La sospensione dell'ARV è sempre una cattiva idea?

Adriano Lazzarin

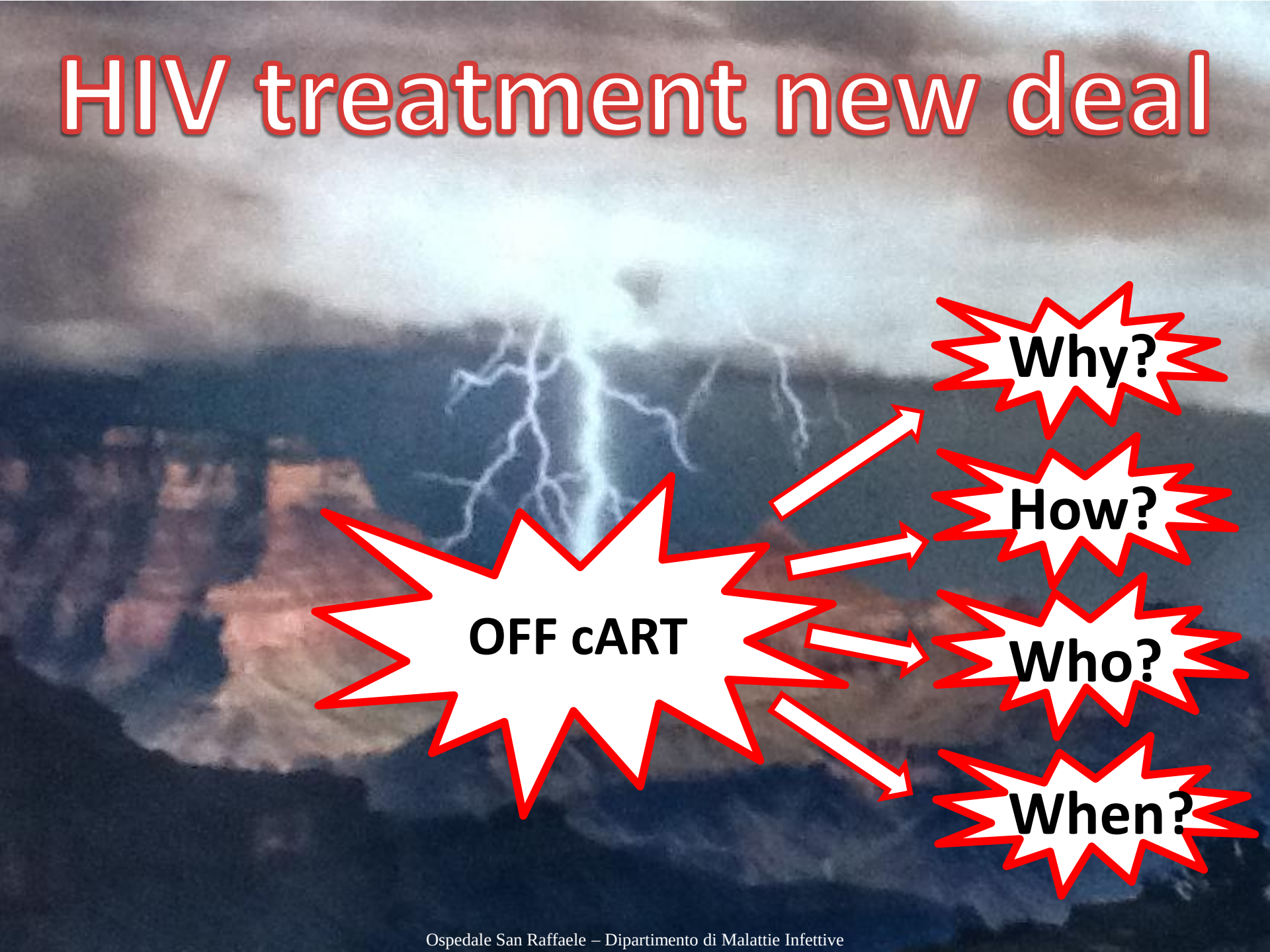
IRCCS Ospedale San Raffaele, Università Vita e Salute, Milano

6 Infect*ivology* To*day*

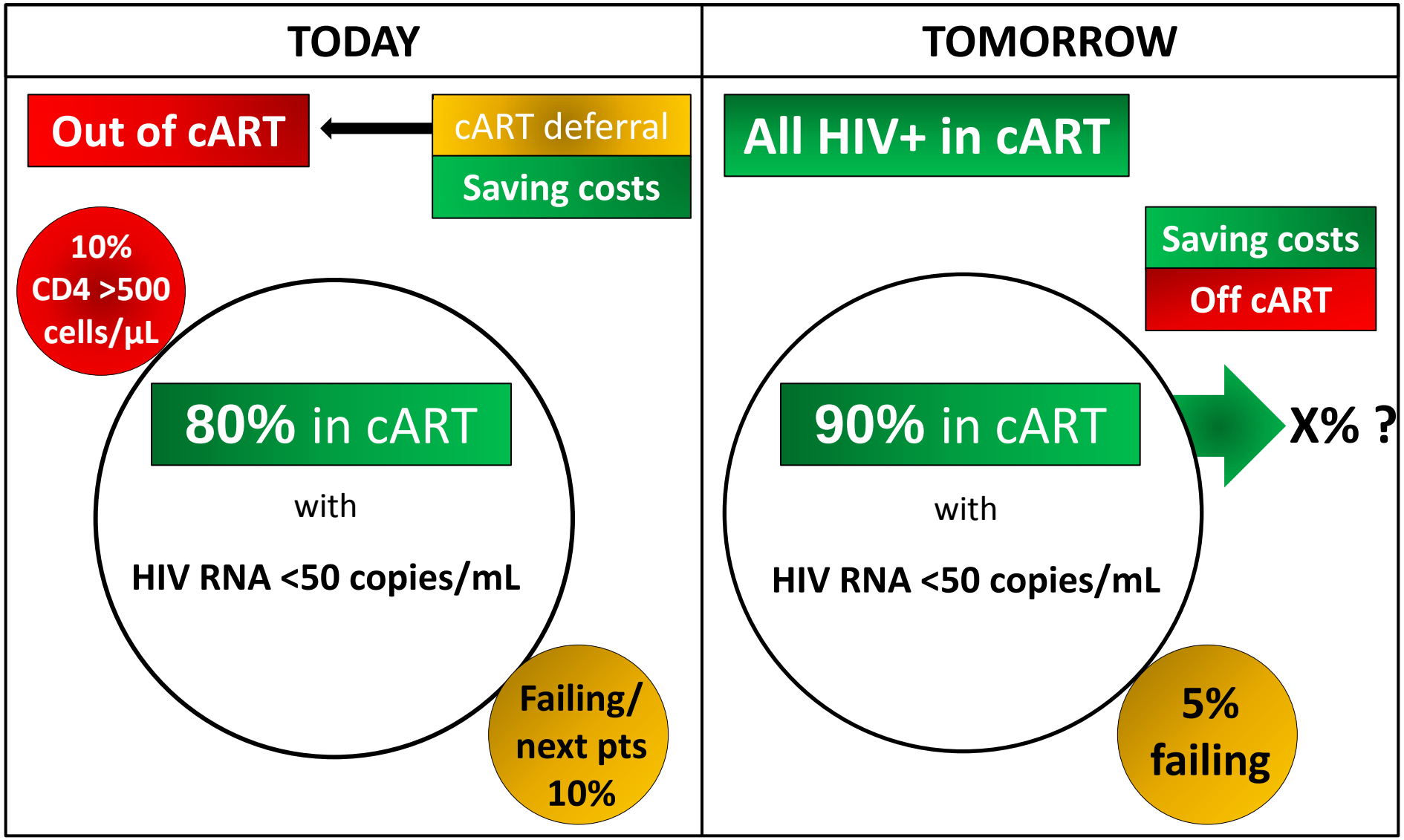
I due principi che guideranno il management dei pazienti HIV trattati con viremia undetectable

Sostenibilità **Appropriatezza**

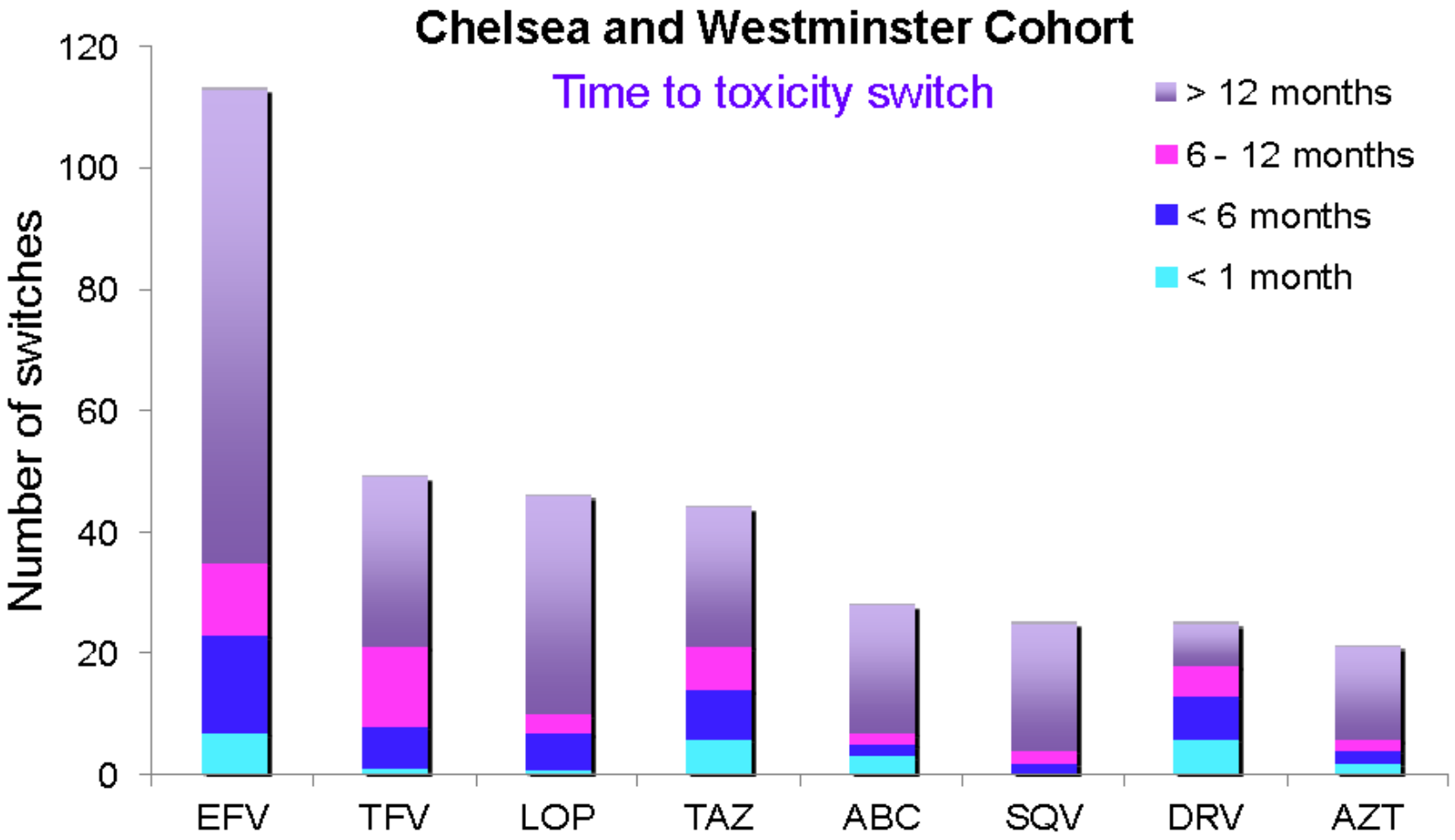
HIV treatment new deal



Moving from today to a tomorrow HIV treatment scenario



Time to toxicity switch not necesarily short



Boyle A et al. Why do patients switch therapy? 18th Annual Conference BHIVA, April 2012

Drug fatigue
the hope: treatment holiday

…moving from ⟶ **never / forever** dilemma

…to ⟶ **IN cART / OFF cART** enigma

Looking for freedom

In cART

Fully suppressed patients

Almost Off cART = Simplification

Off cART = Strategic Treatment Interruption (STI)

SMART study

Inferior Clinical Outcome of the CD4$^+$ Cell Count–Guided Antiretroviral Treatment Interruption Strategy in the SMART Study: Role of CD4$^+$ Cell Counts and HIV RNA Levels during Follow-up

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group[a]

Conclusions. The higher risk of OD/death in DC patients was associated with (1) spending more follow-up time with relative immunodeficiency and (2) living longer with uncontrolled HIV replication even at higher CD4$^+$ cell counts. Ongoing HIV replication at a given CD4$^+$ cell count places patients at an excess risk of OD/death.

Trial registration. ClinicalTrials.gov identifier: NCT00027352.

JID 2008:197

BASTA study

Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial

Franco Maggiolo[a], Diego Ripamonti[a], Gianpietro Gregis[a], Gianpaolo Quinzan[a], Annapaola Callegaro[b] and Fredy Suter[a]

Conclusions: Prolonged STI in patients with fully suppressed virus and marked immune reconstitution is generally safe. The main predictor of CD4 cell decline is the nadir CD4 cell count. Pulse therapy warrants further careful prospective evaluation to investigate virological and clinical outcomes over a very long period.

AIDS 2004, **18**:439–446

FOTO study

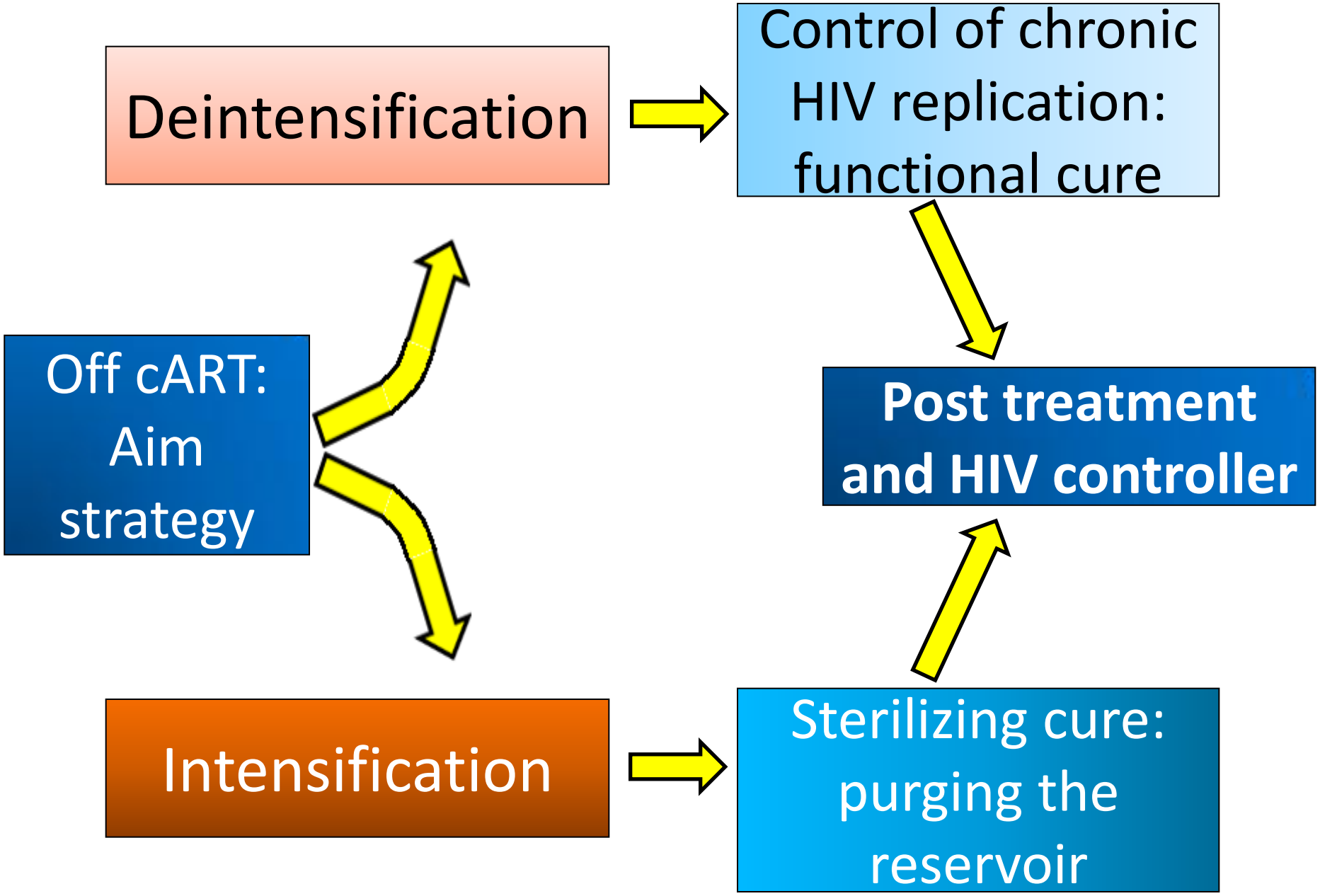
Pilot Study of a Novel Short-Cycle Antiretroviral Treatment Interruption Strategy: 48-Week Results of the Five-Days-On, Two-Days-Off (FOTO) Study

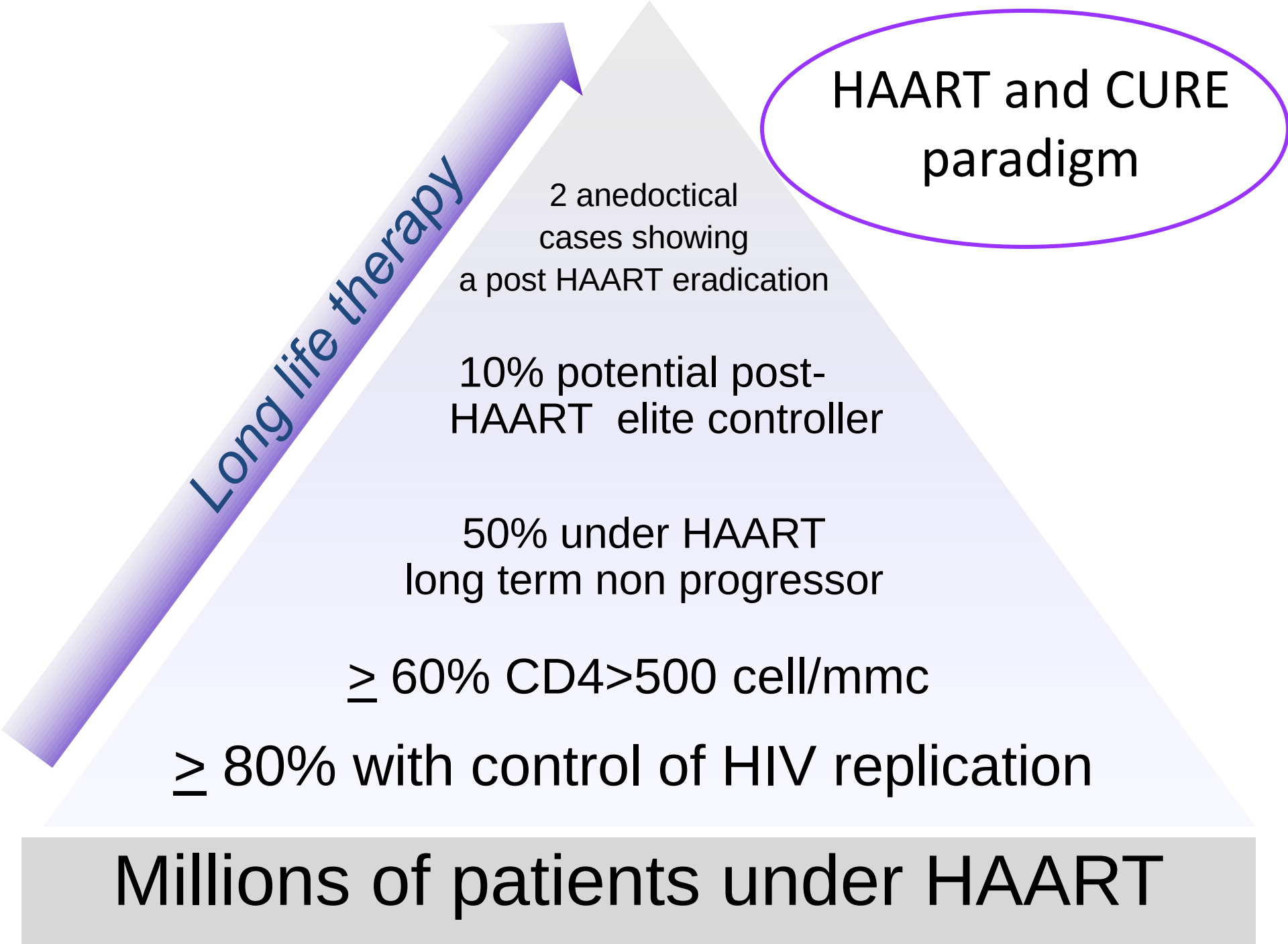
Calvin J. Cohen, MD,[1–3] MSc, Amy E. Colson, MD, MPH,[1,2,4]
Alexander G. Sheble-Hall, BSN, ACRN,[1] Karen A. McLaughlin, CCRC,[1]
and Gene D. Morse, PharmD[5]

[1]Community Research Initiative of New England, Boston, Massachusetts; [2]Harvard Medical School, Boston, Massachusetts; [3]Harvard Vanguard Medical Associates, Boston, Massachusetts; [4]Cambridge Health Alliance, Cambridge, Massachusetts; [5]Clinical Education and Research at the University of Buffalo, Amherst, New York, USA

Conclusion: If validated, the FOTO treatment strategy with efavirenz-based regimens could avoid the viremia witnessed in longer cycle structured treatment interruptions yet still ameliorate a number of problems associated with the current paradigm of daily ART for HIV infection, including the high cost of therapy and the pill fatigue that, in many patients, leads to erratic adherence and ultimately treatment failure.

HIV Clin Trials 2007;8(1):19–23

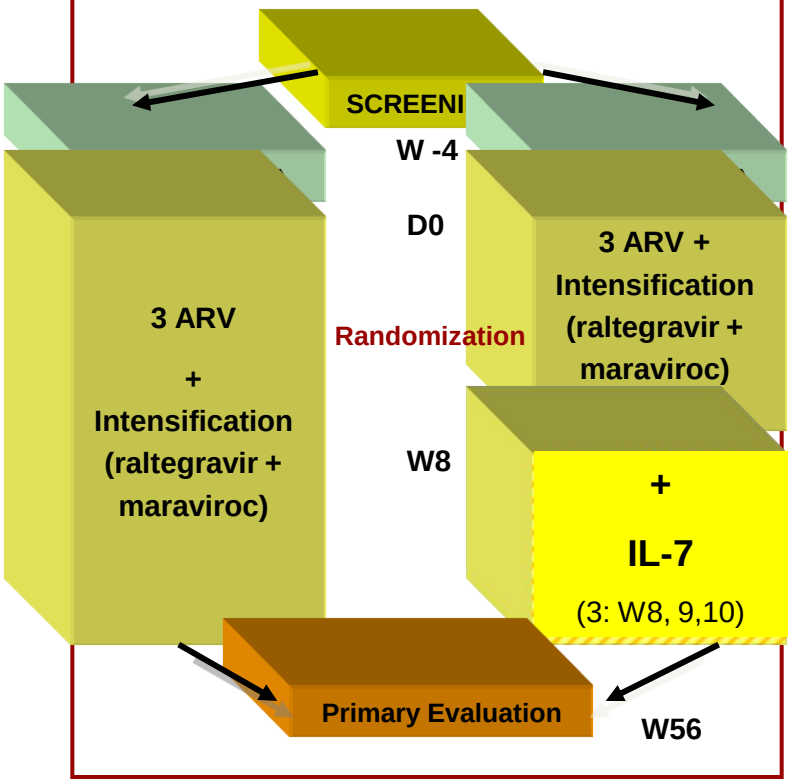

Deintensification
Control of chronic HIV replication: functional cure
Off cART: Aim strategy
Post treatment and HIV controller
Intensification
Sterilizing cure: purging the reservoir


HAART and CURE paradigm
Long life therapy
2 anedoctical cases showing a post HAART eradication
10% potential post-HAART elite controller
50% under HAART long term non progressor
≥ 60% CD4>500 cell/mmc
≥ 80% with control of HIV replication
Millions of patients under HAART

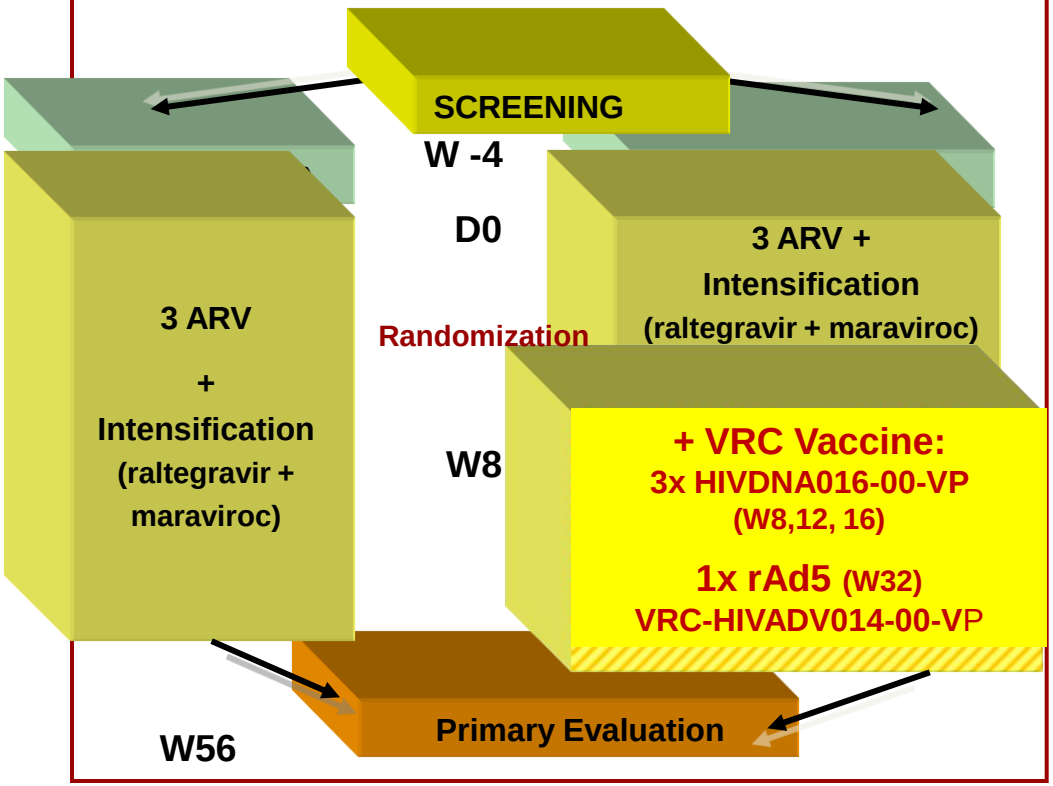
The EraMune-01 and -02 Trials : Parallel Study Design

International, multicenter, randomized, non-comparative controlled study of therapeutic intensification plus immunomodulation in HIV-infected patients with long-term viral suppression

ERAMUNE-01 (Europe, PI: C Katlama)



ERAMUNE-02 (USA, PI: R Murphy)



r-hIL-7 (CYT107) injections at 20 µg/Kg/week (1 per week)

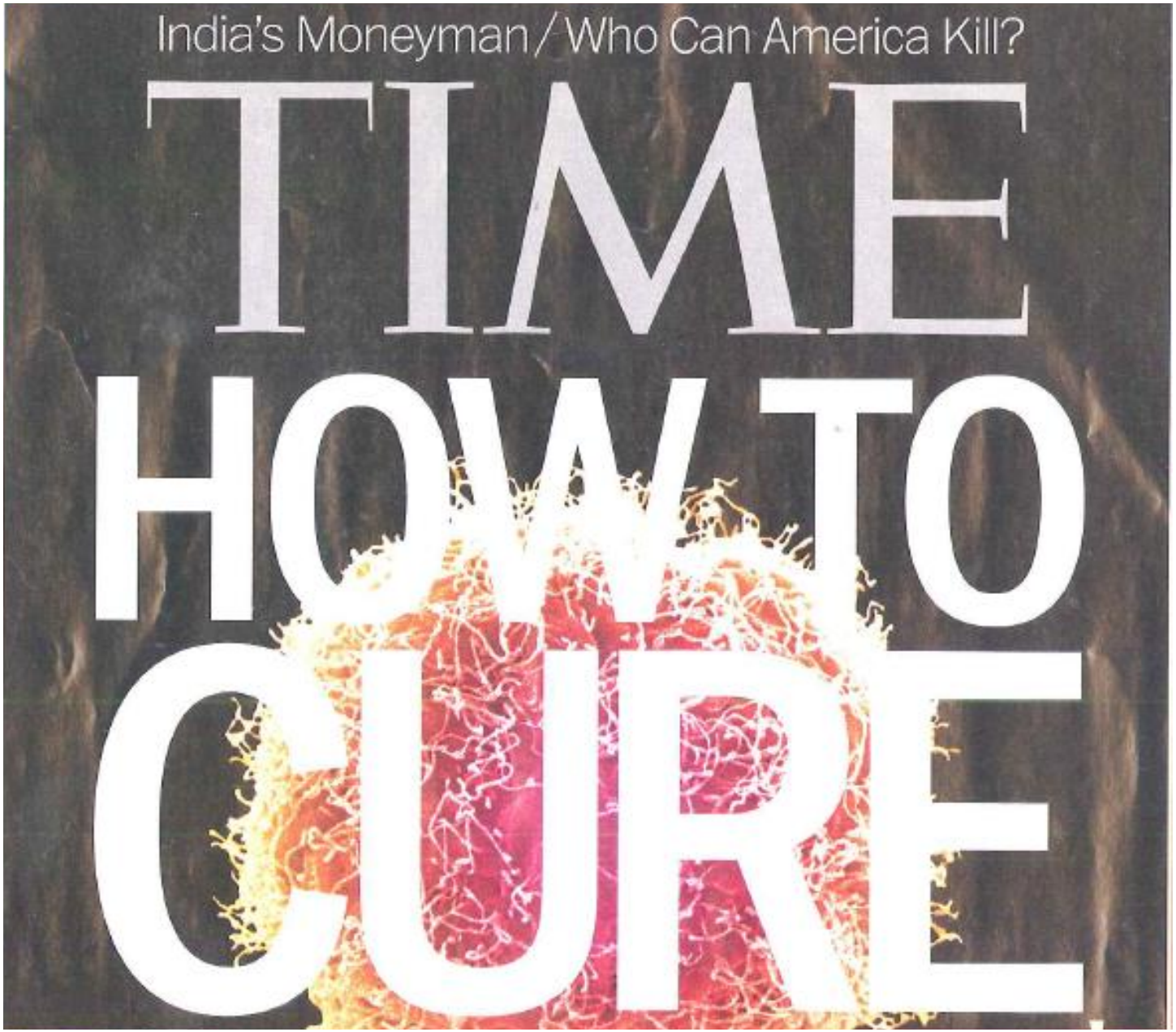
VRC: HIVDNA016-00-VP : 3 DNA clade B HIV-1 Gag, Pol, or Nef
3 DNA HIV-1 Env clade A, B and C,
HIV-Ad5 VRC-HIVADV014-00-VP (clade B HIV-1 Gag Pol fusion protein, + clade A, B, and C Env proteins

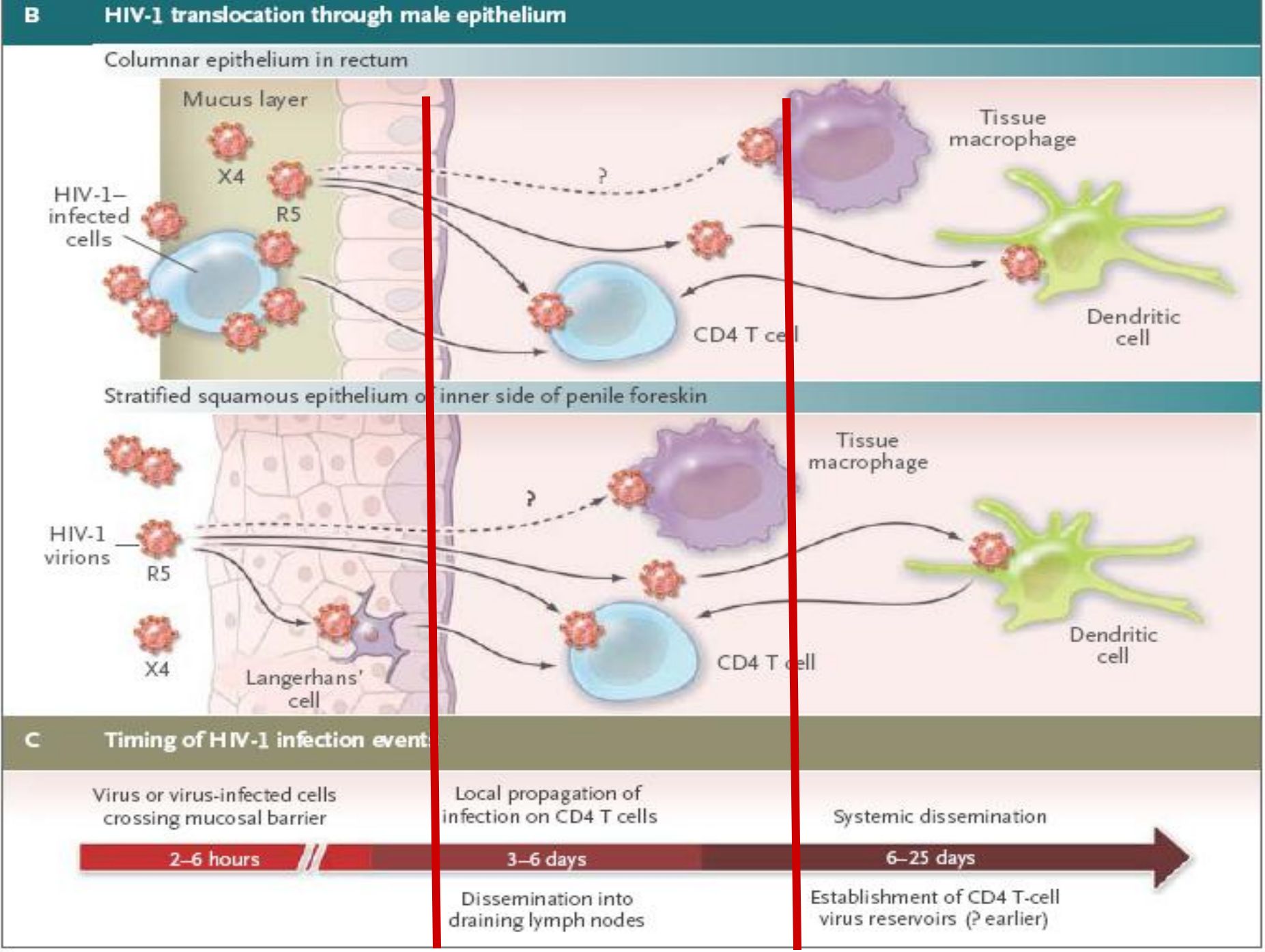
- **Similar Primary objective: Decrease in the HIV-1 viral reservoir**
- Results expected: Eramune-01: December 2012; Eramune-02: March 2013

"Functional Cure" Child: Standard HIV-1 Assays Undetectable to Age 26 Mos

- ART regimens: ZDV/3TC + NVP (31 hours – 7 days)
- ZDV/3TC + LPV/RTV (7 days – 18 months)
- Plasma VL on ART displayed typical biphasic decay from baseline VL 19,812 c/mL
  - VL undetectable by < 30d of age
  - VL remained undetectable though > 80d of age
- Assessments at Mos 24 and 26
  - Western blot negative
  - No HIV-specific CD8+ or CD4+ T-cell responses
  - Standard HIV-1 RNA and HIV-1 DNA undetectable
  - By ultrasensitive assays
    - **Mo 24**: HIV-1 RNA 1 c/mL; HIV-1 DNA < 2.7 c/million PBMCs
    - **Mo 26**: HIV-1 DNA 4 c/million PBMCs
- Clinical trials of exposed infants treated with ART recommended

Persaud D, et al. CROI 2013. Abstract 48LB.


India's Moneyman / Who Can America Kill?
TIME
HOW TO
CURE


B
HIV-1 translocation through male epithelium
Columnar epithelium in rectum
Mucus layer
X4
R5
HIV-1–infected cells
?
Tissue macrophage
CD4 T cell
Dendritic cell
Stratified squamous epithelium of inner side of penile foreskin
HIV-1 virions
R5
X4
?
Tissue macrophage
Langerhans' cell
CD4 T cell
Dendritic cell
C
Timing of HIV-1 infection events
Virus or virus-infected cells crossing mucosal barrier
2–6 hours
Local propagation of infection on CD4 T cells
3–6 days
Dissemination into draining lymph nodes
Systemic dissemination
6–25 days
Establishment of CD4 T-cell virus reservoirs (? earlier)

Early Treatment of Pts With Acute HIV Infection Restricts Seeding of Reservoirs

- RV254/SEARCH 010: ongoing, prospective, open-label study of subjects seeking voluntary HIV testing (n = 75 with Fiebig stage I-III acute infection)
- Before ART, HIV reservoir seeding limited
  - Integrated HIV-1 DNA undetectable in PBMCs (92%) and sigmoid colon (88%) of most Fiebig I pts
  - Lower infection frequencies of central memory CD4+ T cells vs other memory cells
- After ART, decline in HIV reservoir size
  - Integrated HIV-1 DNA undetectable in PBMCs in 90% of pts at 1 yr
  - Reservoir primarily in transitional and effector memory CD4+ T cells
- Suggests very early ART may prevent seeding of reservoirs

Fiebig Stages

- Fiebig I: RNA+, p24 neg, 3rd-gen ELISA neg
  - Would not be detected by 4th-gen ELISA
- Fiebig II: RNA+, p24+, 3rd-gen ELISA neg
- Fiebig III: 3rd-gen ELISA+, WB neg

Ananworanich J, et al. CROI 2013. Abstract 47.

A true drug FREE generation?

OPEN ACCESS Freely available online

PLOS | PATHOGENS

Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión[1]*, Charline Bacchus[2], Laurent Hocqueloux[3], Véronique Avettand-Fenoel[4,5], Isabelle Girault[6], Camille Lecuroux[6], Valerie Potard[7,8], Pierre Versmisse[1], Adeline Melard[4], Thierry Prazuck[3], Benjamin Descours[2], Julien Guergnon[2], Jean-Paul Viard[5,9], Faroudy Boufassa[10], Olivier Lambotte[6,11], Cécile Goujard[10,11], Laurence Meyer[10,12], Dominique Costagliola[7,8,13], Alain Venet[6], Gianfranco Pancino[1], Brigitte Autran[2], Christine Rouzioux[4,5]*, the ANRS VISCONTI Study Group[¶]

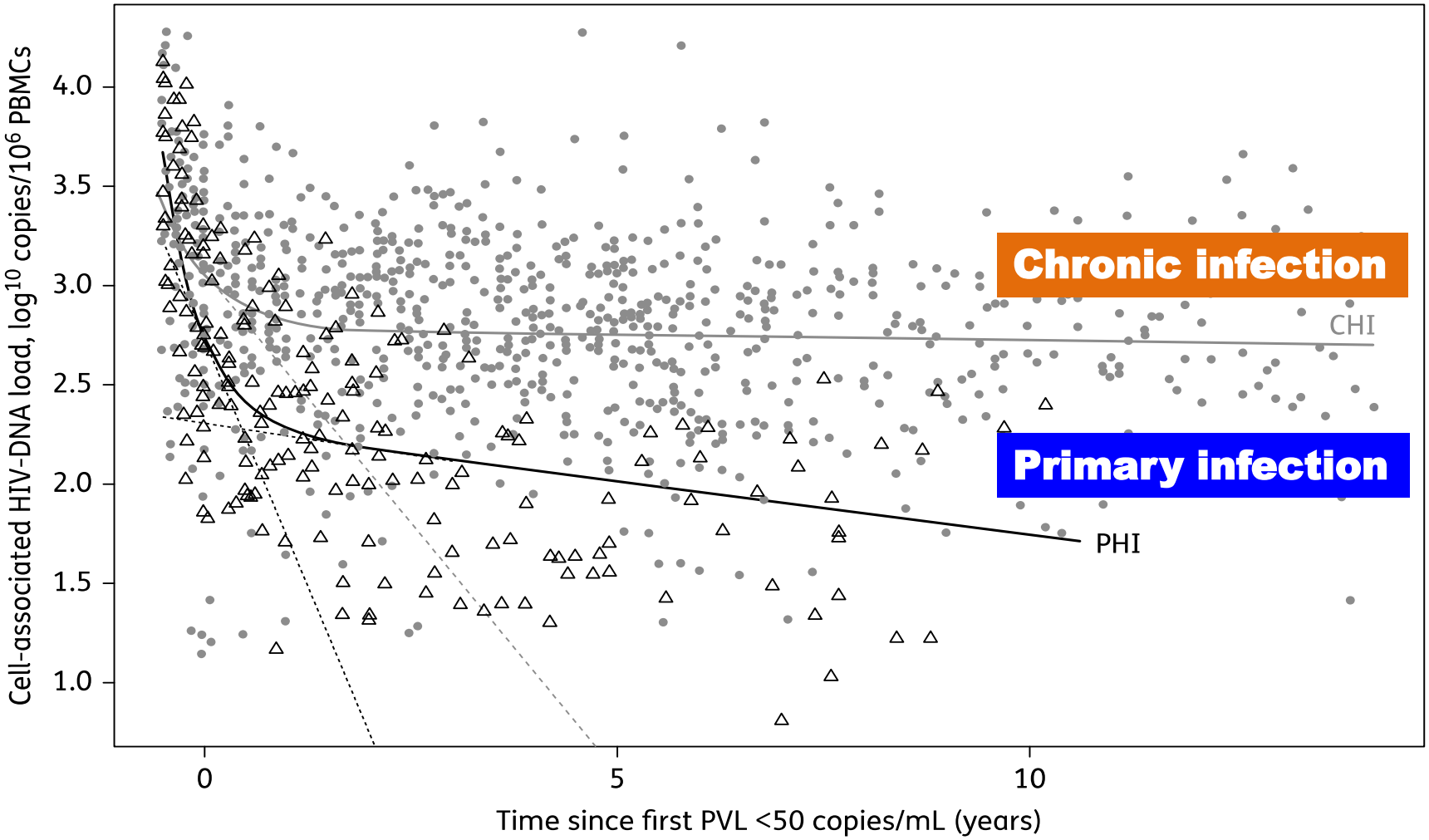
1 Institut Pasteur, Unité de Régulation des Infections Rétrovirales, Paris, France, **2** Université Pierre et Marie Curie, INSERM UMR-S 945 Immunité et Infection, Hôpital Pitié-Salpêtrière, Paris, France, **3** Centre Hospitalier Régional d'Orléans, Service des Maladies Infectieuses et Tropicales, Orléans, France, **4** AP-HP, CHU Necker-Enfants Malades, Laboratoire de Virologie, Paris, France, **5** EA 3620, Université Paris-Descartes, Sorbonne Paris Cité, Paris, France, **6** INSERM U1012, Université Paris-Sud 11, Le Kremlin Bicêtre, France, **7** UPMC Univ Paris 06, UMR_S 943, Paris, France, **8** INSERM, U943, Paris, France, **9** AP-HP, Hôtel-Dieu, Paris, France, **10** INSERM U1018, Université Paris-Sud 11, Le Kremlin Bicêtre, France, **11** AP-HP, Hôpital de Bicêtre, Service de Médecine Interne, Le Kremlin Bicêtre, France, **12** AP-HP, Hôpital de Bicêtre, Département d'épidémiologie, Le Kremlin Bicêtre, France, **13** AP-HP, Groupe hospitalier Pitié-Salpétrière, Service de Maladies Infectieuses et Tropicales, Paris, France

Post-Treatment controllers: conclusions

- EARLY start in PHI (High CD4/CD8 ratio!)
- Prolonged treatment with HIV RNA < 50 copies/μL (52m)
- Median HIV RNA <50 post HAART interruption (75m)
- HIV DNA <2 $\log_{10}$ copies/10^6PBMC
- 5/32 (PTC 15.6% vs EC <0.5%)

ANRS HIV RESERVOIR WORKING GROP. AIDS 2010 – research letter

HIV DNA higher and more stable in patients treated at chronic compared to acute phase



Hocqueloux L, et al. J Antimicrob Chemother. 2013 Jan 20

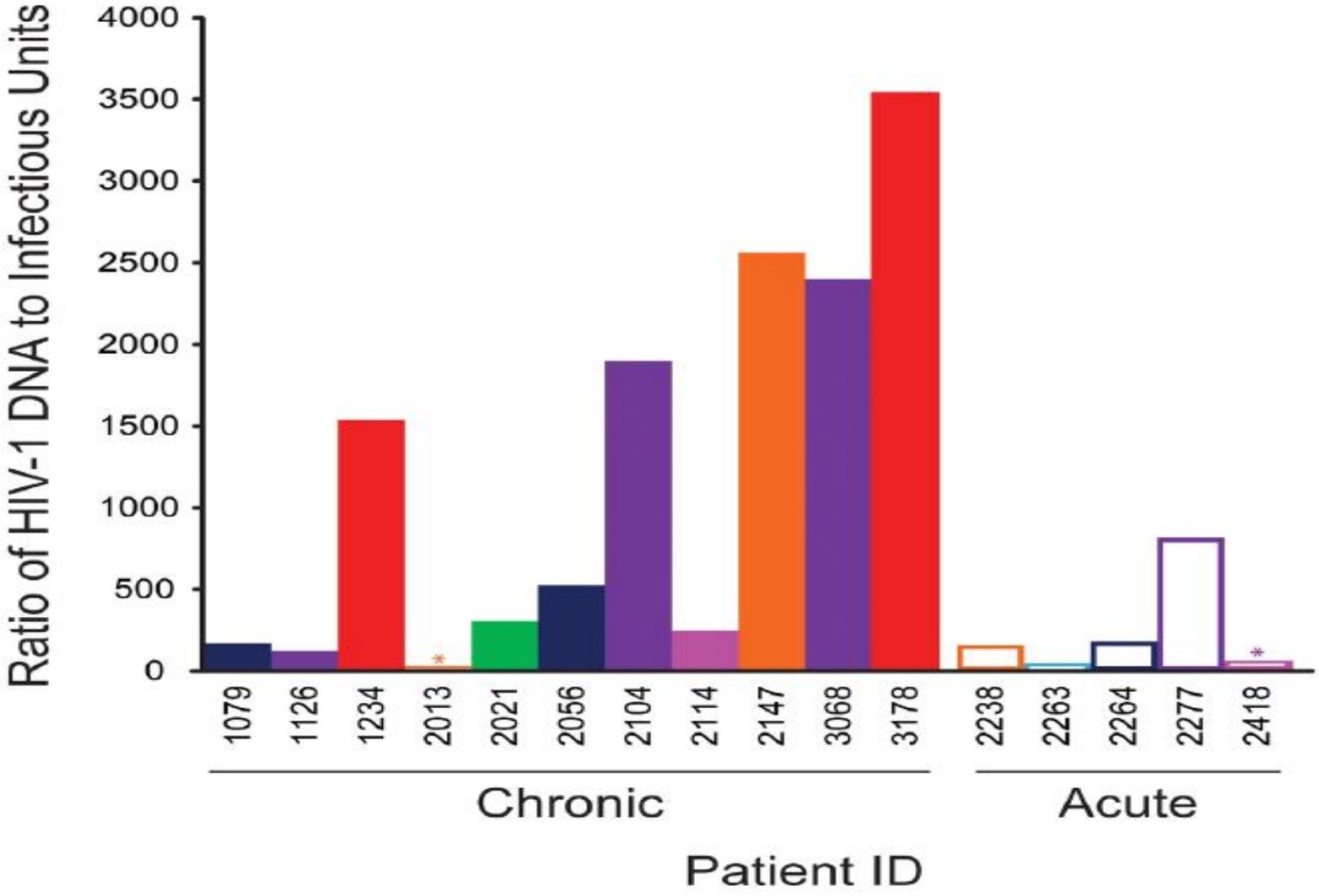
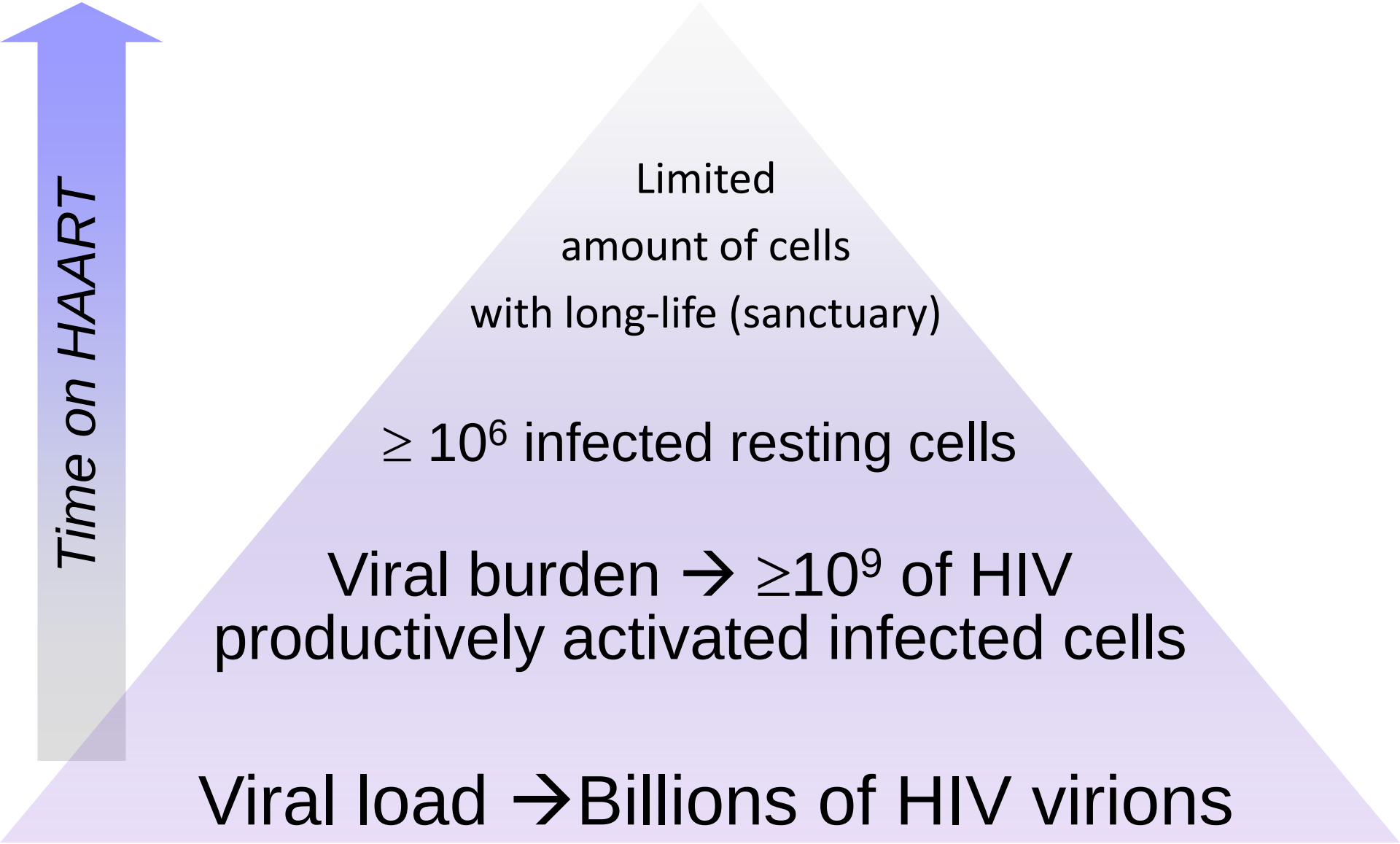
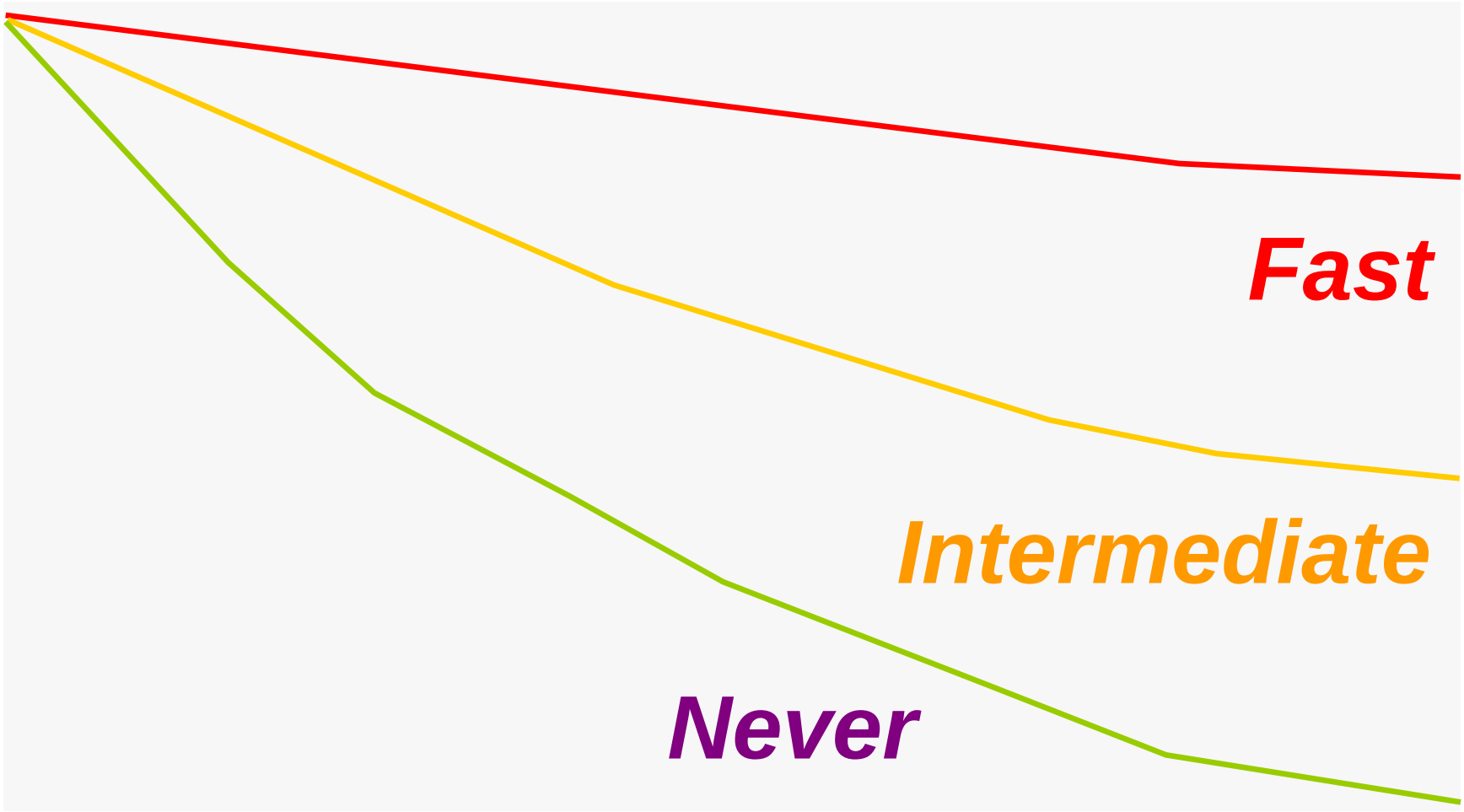


Figure 3. Ratio of infected cell frequencies determined by droplet digital PCR for HIV-1 DNA or by viral outgrowth assay. Analysis was done on the same sample of purified resting $CD4^+$ T cells. * indicates maximum values in cases in which the HIV-1 DNA level was below the limit of detection (2 copies/ml).
doi:10.1371/journal.ppat.1003174.g003

Evolution of HIV infection under HAART



Time to relapse

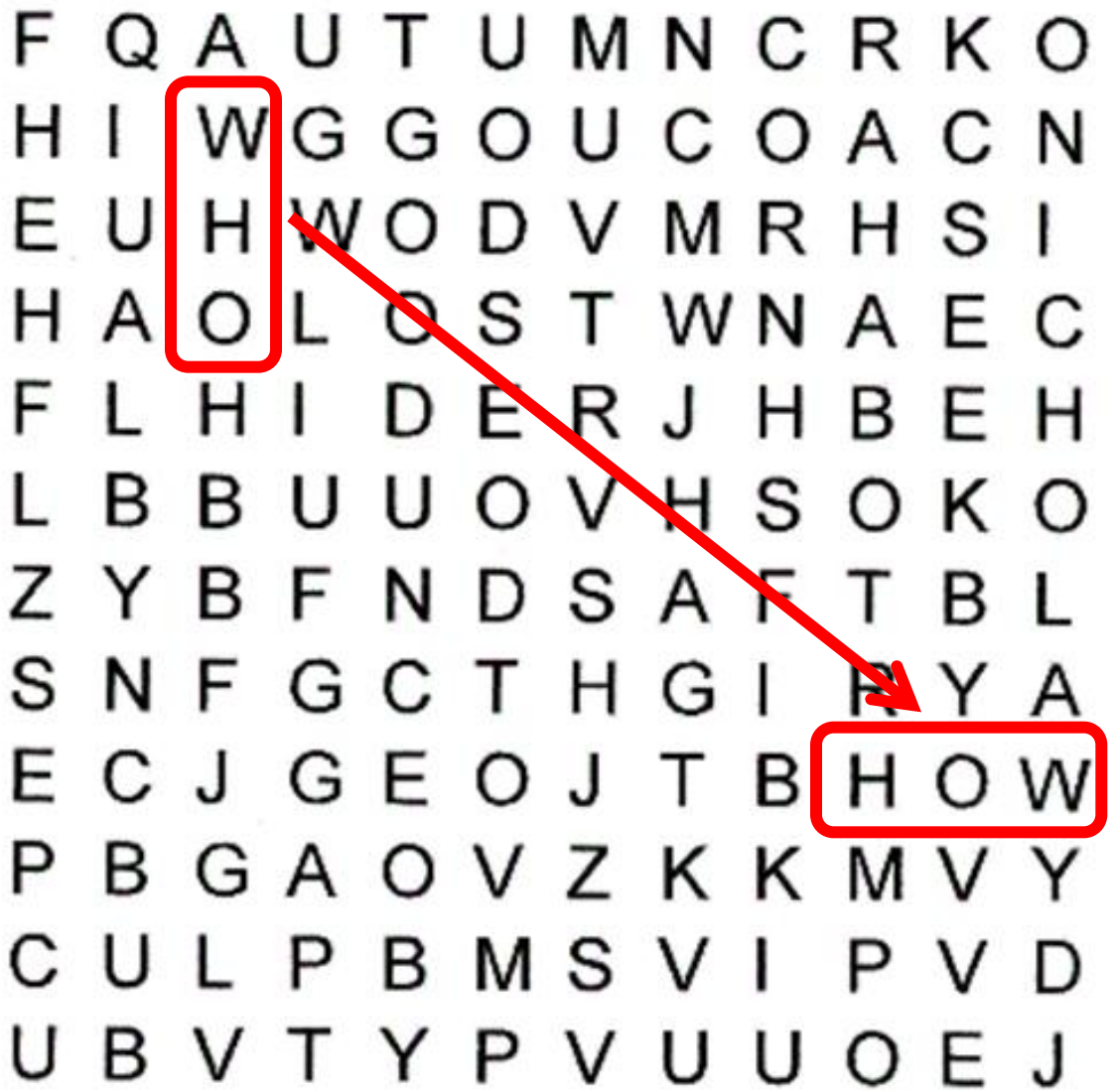


HAART success

it's not only a question of time

Long-Life HAART

PHI therapy


F Q A U T U M N C R K O
H I W G G O U C O A C N
E U H W O D V M R H S I
H A O L O S T W N A E C
F L H I D E R J H B E H
L B B U U O V H S O K O
Z Y B F N D S A F T B L
S N F G C T H G I R Y A
E C J G E O J T B H O W
P B G A O V Z K K M V Y
C U L P B M S V I P V D
U B V T Y P V U U O E J

“Channeling” the candidate selection

a) cART efficacy markers

- Treatment lenght
- HIV RNA < 1 copies/mL
- CD4+ count > 500 cells/µL
- HIV DNA < $2\log_{10}$ copies/mL
- Where does HIV persist

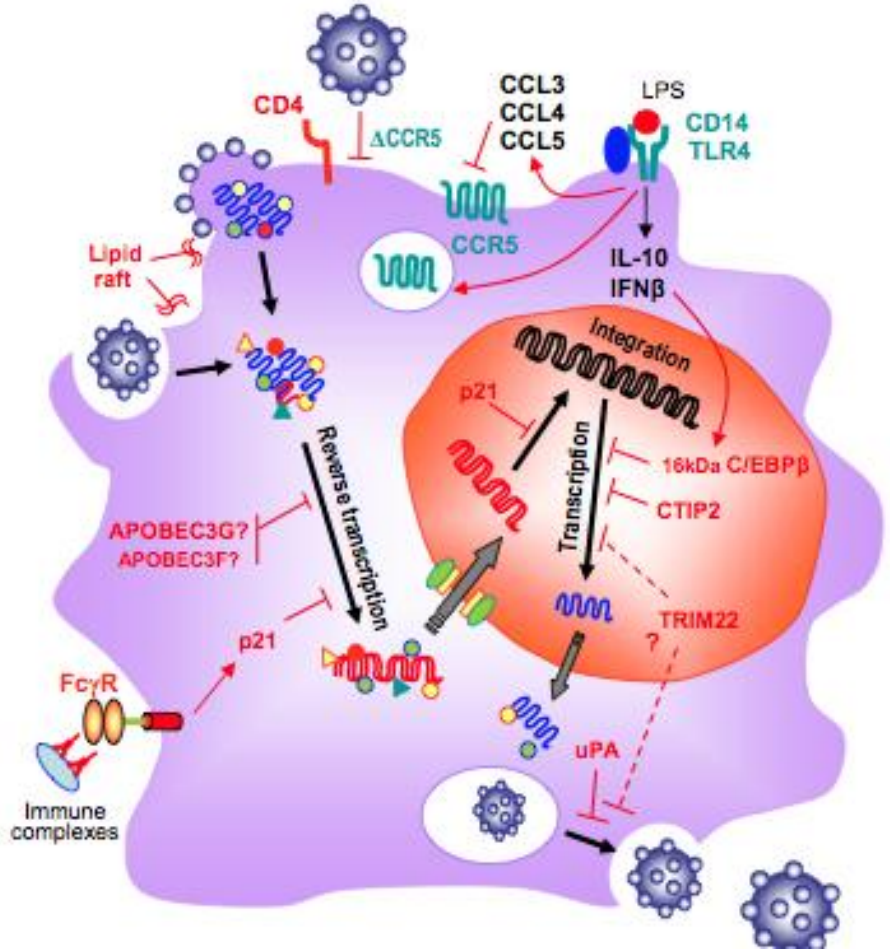
b) Favourable VIRUS / HOST interactions in the reservoir

c) Favourable immuno-genotype profile

d) Immuno-phenotype modelling treatment

Latent infection of macrophages and microglial cells

- In early disease following primary infection; in treated patients
- Restriction of HIV replication at different steps and by different mechanisms



Bergamaschi & Pancino, Retrovirology 2010

Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy

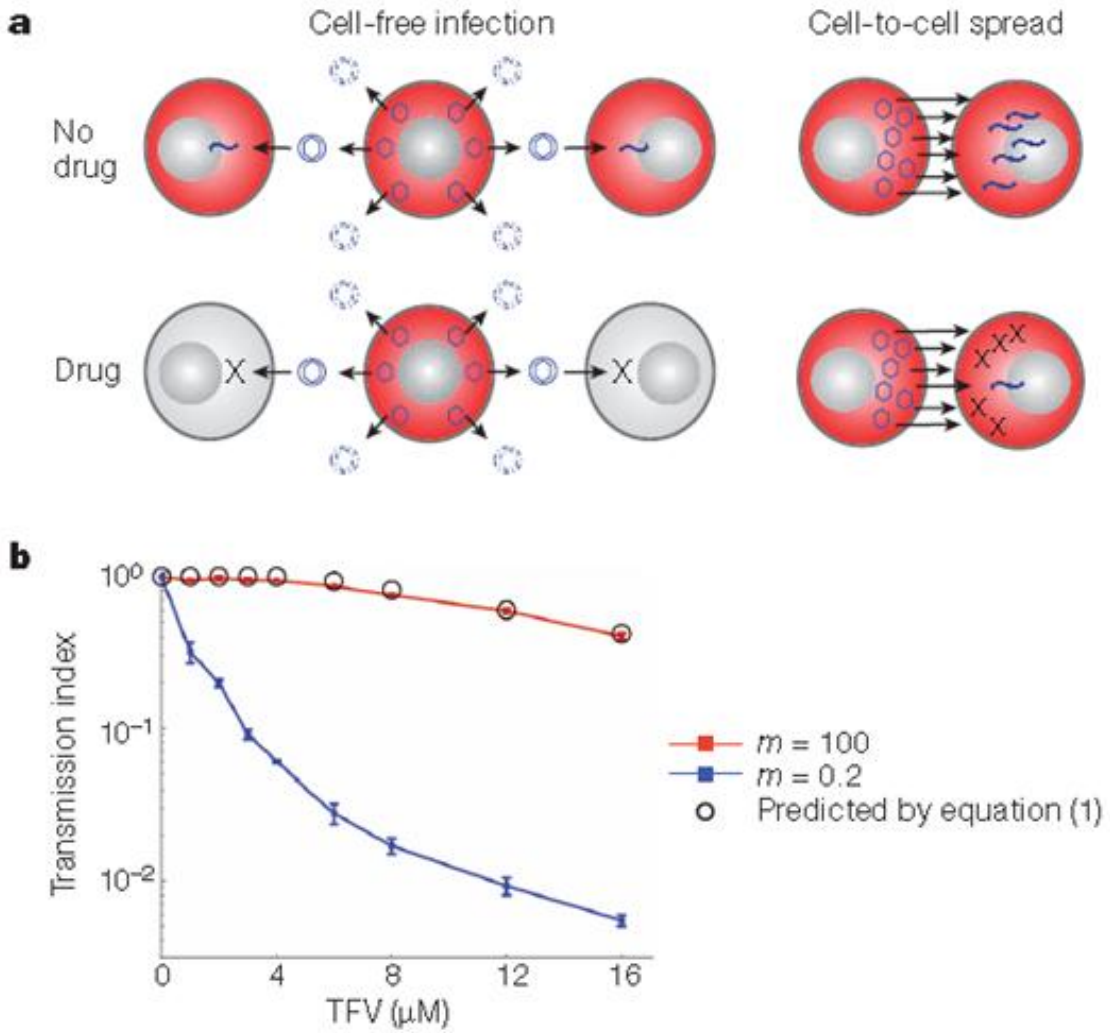


Figure 1 | Multiple infections per cell decrease sensitivity to drug.

Sigal et al. Nature 2011;477

Research Letters

AIDS 2007, **21**:1043–1058

Replication-competent HIV strains infect HIV controllers despite undetectable viremia (ANRS EP36 study)

Aurelia Lamine[a], Anne Caumont-Sarcos[b], Marie-Laure Chaix[c], Asier Saez-Cirion[d], Christine Rouzioux[c], Jean-François Delfraissy[a,e], Gianfranco Pancino[d] and Olivier Lambotte[a,e]

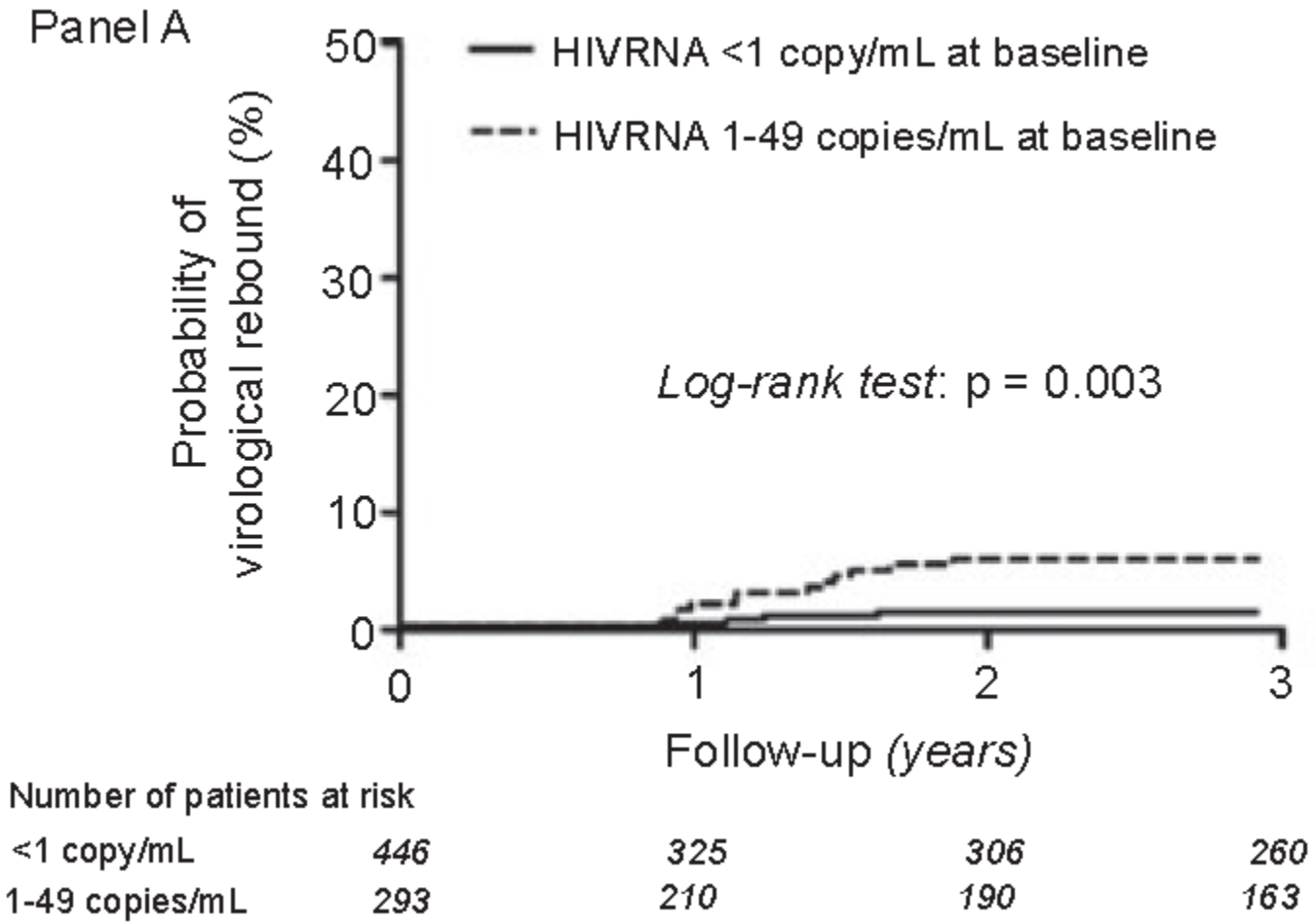
RESEARCH NOTE

Virological rebound in human immunodeficiency virus-infected patients with or without residual viraemia: results from an extended follow-up

N. Gianotti[1], L. Galli[1], S. Salpietro[1], M. Cernuschi[1], S. Bossolasco[1], M. Maillard[1], V. Spagnuolo[1], F. Canducci[2], M. Clementi[3,4], A. Lazzarin[1,4] and A. Castagna[1]

1) Infectious Diseases Department, San Raffaele Scientific Institute, Milan, 2) Microbiology Institute, Insubria University, Varese, 3) Microbiology and Virology Unit, San Raffaele Scientific Institute, Milano and 4) Faculty of Medicine, Università Vita-Salute San Raffaele, Milan, Italy

Time to virological rebound according to study groups



Gianotti et al; Clinical Microbiology and Infection 2013;

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

The International HIV Controllers Study *(i)*

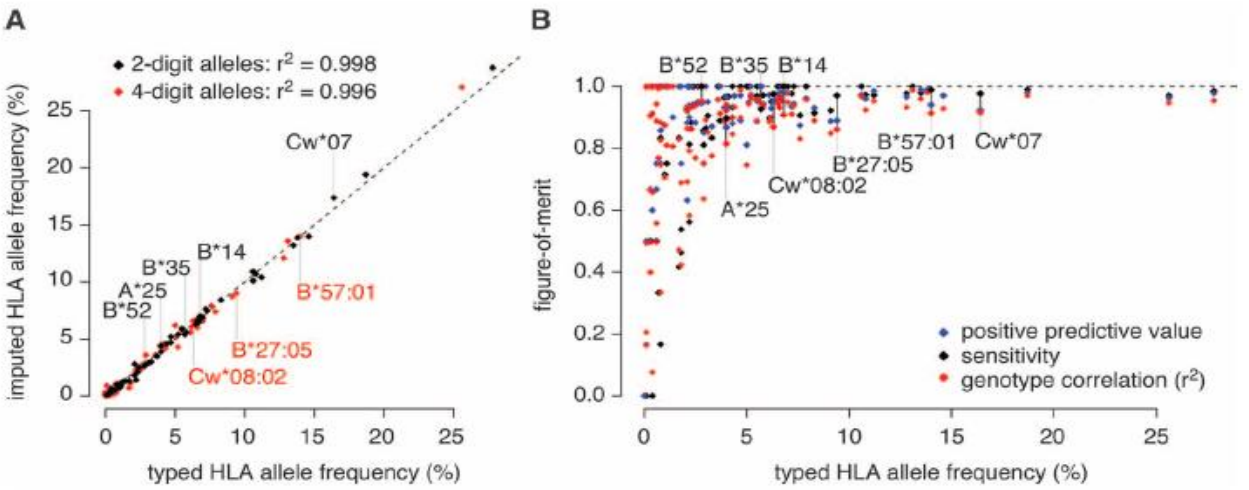
- The study examined host genetic variability in unprecedented numbers of persons able to spontaneously control HIV replication to <2,000 RNA copies/ml and compared these to persons with progressive infection
- >1,500 such subjects were successfully recruited through >200 collaborators worldwide (OSR as a partner)

The Major Genetic Determinants of HIV-1 Control Affect HLA Class I Peptide Presentation
The International HIV Controllers Study
Science **330**, 1551 (2010);
DOI: 10.1126/science.1195271

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

HLA-B, HLA-C... HLA-E

Comment on "Influence of HLA-C Expression Level on HIV Control"

Elisa Lo Monaco,[1] Elisa Tremante,[1] Priscilla Biswas,[2] Martin P. Cranage,[3] Donato Zipeto,[4] Alberto Beretta,[2] Patrizio Giacomini[1]*

Apps *et al.* (Reports, 5 April 2013, p. 87) found that high human leukocyte antigen C (HLA-C) expression favors HIV-1 control. However, as noted here, HLA-C was assessed with a monoclonal antibody (DT9) that cross-reacts with HLA-E. In the context of the available evidence, this is consistent with the idea that the two leukocyte antigens collaborate to keep the HIV-1 virus at bay.

Response to Comment on "Influence of HLA-C Expression Level on HIV Control"

Richard Apps[1,2] and Mary Carrington[1,2]*

Lo Monaco *et al.* propose that human leukocyte antigen E (HLA-E) and HLA-C expression levels both contribute to HIV control. The minimal, flat level of cell surface HLA-E detectable by staining with available HLA-E–specific antibodies questions a role for differential HLA-E expression in determining HIV control. Evidence remains far stronger that HLA-C expression levels as detected by the DT9 antibody specifically affect HIV control.

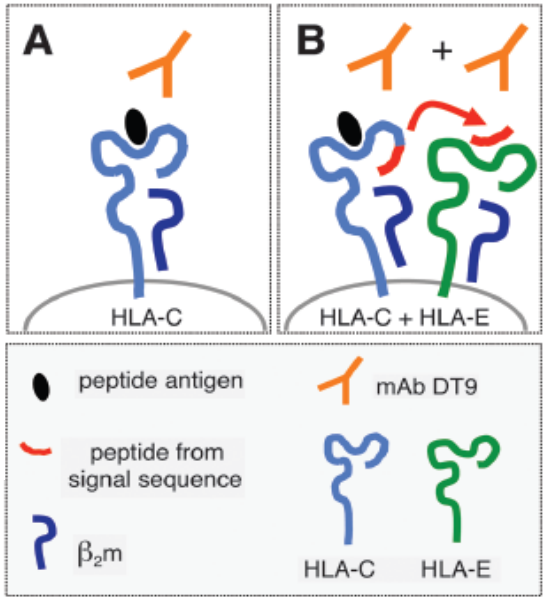


Fig. 1. HLA-C and HLA-E: linked expression, reactivity with mAb DT9, and possible collaborative protection from HIV-1. Two patterns of

HIV controllers: a genetically determined or inducible Phenotype?

- In the CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) study, 11 out of 259 patients (4%) who started treatment within 3 months of seroconversion were able to maintain spontaneous undetectable viraemia for 24 months following treatment interruption.

BRIEF REPORT

Immunovirologic Control 24 Months After Interruption of Antiretroviral Therapy Initiated Close to HIV Seroconversion

Sara Lodi, PhD, MSc; Laurence Meyer, MD, PhD; Anthony D. Kelleher, PhD, MB; Magdalena Rosinska, PhD; Jade Ghosn, MD, PhD; Mette Sannes, MLT; Kholoud Porter, PhD

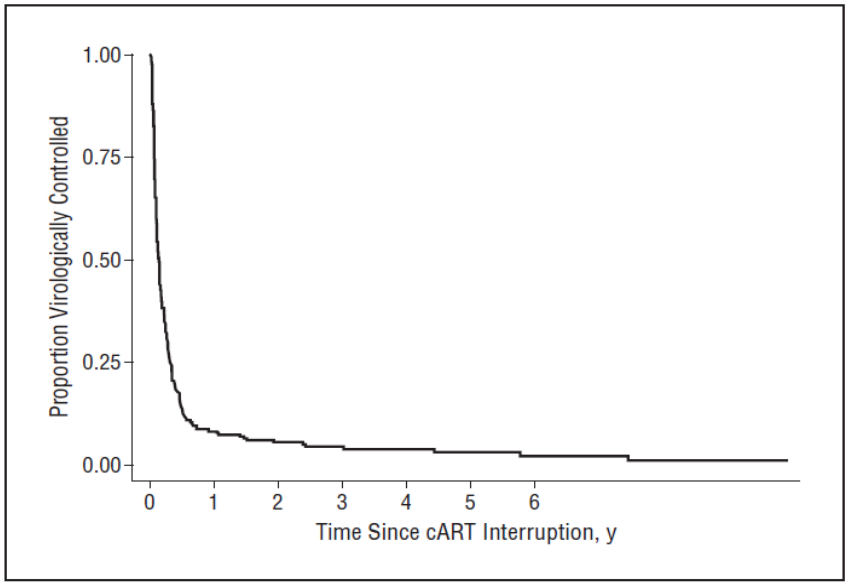


Figure. Kaplan-Meier estimate of the proportion of patients maintaining virologic control after interruption of short-course cART initiated within 3 months of HIV seroconversion. Loss of virologic control is defined as experiencing at least 2 consecutive HIV RNA levels of more than 50 copies/mL or reinitiation of cART. cART indicates combined antiretroviral therapy; and HIV, human immunodeficiency virus.

ARCH INTERN MED/VOL 172 (NO. 16), SEP 10, 2012 WWW.ARCHINTERNMED.COM

REVIEW

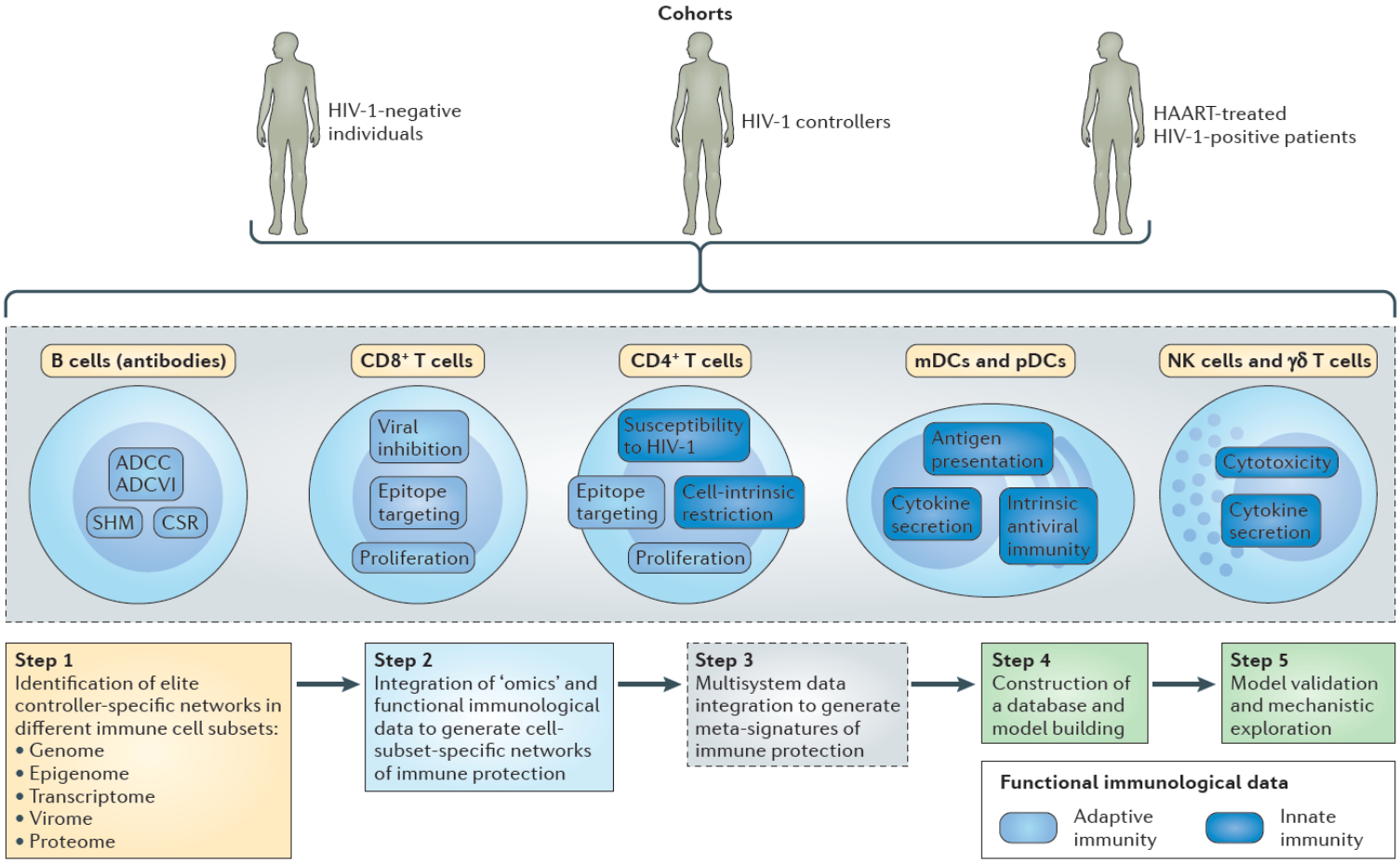
HIV controllers: A multifactorial phenotype of spontaneous viral suppression

Jacques Thèze [a,b,*], Lisa A. Chakrabarti [a], Benoît Vingert [a], Filippos Porichis [c], Daniel E. Kaufmann [c,d,**]

[a] *Unité d'Immunogénétique Cellulaire, Institut Pasteur, 75015, Paris, France*
[b] *Centre Médical Necker Pasteur, Institut Pasteur, 75015, Paris, France*
[c] *Ragon Institute of MGH, MIT and Harvard, Massachusetts General Hospital, Boston, MA 02114, USA*
[d] *Division of Infectious Diseases, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA*

Clinical Immunology (2011) 141, 15–30

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



Walker BD & Yu XG. Nat Rev Immunol, 2013

Unravelling the mechanisms of durable control of HIV-1

Bruce D. Walker[1,2] *and Xu G. Yu*[1]

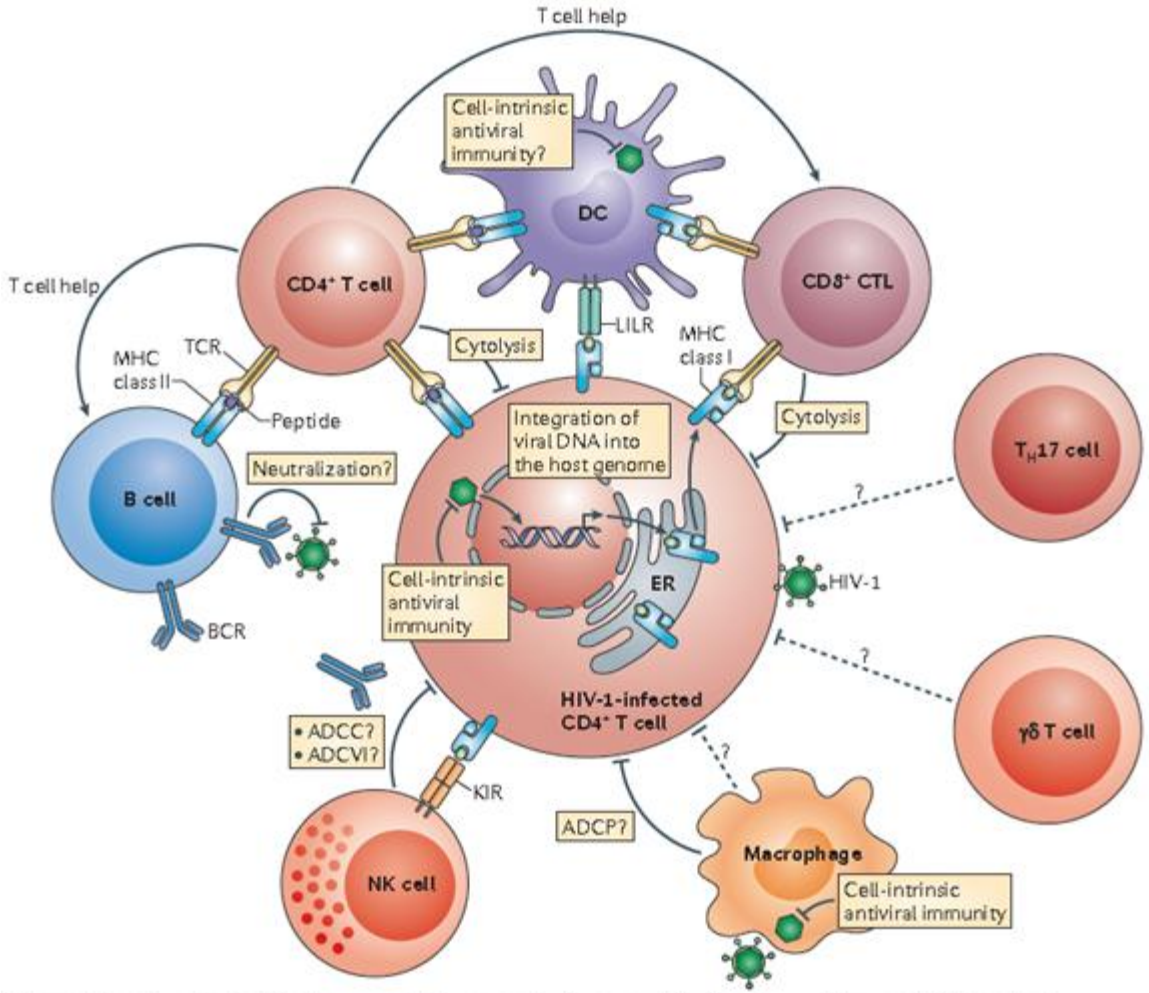


Figure 1 | **Innate and adaptive immune defence mechanisms contributing to spontaneous HIV-1 control.**

***Nature 2013;* 13: 487–498**

STI the "W_{ide}" factor : off cART, new deal

Safety and efficacy of the peptide-based therapeutic vaccine for HIV-1, Vacc-4x: a phase 2 randomised, double-blind, placebo-controlled trial

Richard B Pollard, Jürgen K Rockstroh, Giuseppe Pantaleo, David M Asmuth, Barry Peters, Adriano Lazzarin, Felipe Garcia, Kim Ellefsen, Daniel Podzamczer, Jan van Lunzen, Keikawus Arasteh, Dirk Schürmann, Bonaventura Clotet, W David Hardy, Ronald Mitsuyasu, Graeme Moyle, Andreas Plettenberg, Martin Fisher, Gerd Fätkenheuer, Margaret Fischl, Babafemi Taiwo, Ingebjørg Baksaas, Darren Jolliffe, Stefan Persson, Øyvind Jelmert, Arnt-Ove Hovden, Maja A Sommerfelt, Vidar Wendel-Hansen, Birger Sørensen

***Lancet Infect Dis 2014;* 14: 291–300**

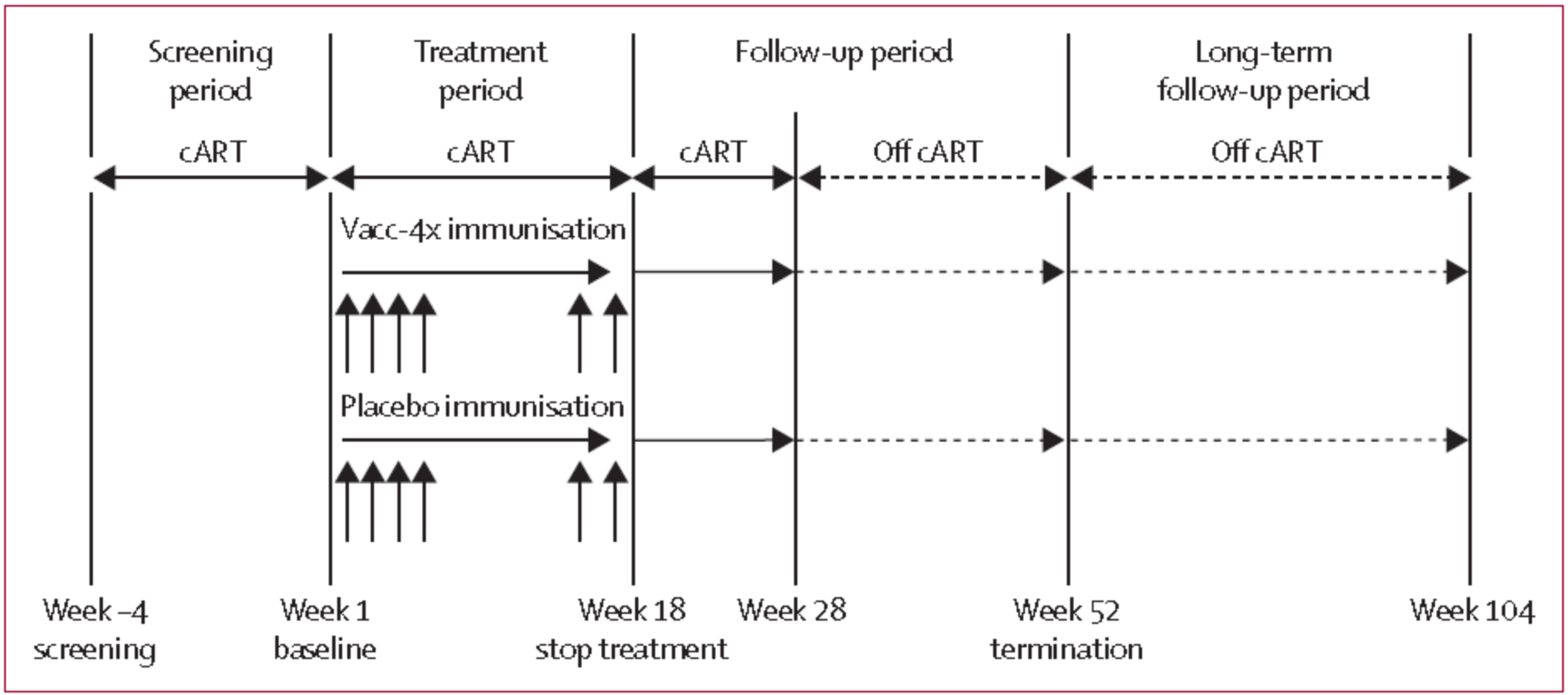


Figure 1: **Study schedule**

cART=combination antiretroviral therapy.

Pollard et al. The Lancet 2014; 14: 291–300

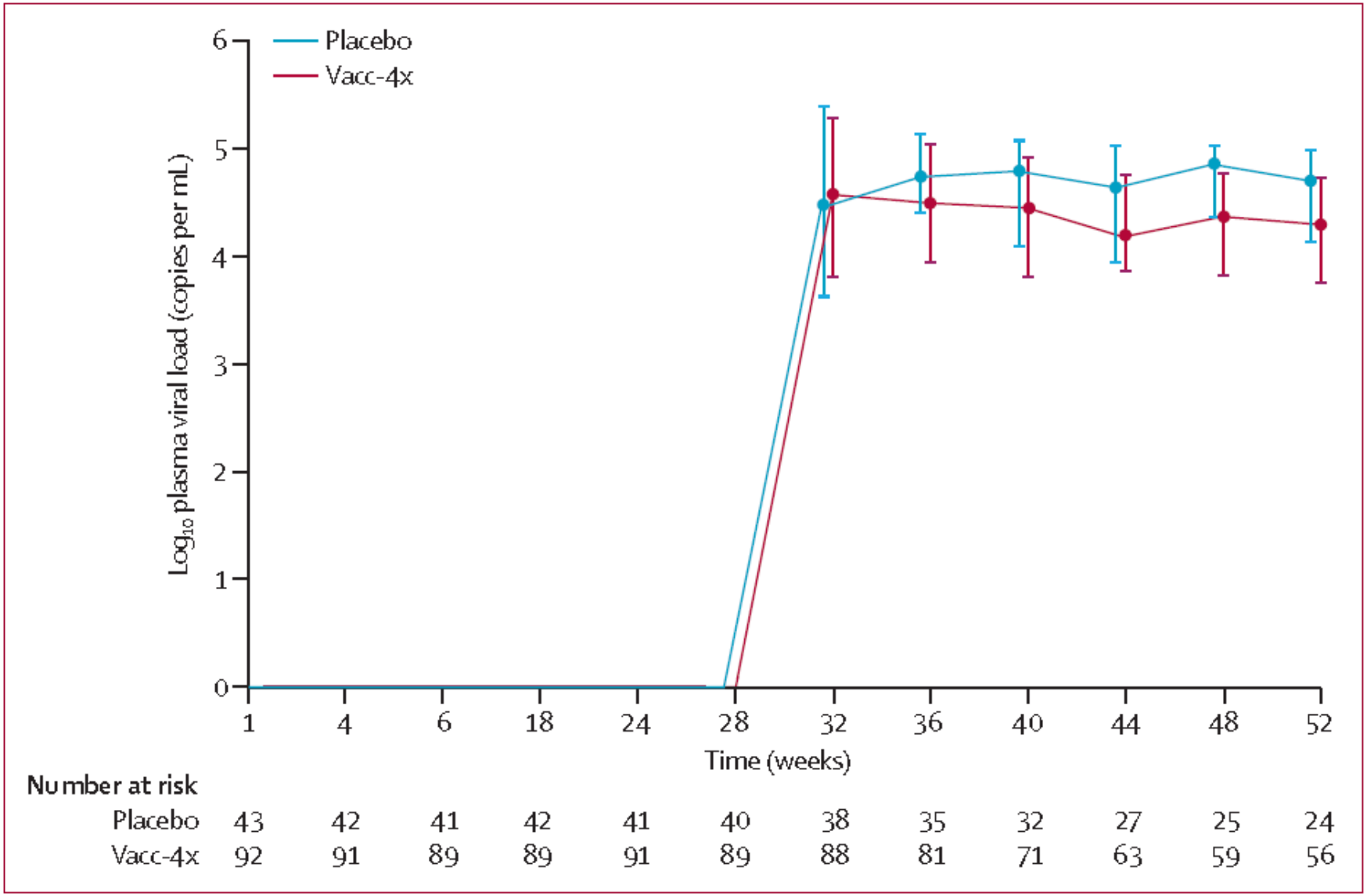
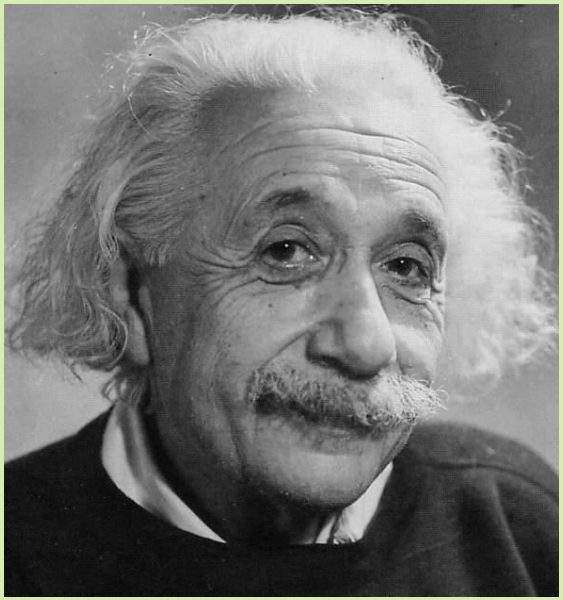


Figure 3: **Viral load over time in the intention-to-treat population**
Data are median (IQR).

Pollard et al. The Lancet 2014; 14: 291–300

Conclusions (?)

- HIV-1 controllers provide tangible evidence that some humans are able to effectively and durably control HIV-1 replication and to prevent HIV-1-associated disease manifestations for extended periods of time
- The observation that this natural control of HIV-1 is also achievable in the absence of specific protective HLA class I polymorphisms holds promise that, in principle, an elite controller phenotype may be therapeutically inducible in a larger number of patients
- This suggests new ideas for the development of broadly applicable strategies to limit the spread of the HIV-1 pandemic
- STIs?



Non penso mai al futuro,
arriva così presto!
Albert Einstein