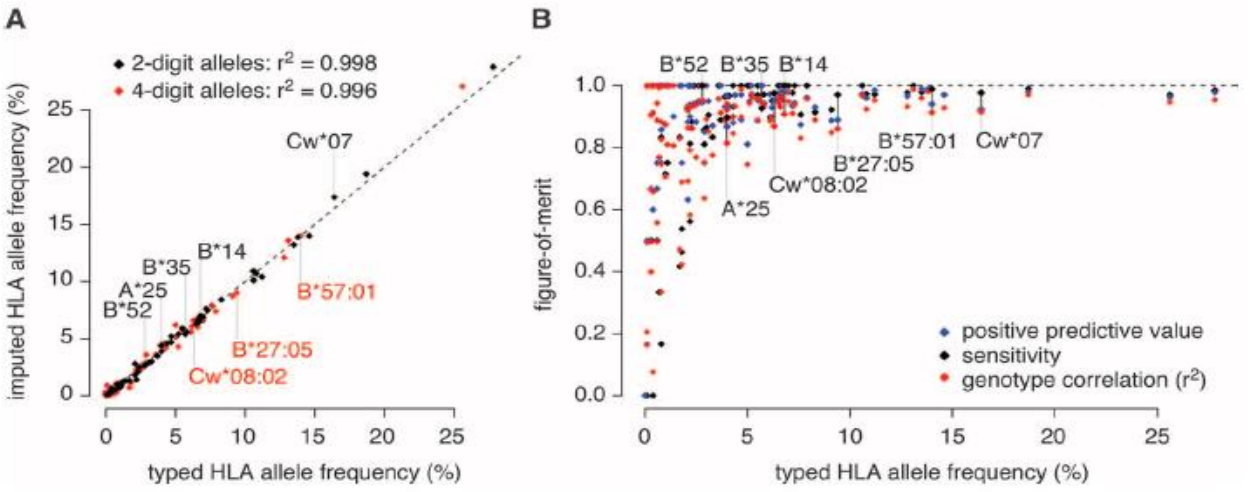


Fig. 2. Imputation quality of classical *HLA* alleles in the European sample. **(A)** Concordance between imputed (*y*-axis) and observed (*x*-axis) frequencies of classical *HLA* types in 371 HIV-1 controllers with four-digit *HLA* types obtained through Sanger sequencing. **(B)** Positive predictive value, sensitivity, and genotype correlation (r^2) with typed alleles as a function of the observed frequency.

www.sciencemag.org **SCIENCE** VOL 330 10 DECEMBER 2010

BEST PERFORMERS: frame the target

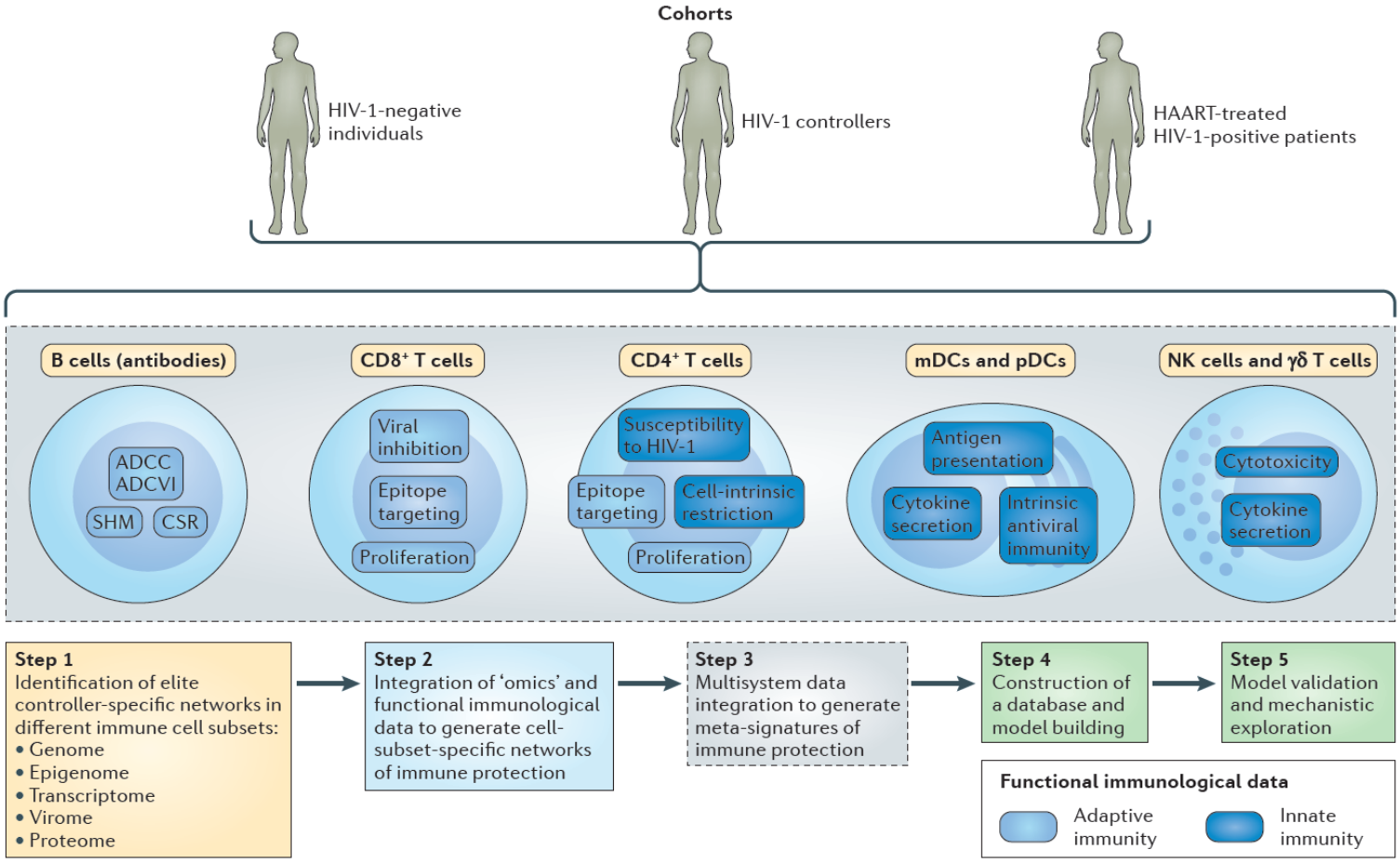
In the long term HIV-RNA suppressed pts the immune response as to be read on the light of a different goal (cure) vs long-term non progression

Key point:

1. Favourable genetic background
2. HIV specific CTL exhaustion
3. Relauch of the role of neutralizing antibodies
4. Controversial benefit of immunotolerance and new reservoir in omeostasis
5. After TI the immune control of HIV replication is necessary every were

Immune control of HIV replication-after ATI seems necessary in order to avoid or delay the restart of cART

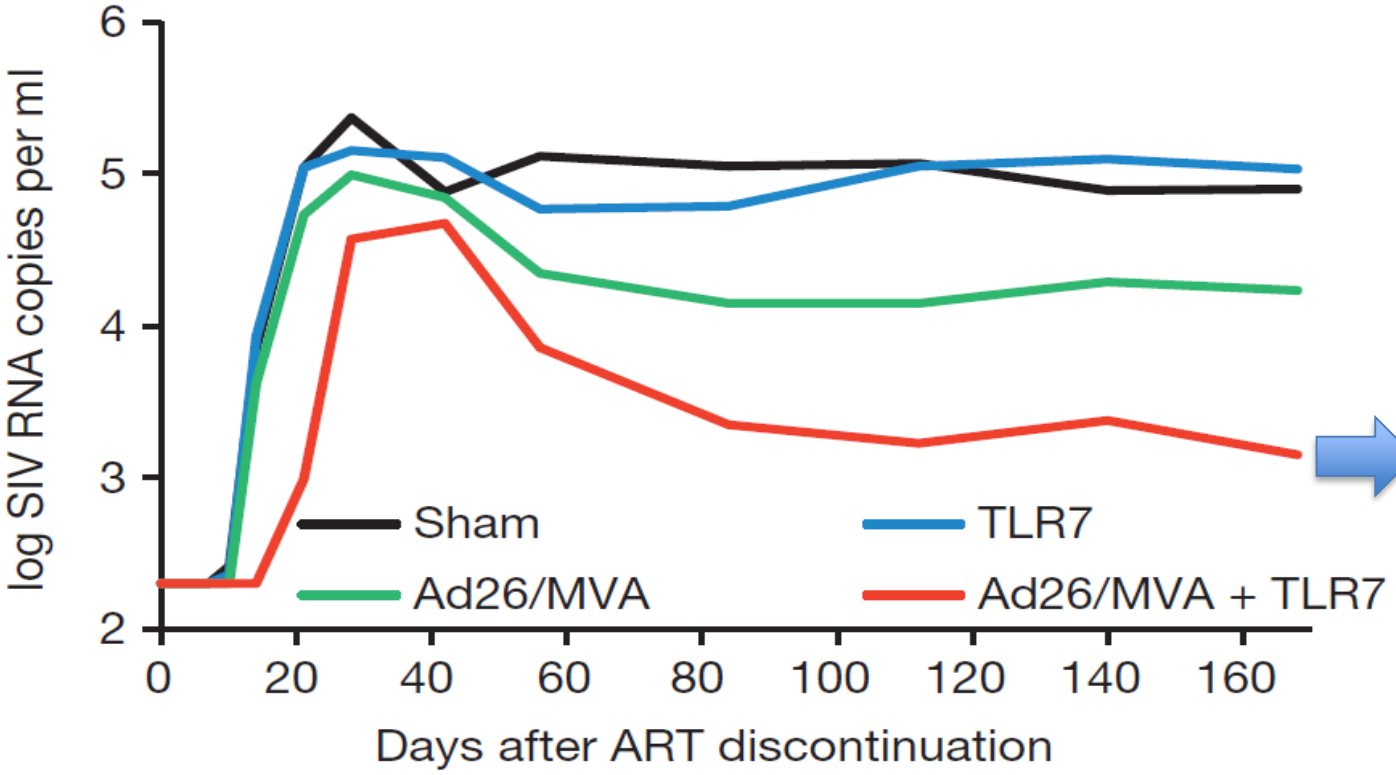
Could an elite controller phenotype be therapeutically inducible in a larger number of patients?



Walker BD & Yu XG. Nat Rev Immunol, 2013

TLR_7 Agonist + Ad26/MVA Vaccine Reduced viral load in Monkeys after ART Discontinuation

4



Total n.° 32

Remission in 3 of 9 with Ad26/MVA+TLR7

Combination TLR_7 Agonist + Ad26/MVA delayed time to viral load rebound and decreased viral load set point and viral DNA.

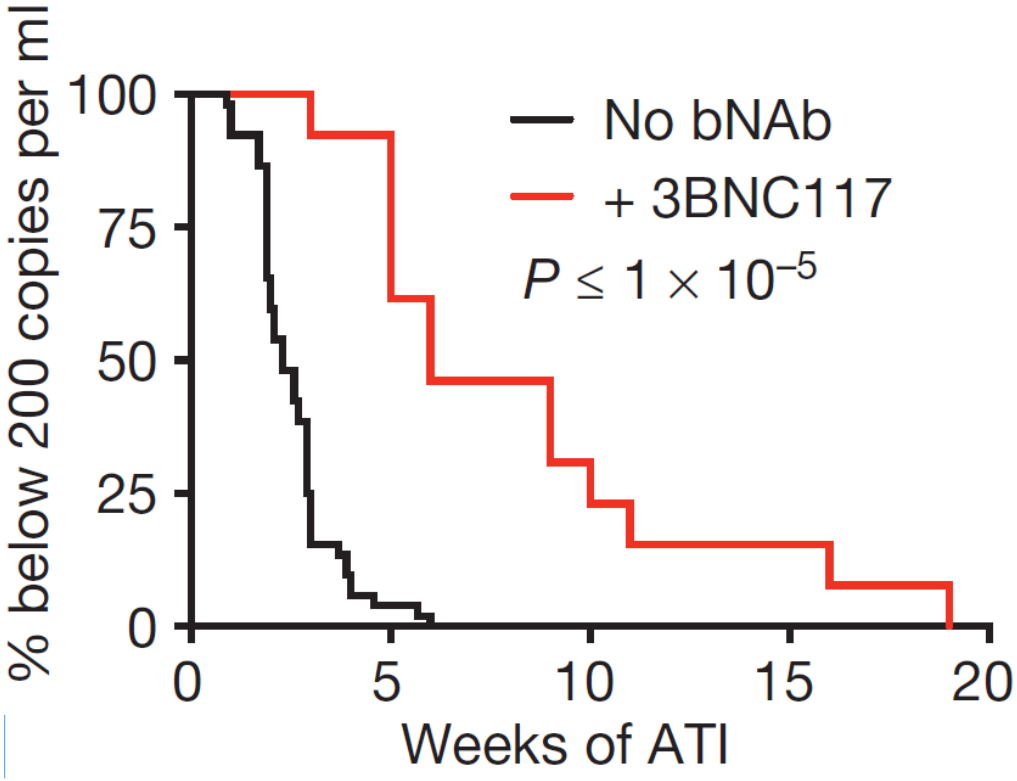
Curr HIV/AIDS Rep (2016) 13:31–37
DOI 10.1007/s11904-016-0299-7

4

Broadly Neutralizing Antibodies for HIV Eradication

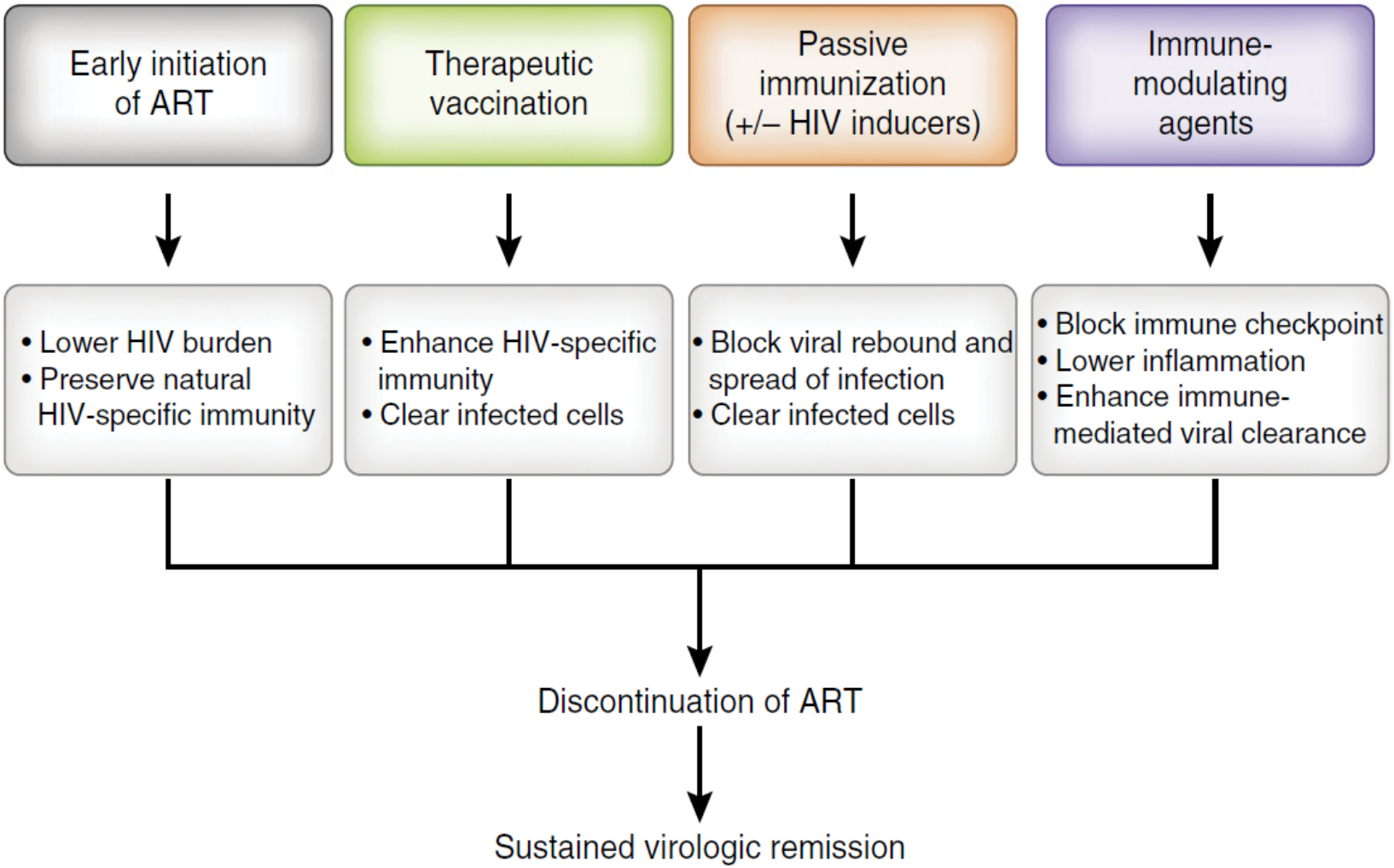
Kathryn E. Stephenson [1,2] · Dan H. Barouch [1,2]

Delay in viral rebound in the presence of 3BNC117.



Johannes F. Scheid[1]

Rethinking ARV treatment for HIV clearance



VOLUME 16 NUMBER 6 JUNE 2015 NATURE IMMUNOLOGY

ENDING HIV