Cure

Dr. Mark Nelson

Chelsea & Westminster Hospital

Executive Committee of the British HIV Association (BHIVA)

GreenShoots FOUNDATION

Available Antiretrovirals 2015

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

- Efavirenz
- Nevirapine
- Etravirine
- Rilpivirine

Protease Inhibitors

- Atazanavir
- Darunavir
- Fos-Amprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Other Classes

Fusion inhibitors

- Enfuvirtide

R5 Inhibitors

- Maraviroc

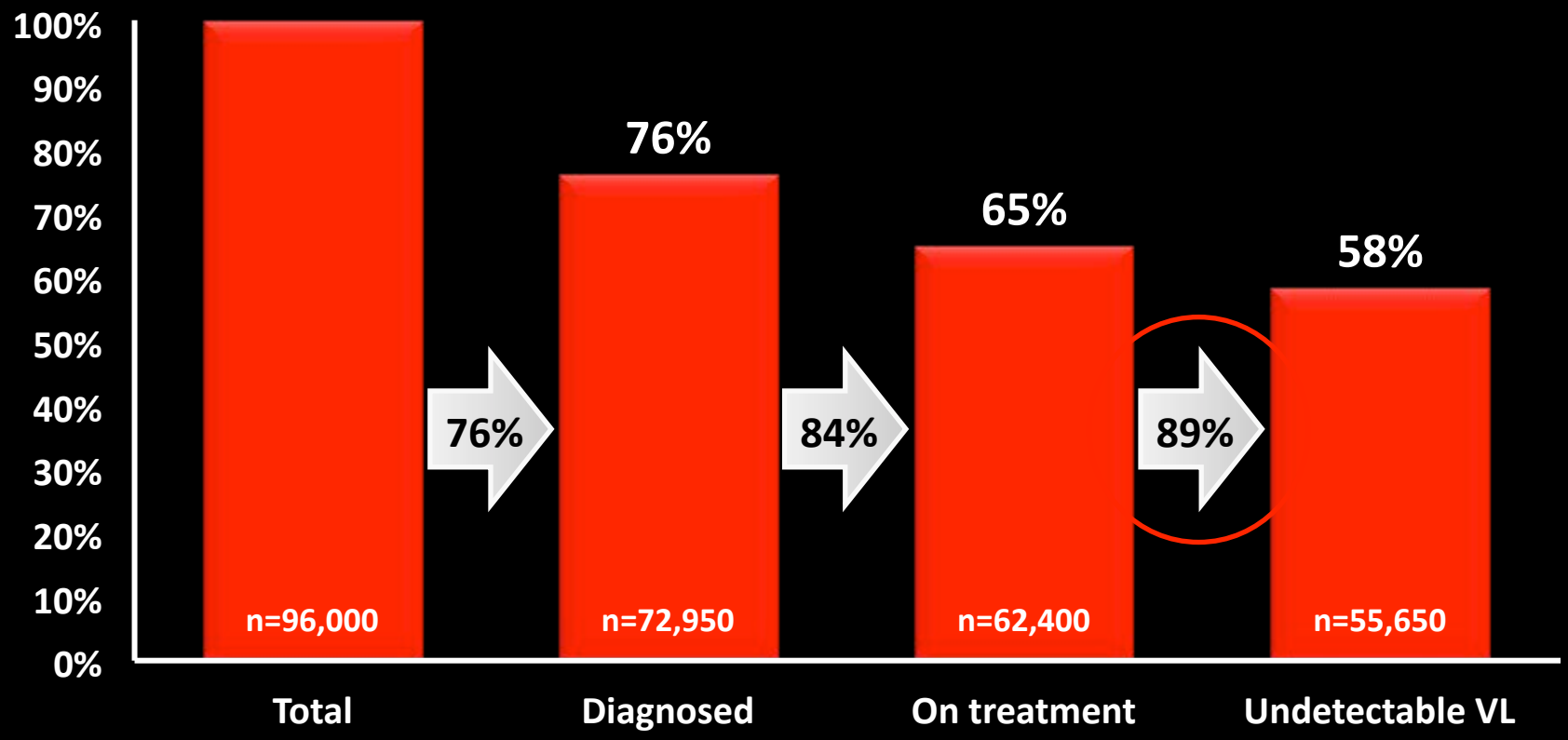
Integrase Inhibitors

- Raltegravir
- Elvitegravir
- Dolutegravir

STR

- TFV/ftc/EFZ
- TFV/ftc/EFZ
- TFV/ftc/cELV

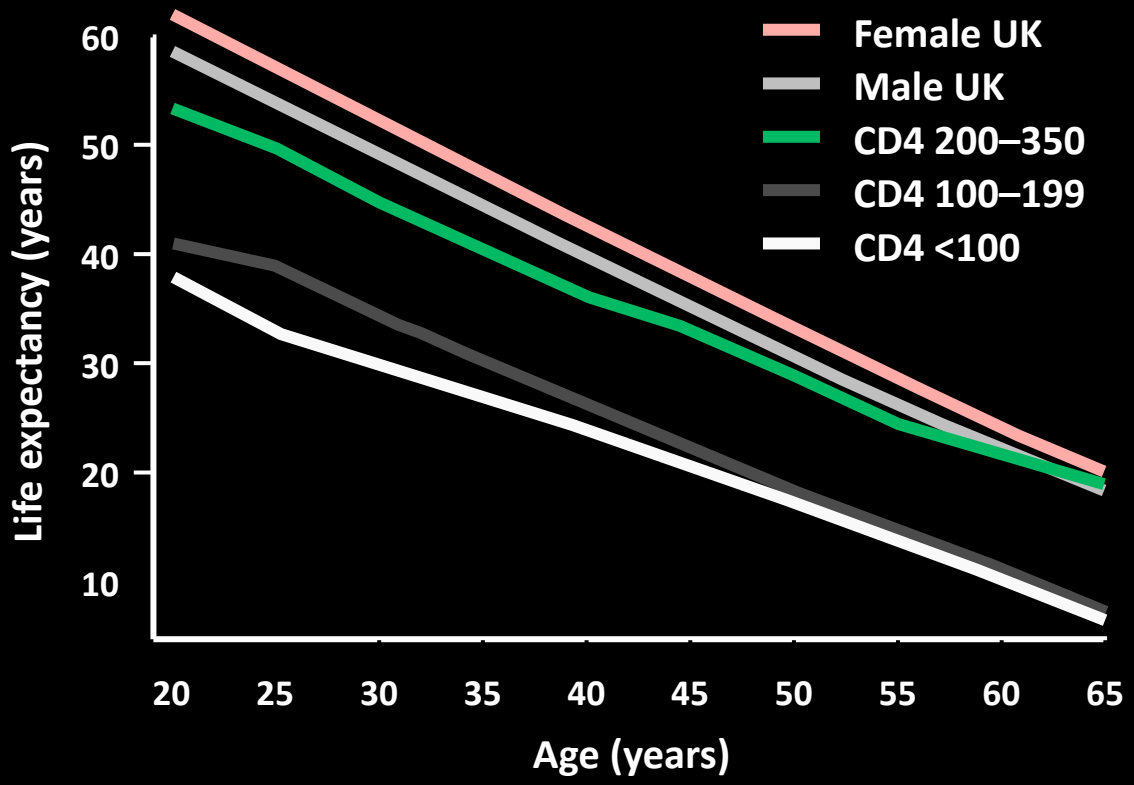
Continuum of care
Persons living with HIV in the UK 2011



HIV and AIDS Reporting System
HIV and STI Department, Health Protection Agency - Colindale

UK CHIC – Life expectancy

Life expectancy by CD4 count compared with UK population



LE at exact age 20 years:
1996- 2008

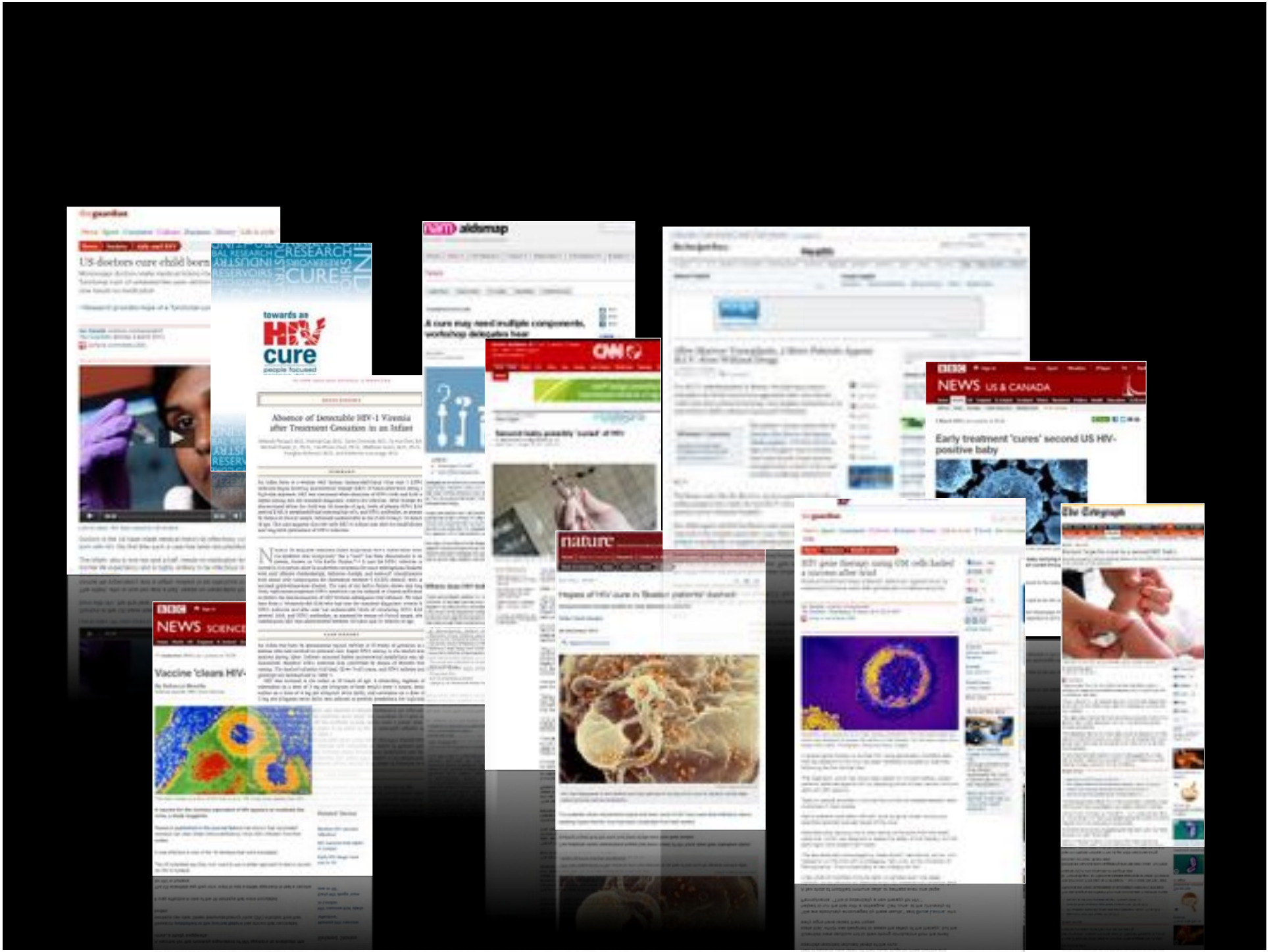
UK women	61.6 yrs
UK men	57.8 yrs
HIV+ women	50.2 yrs
HIV+ men	39.5 yrs
1996–99 HIV+	30.0 yrs
2006–08 HIV+	45.8 yrs

Start triple ART post 2000

CD4 200–350	53.4 yrs
CD4 100–199	41.0 yrs
CD4 <100	37.9 yrs

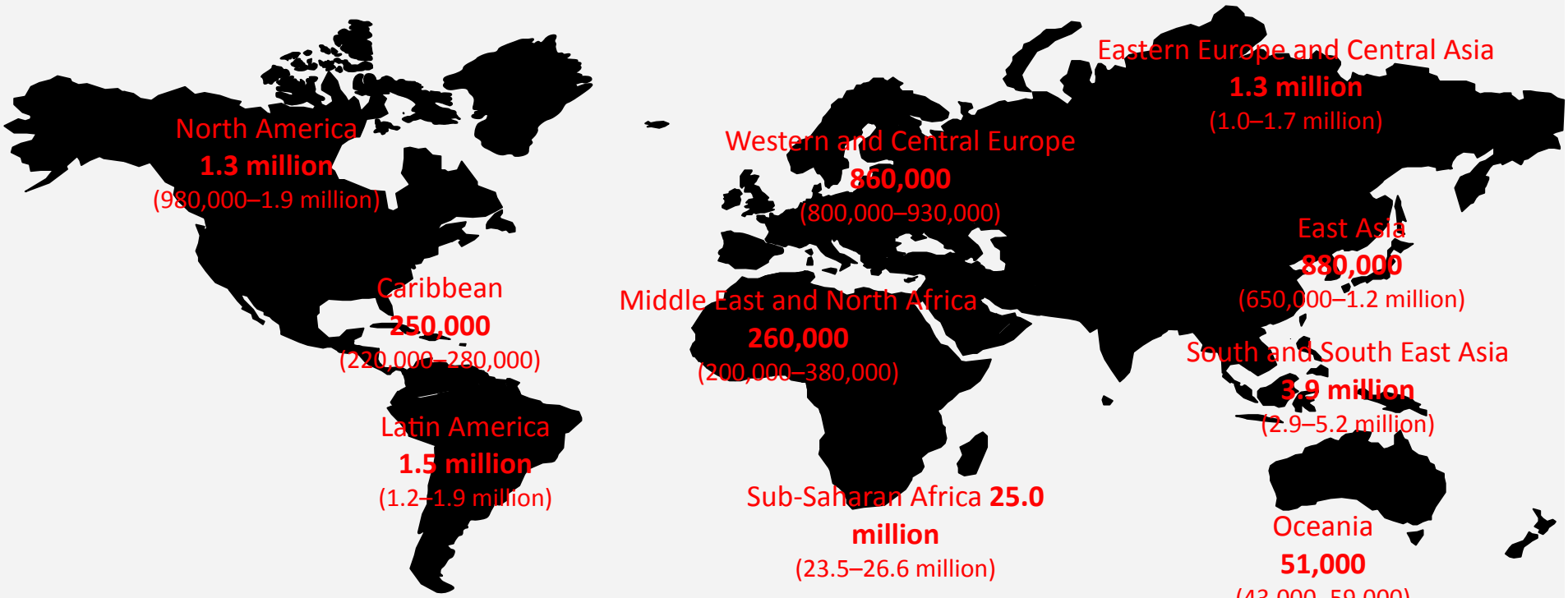
Impact on life expectancy of late diagnosis and treatment of HIV-1 infected individuals:
UK CHIC M May, M Gompels, C Sabin for UK CHIC. HIV10 Glasgow abstract 1629596


THE GRAYING OF AIDS
stories from an aging epidemic


towards an
HIV
cure
people focused
Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant
aidsmap
A cure may need multiple components, workshop delegates hear
CNN
Second baby possibly 'cured' of HIV
NEWS US & CANADA
Early treatment 'cures' second US HIV-positive baby
NEWS SCIENCE
Vaccine 'clears HIV-
nature
Hopes of HIV cure in 'Boston patients' dashed
The Telegraph

It is important to remember why ongoing research is necessary…

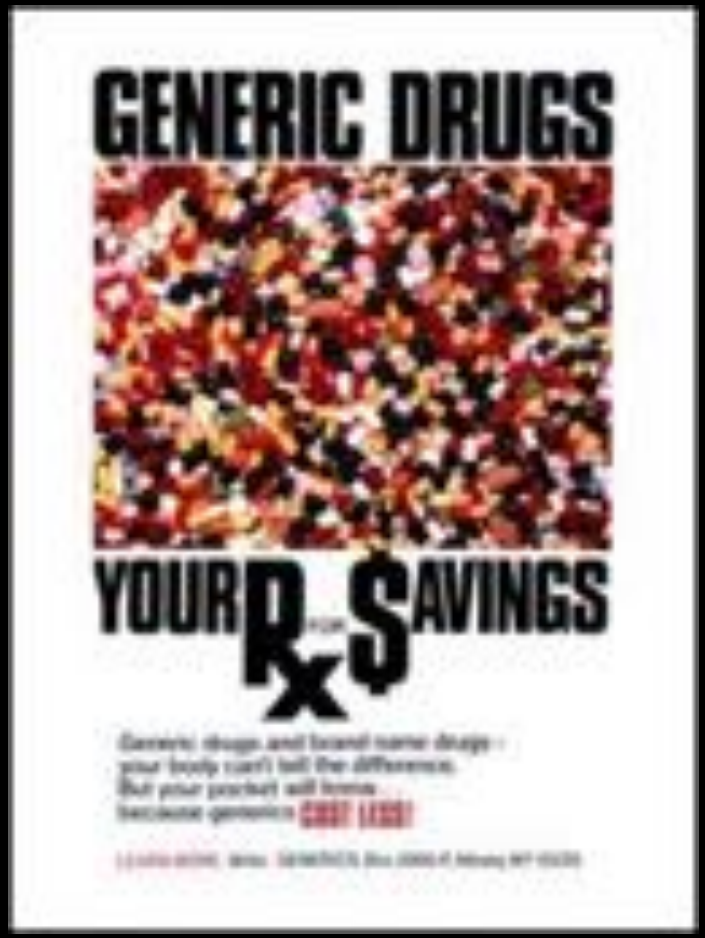
Adults and children estimated to be living with HIV in 2012

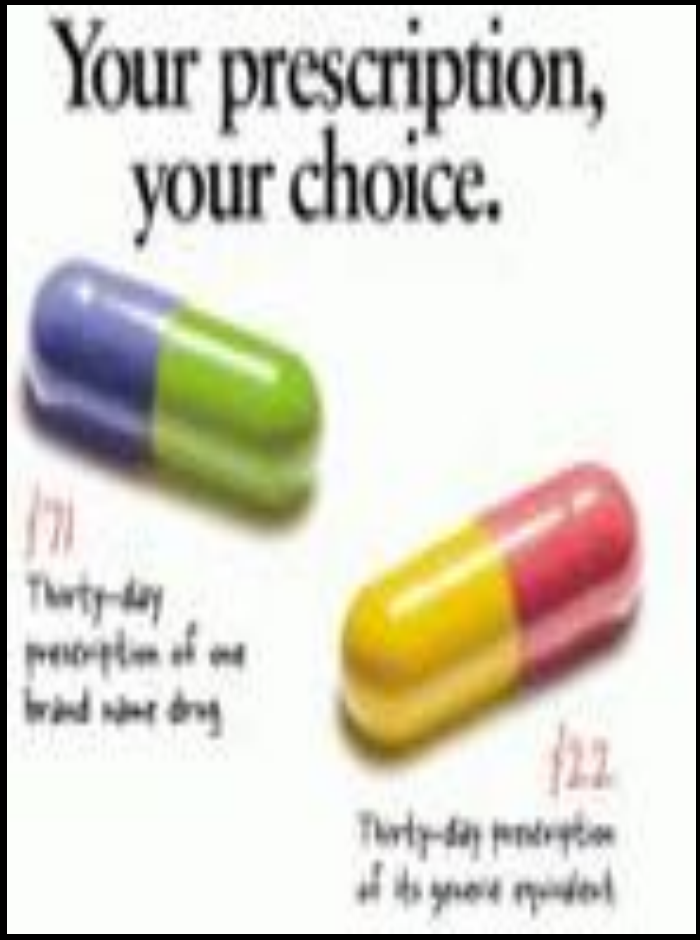


UNAIDS. Global Report. Available from: http://www.unaids.org/en/dataanalysis/knowyourepidemic/. Accessed February 2014.

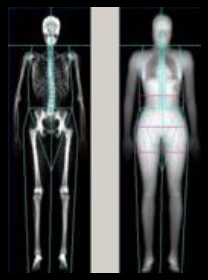

NHS

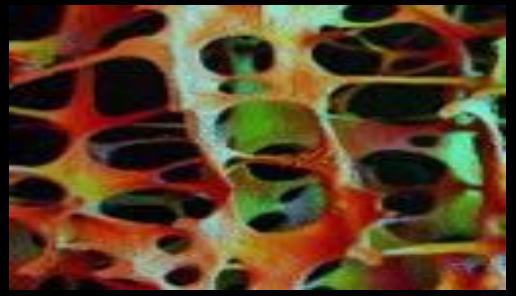
Generics

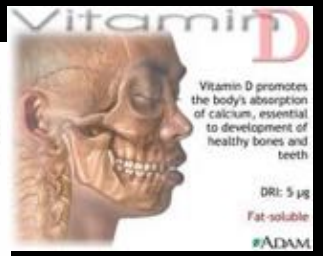

GENERIC DRUGS
YOUR Rx $AVINGS


Your prescription, your choice.
$71
Thirty-day prescription of one brand name drug
$22
Thirty-day prescription of its generic equivalent


Lipemic






Vitamin D
Vitamin D promotes the body's absorption of calcium, essential to development of healthy bones and teeth
DRI: 5 µg
Fat-soluble
A.D.A.M.

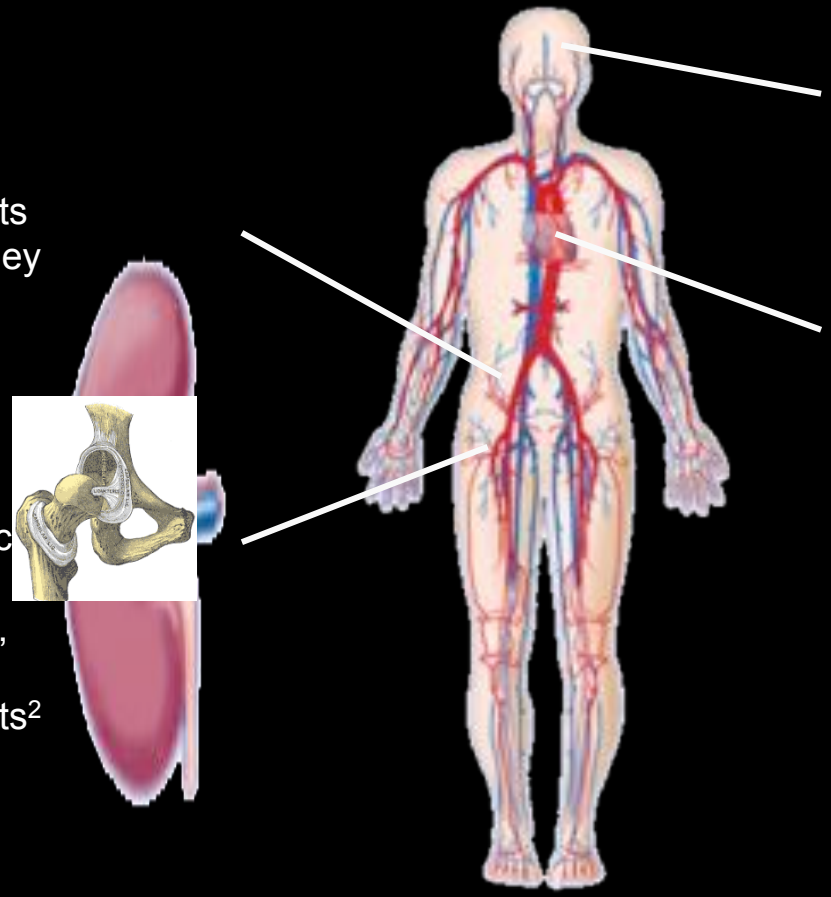
Emerging co-morbidities in HIV

Renal dysfunction

30% of HIV+ patients have abnormal kidney function[1]

Reduced bone mineral density

Increased prevalenc of osteoporosis or osteopenia in spine, hip or forearm: 63% of HIV+ patients[2]



Neurocognitive dysfunction

Neurological impairment present in ≥50% HIV+ patients[3]

Cardiovascular disease

75% increase in risk of acute MI[4]

Cancer

Increased risk of non-AIDS-defining cancers e.g. anal, vaginal, liver, lung, melanoma, leukemia, colorectal and renal[5]

Frailty

Increased frailty phenotype if HIV infected 3-14x; Associated with CD4 count

1. Gupta SK *et al. Clin Infect Dis* 2005;**40**:1559–85.
2. Brown TT *et al. J Clin Endocrinol Metab* 2004;**89**(3):1200–06.
3. Clifford DB. *Top HIV Med* 2008;**16**(2):94–98.
4. Triant VA *et al. J Clin Endocrinol Metab* 2007;**92**:2506–12.
5. Patel P *et al. Ann Intern Med* 2008;**148**:728–36.

Emerging co-morbidities in HIV

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Increased prevalenc

? 15 years older

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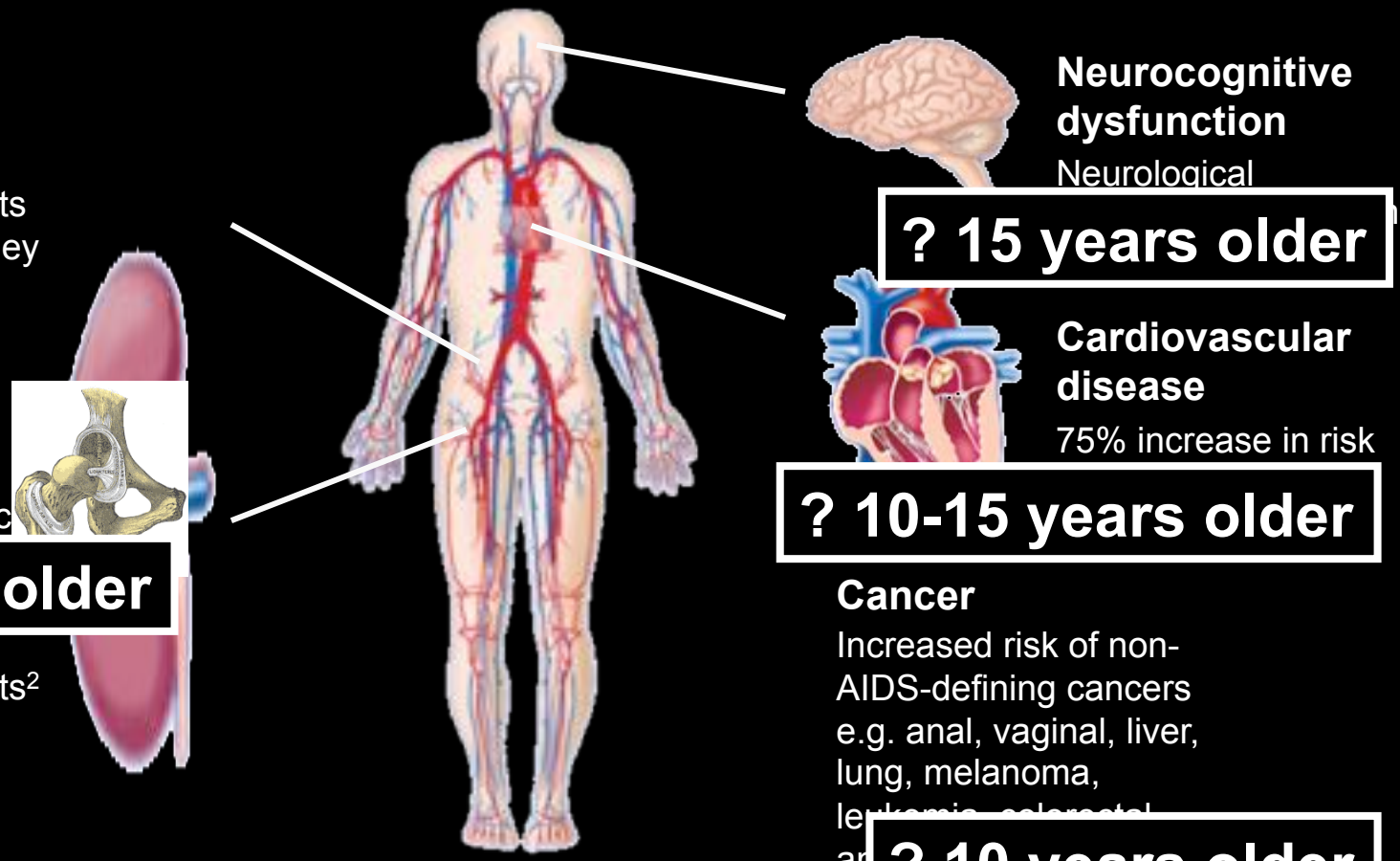

Neurocognitive dysfunction

Neurological

? 15 years older

Cardiovascular disease

75% increase in risk

? 10-15 years older

Cancer

Increased risk of non-AIDS-defining cancers e.g. anal, vaginal, liver, lung, melanoma,

? 10 years older

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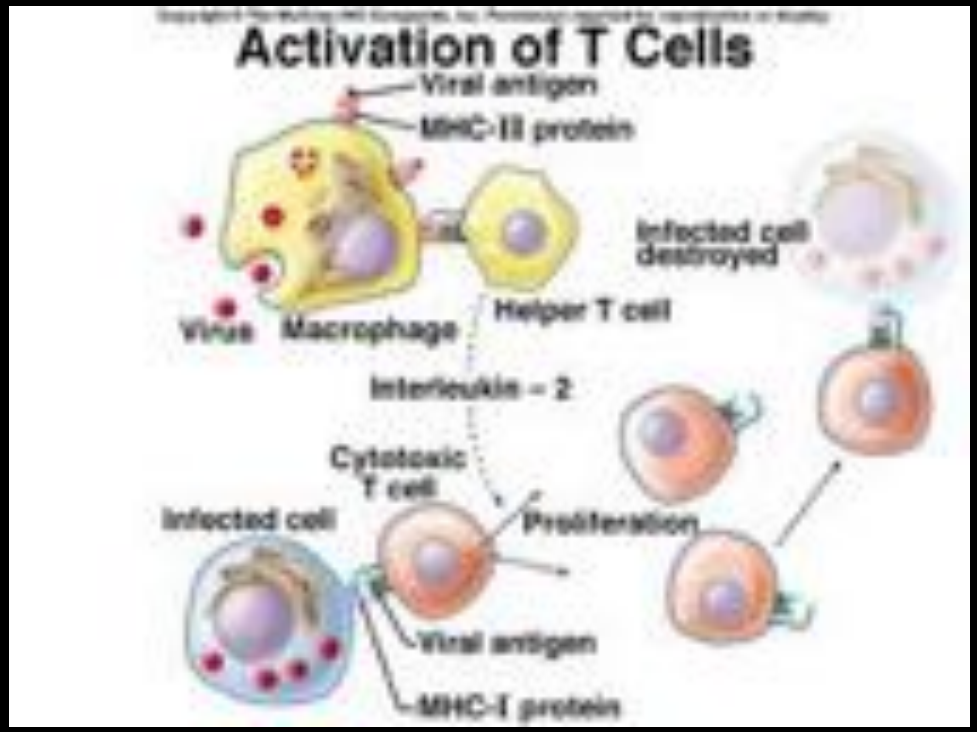
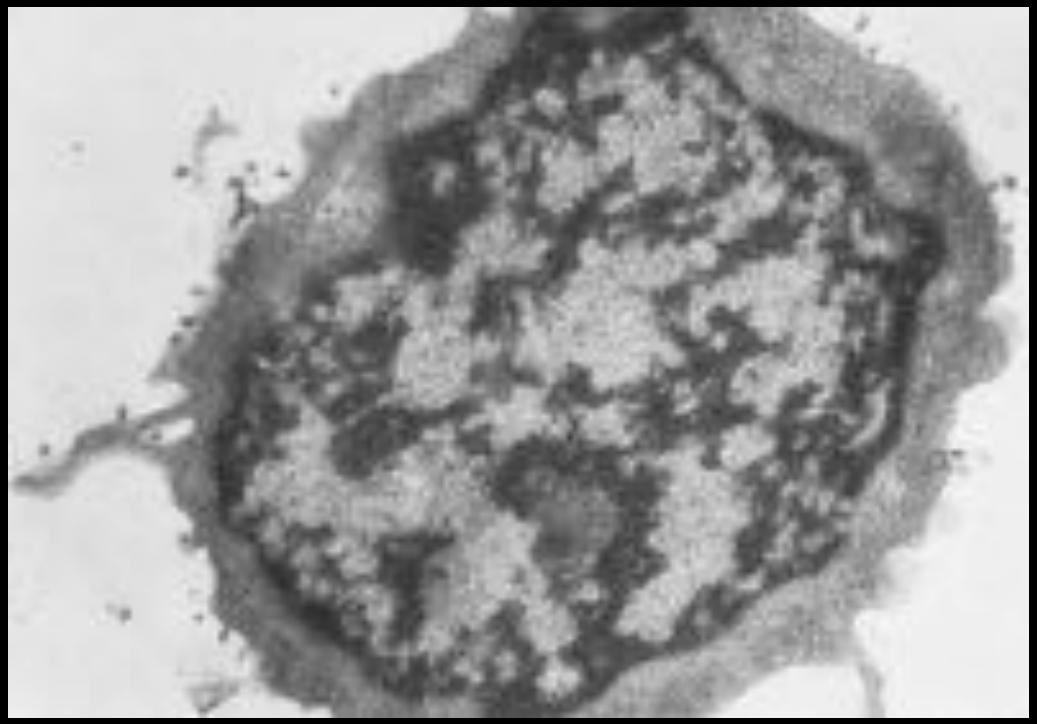

Activation of T Cells
Viral antigen
MHC-II protein
Infected cell destroyed
Virus
Macrophage
Helper T cell
Interleukin – 2
Cytotoxic T cell
Infected cell
Proliferation
Viral antigen
MHC-I protein


Obesity
Diabetes
Gingivitis
Cardio Vascular Disease
Eye Disorders
Joint Pain
Colon, Breast & Lung Cancers
Metabolic Syndrome
Infection
Injury
Arthritis
Alzheimer's Disease
Asthma Allergies
Ulcerative Colitis & Inflammatory Bowel Disease
Inflammation

What is a normal CD4 count?



What is a normal CD4 count?

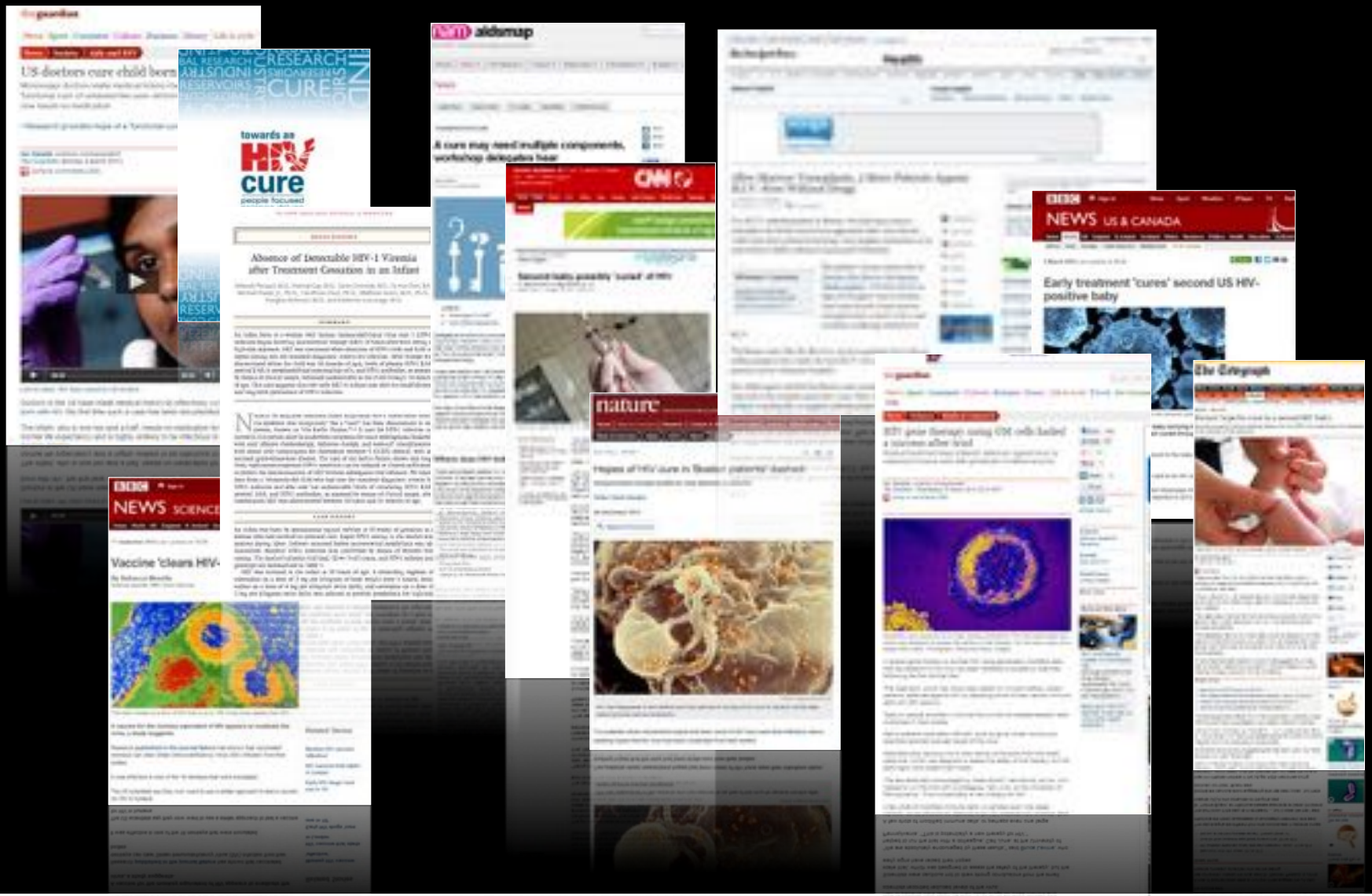
CD4+ counts in seronegative Caucasians and African–Americans

Summary statistics for CD4+ counts

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	16 (11037)	1011 (1005-1017)	940 (834-1030)	796-1109
Mixed USA	8 (4083)	1006 (995-1018)	998 (882-1027)	771-1075
African American	2 (1006)	1077 (1054-1099)	1078 (1055-1100)	1055-1100
Combo	25 (16126)	1014 (1008-1019)	**952 (840-1036)**	771-1109

CI, confidence interval; IQR, interquartile range.
Supplement to Le et al. NEJM 2013;368:218–30.

Cure coverage continues…



What do we mean by ‘curing HIV’?

Sterilising Cure

TRADITIONAL INFECTIOUS DISEASE MODEL

- The ‘Berlin’ patient
- Aviraemia – plasma viral load <1 copy/ml
- No replication competent virus
- No detectable HIV-infected cells

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- No detectable HIV-infected cells

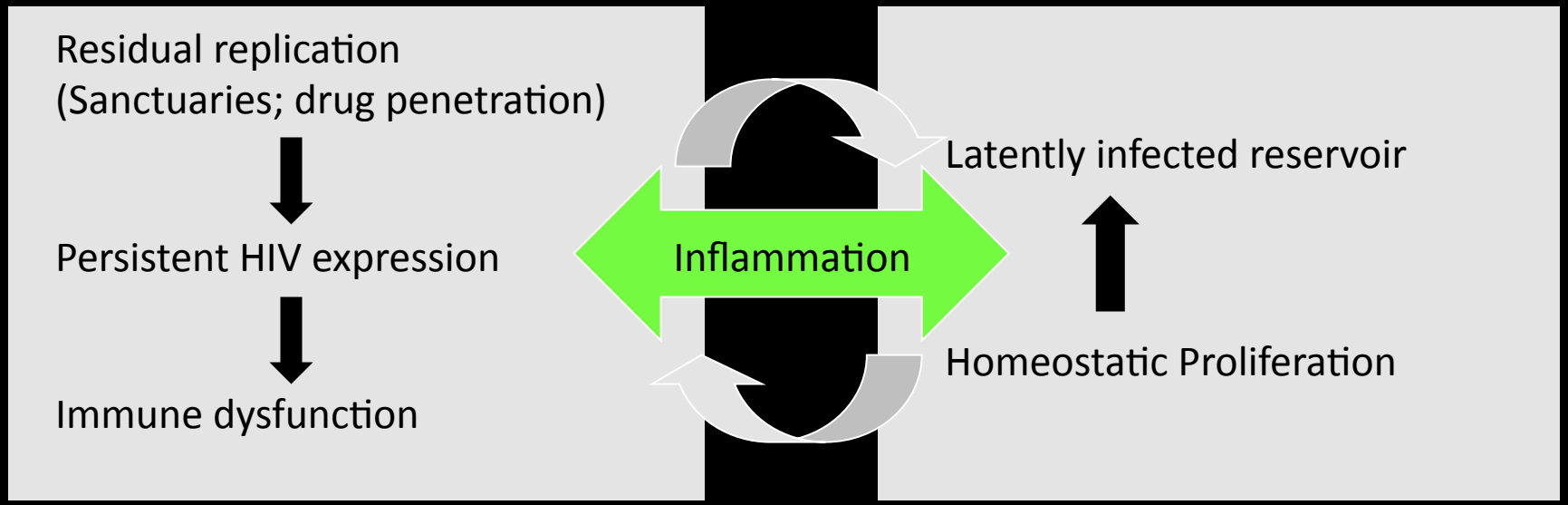
'Functional' Cure

"CANCER" MODEL

- Clinically undetectable viraemia in absence of ART
- No disease progression
- No CD4 cell loss
- No transmission
- But…no agreed duration

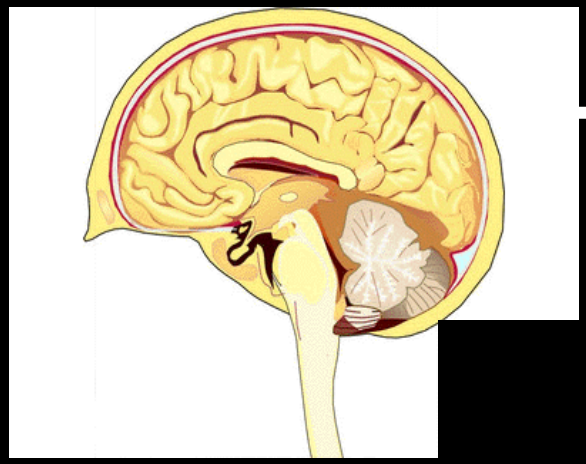
Why can't we cure HIV with ARV Drugs

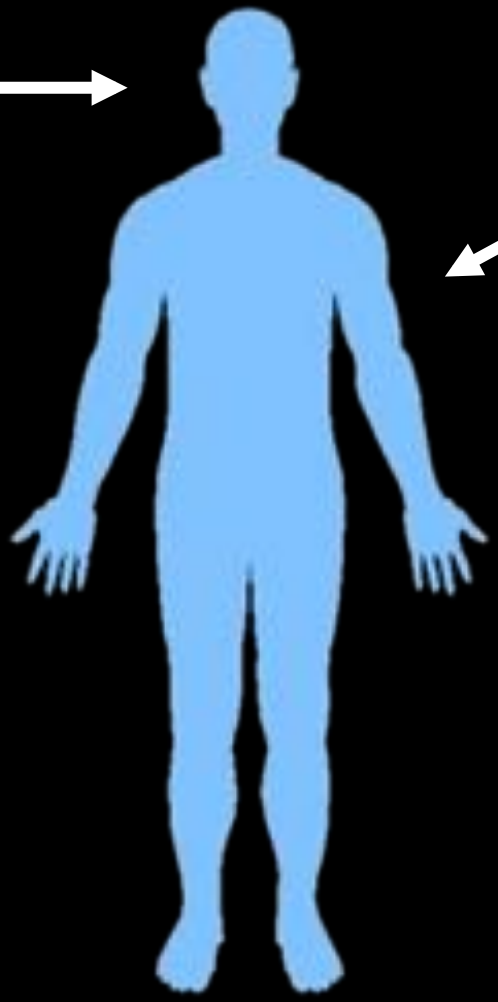
A game of hide and sleep?

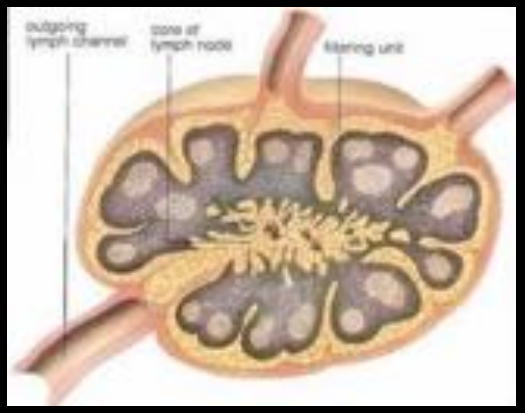


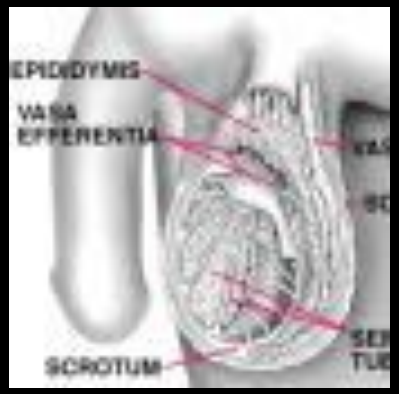
These are not mutually exclusive mechanisms; will multiple approaches be required?

Anatomical reservoirs



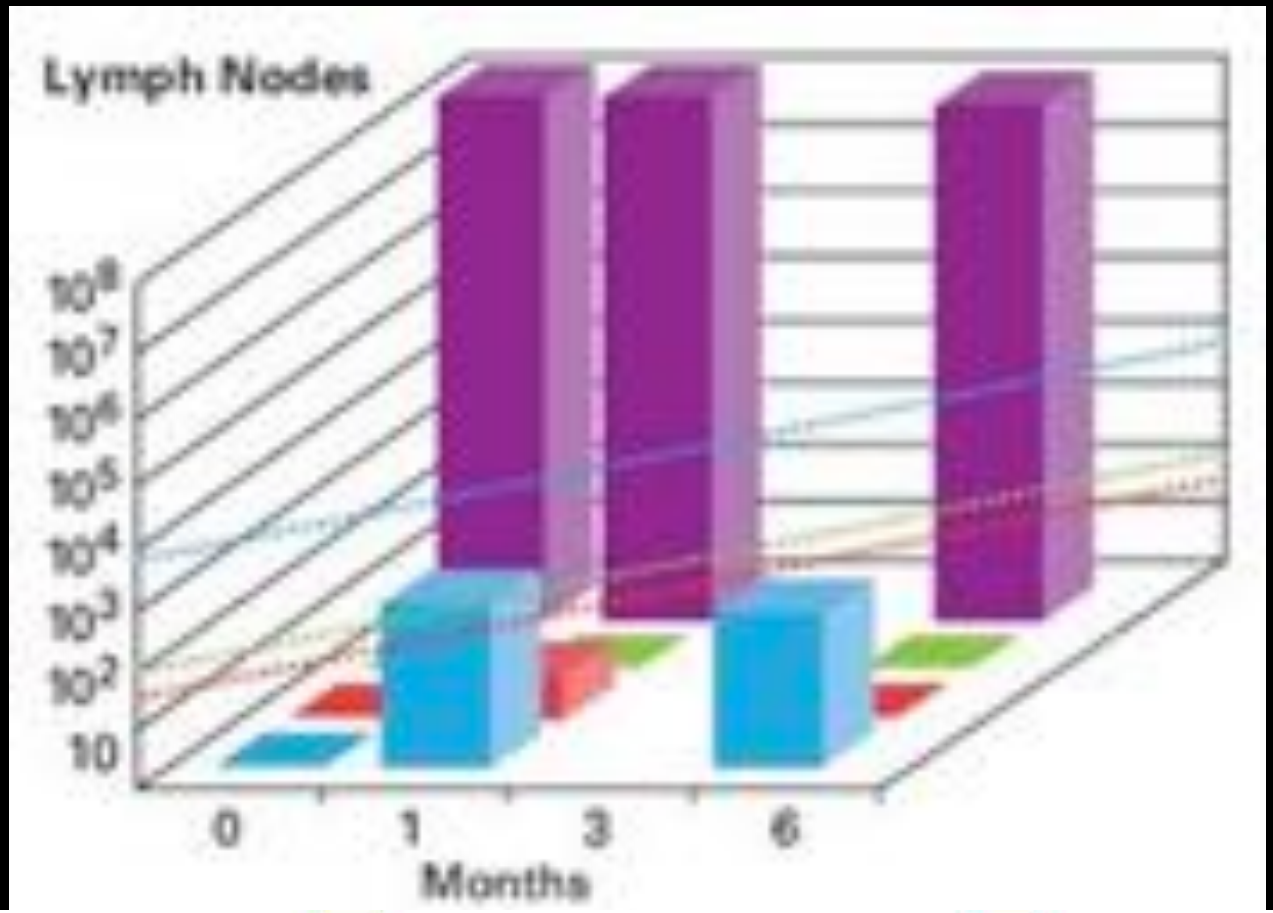






BELIEVERS VS NON-BELIEVERS

Variable penetration of ARV in tissue

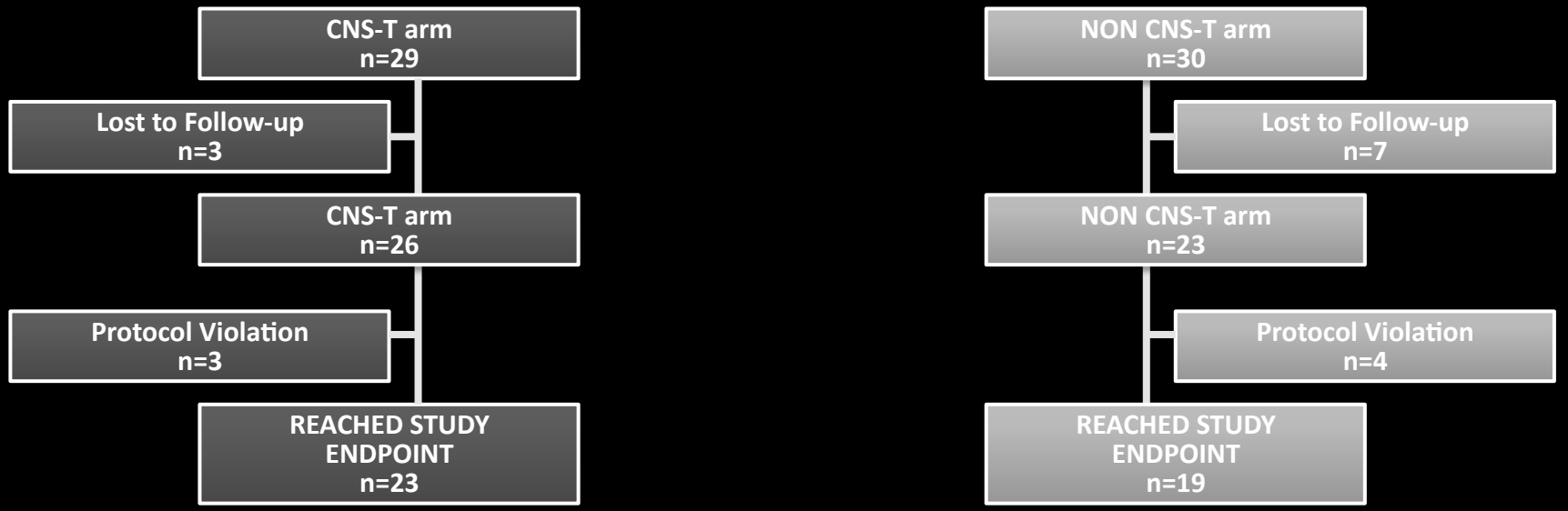


Fletcher, 19th CROI, Seattle 2012

CNS Targeted HAART: A Randomized Trial for HIV Associated Neurocognitive Disorders (HAND)

- Eligibility:
  - HAND – Impaired on NP testing
  - Stable (>8 weeks) on HAART or no HAART
  - Planned change to ART
    - VF, AEs or HAND despite ART
  - Exclude major comorbidity or substance use

Study Population



Ellis R, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 20.

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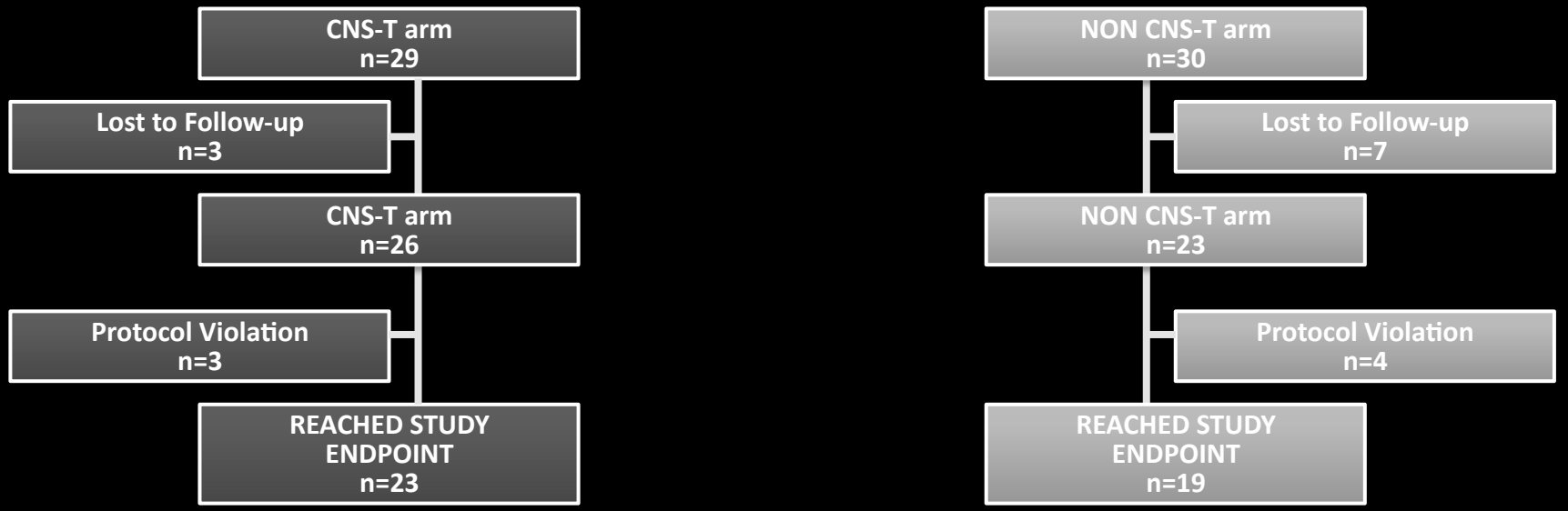


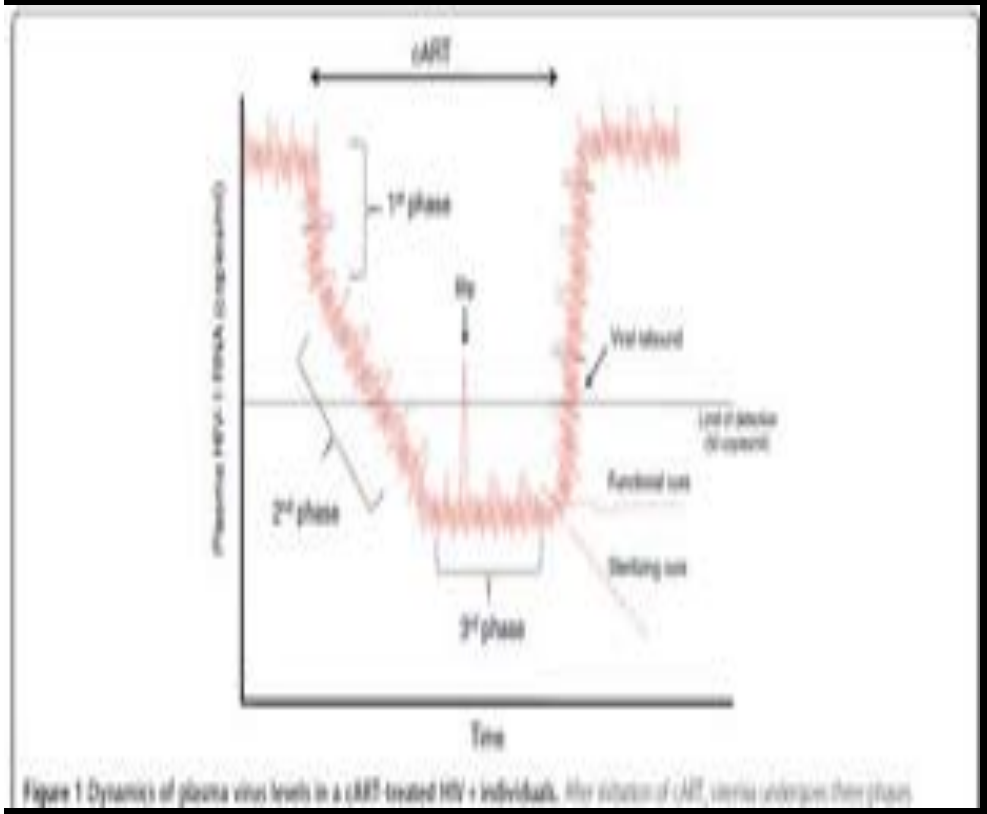
Ellis R, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 20.

Baseline Characteristics, Study Treatments and Outcomes

	CNS-T	Non-CNS-T	*P*
ARV Naïve	35%	26%	0.55
Plasma VL < 50 c/mL	27%	26%	0.71
Entry CD4	213 [5, 964]	306 [3, 1224]	0.39
Nadir CD4 < 200	16 (67%)	8 (38%)	0.08
Study Treatment			
# ARV agents	4	3	0.06
Relative PSS	1	0.95	0.19
3 most frequent ARVs	LPV, ZDV, FTC	DRV, TDF, ETV	--
Adjusted GDS change	-0.14	-0.07	0.76
Plasma VL<50 Week 16	54%	82%	0.065
CSF VL<50 Week 16	68%	87%	0.17

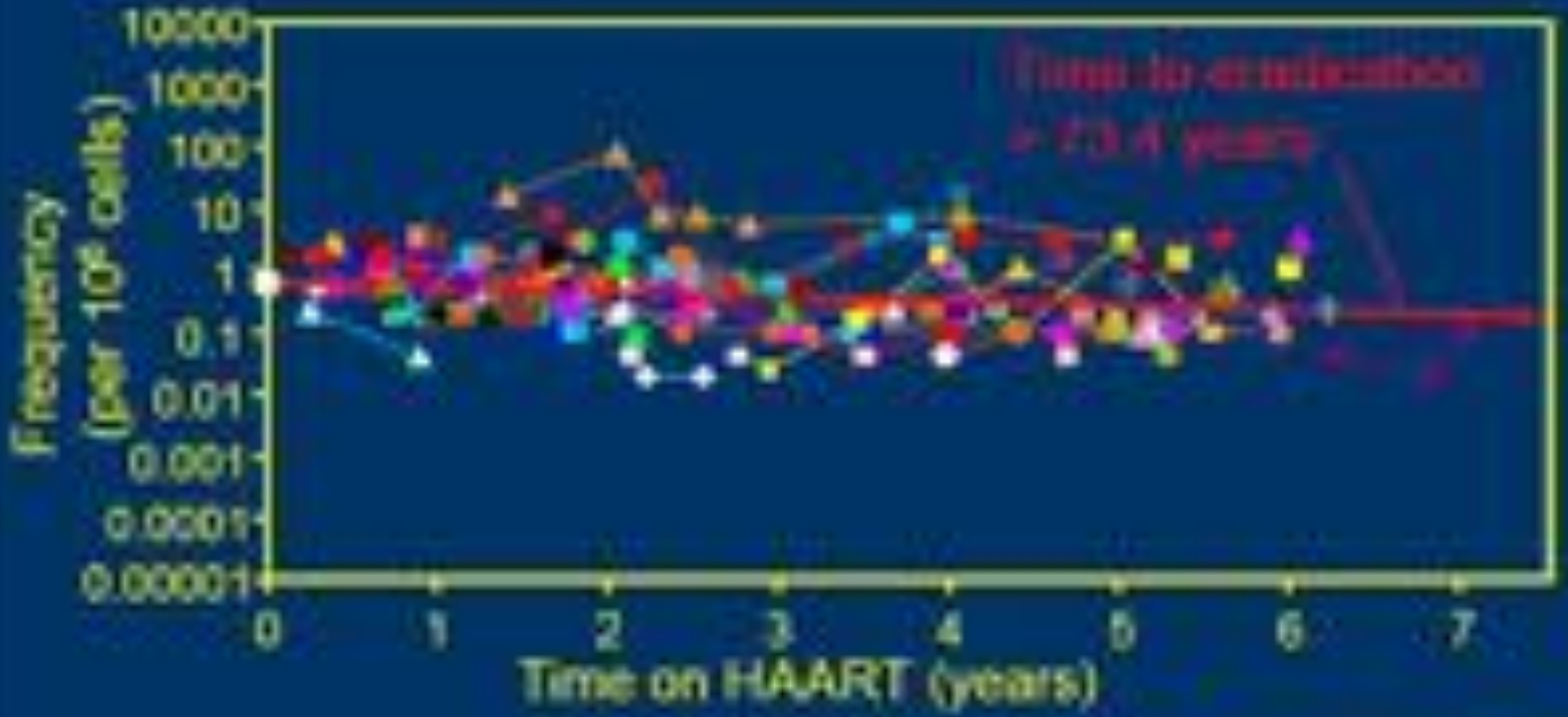
The Latent Reservoir

- Frequency 1/1,000,000
- Size 100,000 – 1,000,000
- Half Life 44 months



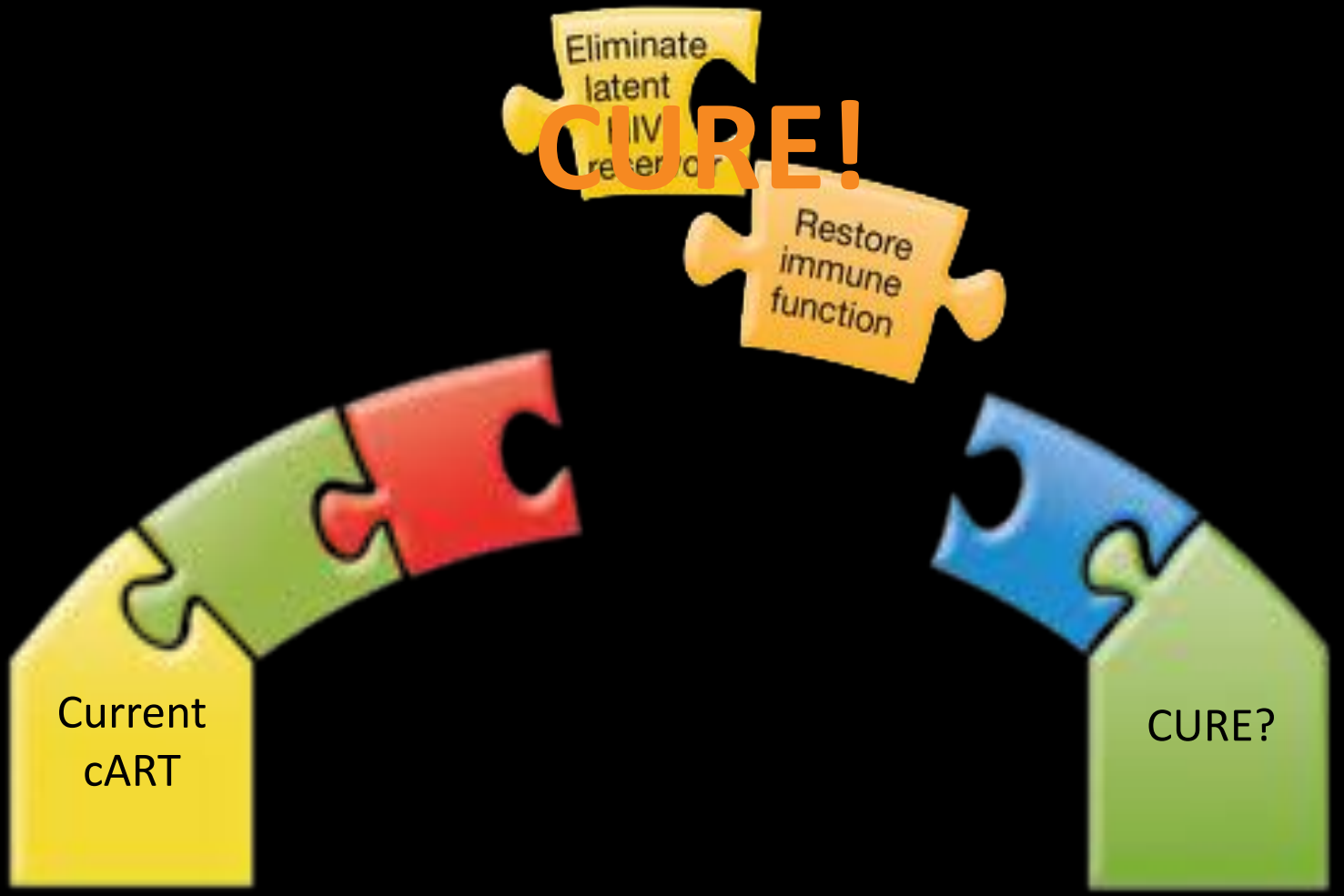
- Phase 1-Decay of activated CD4 cells
- Phase 2- Decay of partially activated CD4 cells,macrophages and dendritic cells
- Phase 3-Derived from activated latent CD4 cells which slowly decay

Slow decay of latently infected CD4+ T cells



Chun et al., PNAS 1997

Bridging the gap from current cART to cure



How to bridge the gap: targeting cure in HIV

Inhibit residual replication

- Enhanced cART: novel drug classes/treatment intensification

'Shock and kill'

- Induce HIV re-activation plus intensive cART*; valproic acid; vorinostat; panobinostat; disulfiram; phorbol ester derivatives; cytokines; immunotoxins

Immune stimulation

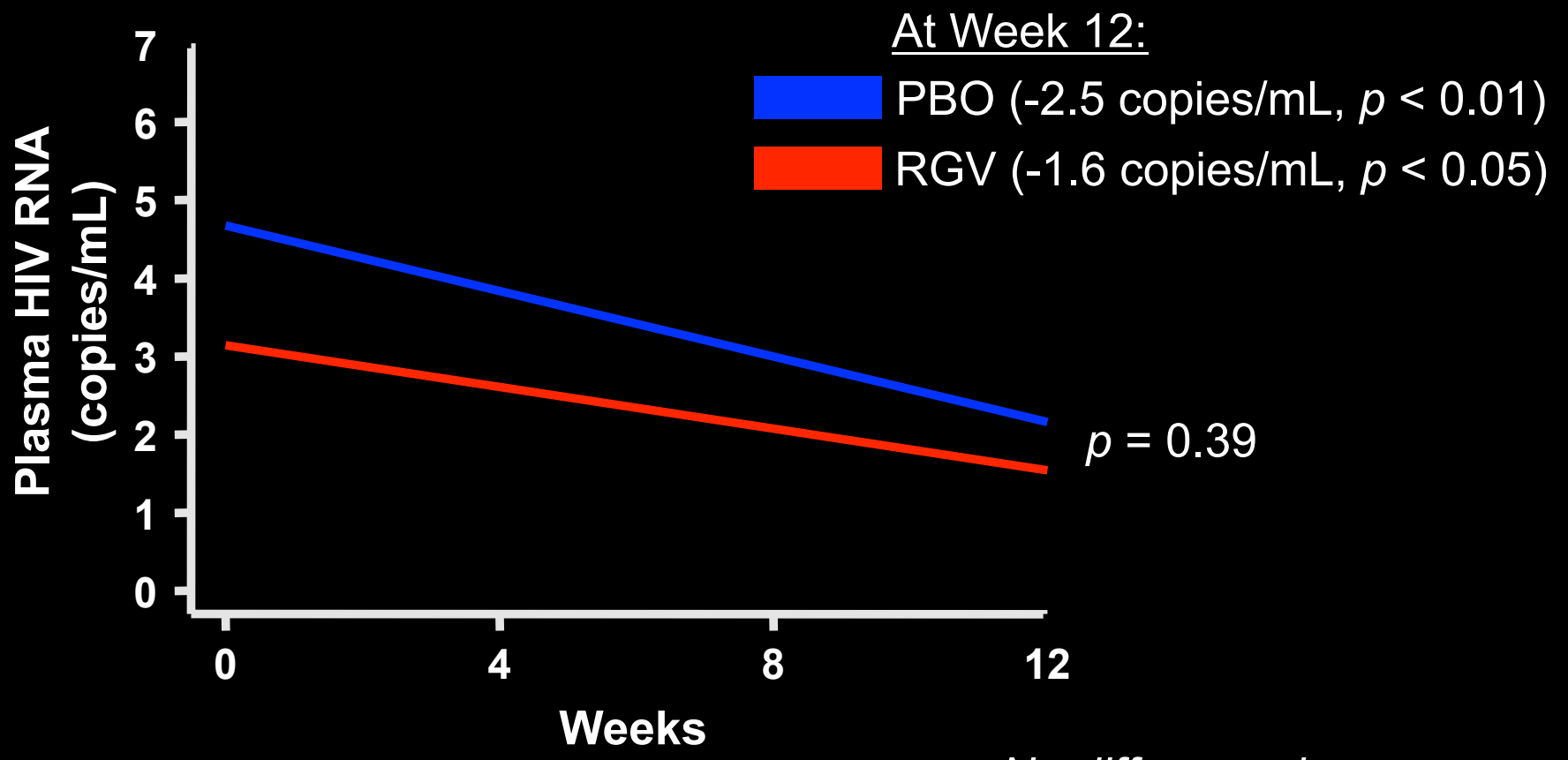
- Cytokines: IL-2, IL-7, IL-21
- Therapeutic vaccines
- Anti-PD-1, anti-PD-L-1

Gene therapy

- Replace or silence
- CCR5 knock-down; siRNA/short hairpin RNA

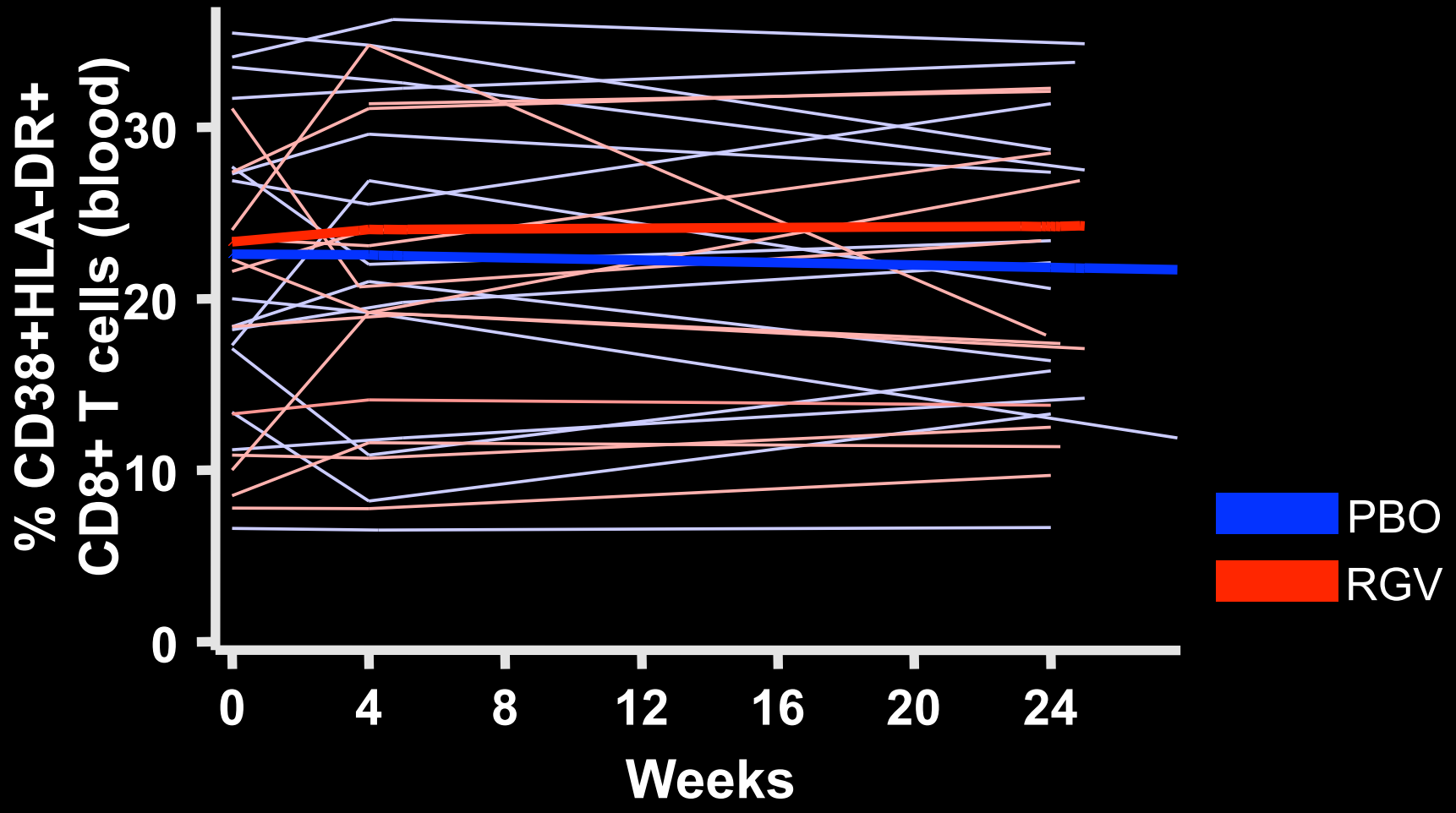
Inhibiting Residual Viral Replication

Raltegravir Intensification Did Not Decrease Plasma HIV RNA More than Placebo



No difference in proportion undetectable at week 12 (p = 0.42)

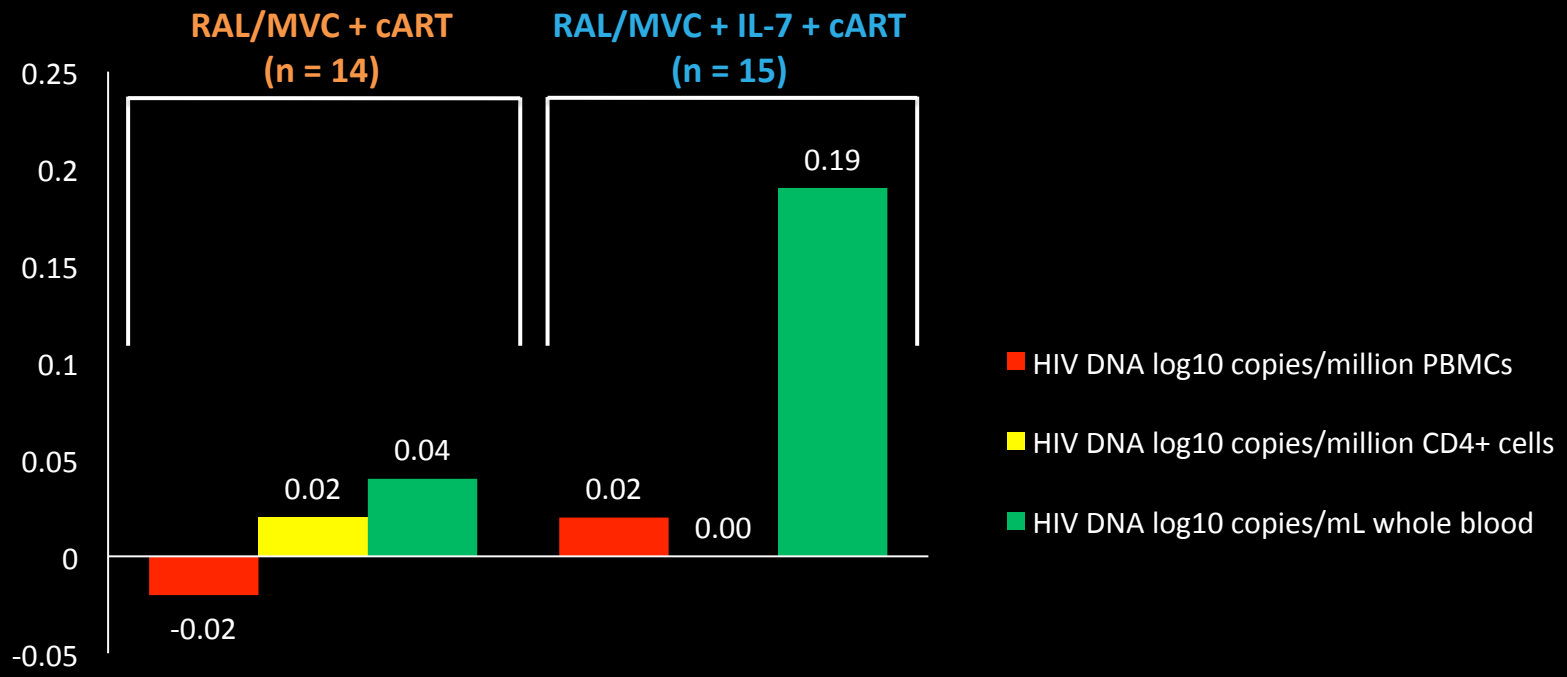
Raltegravir Intensification Had No Effect on CD8+ T Cell Activation



Inhibit residual replication: cure is unlikely with treatment intensification of current cART

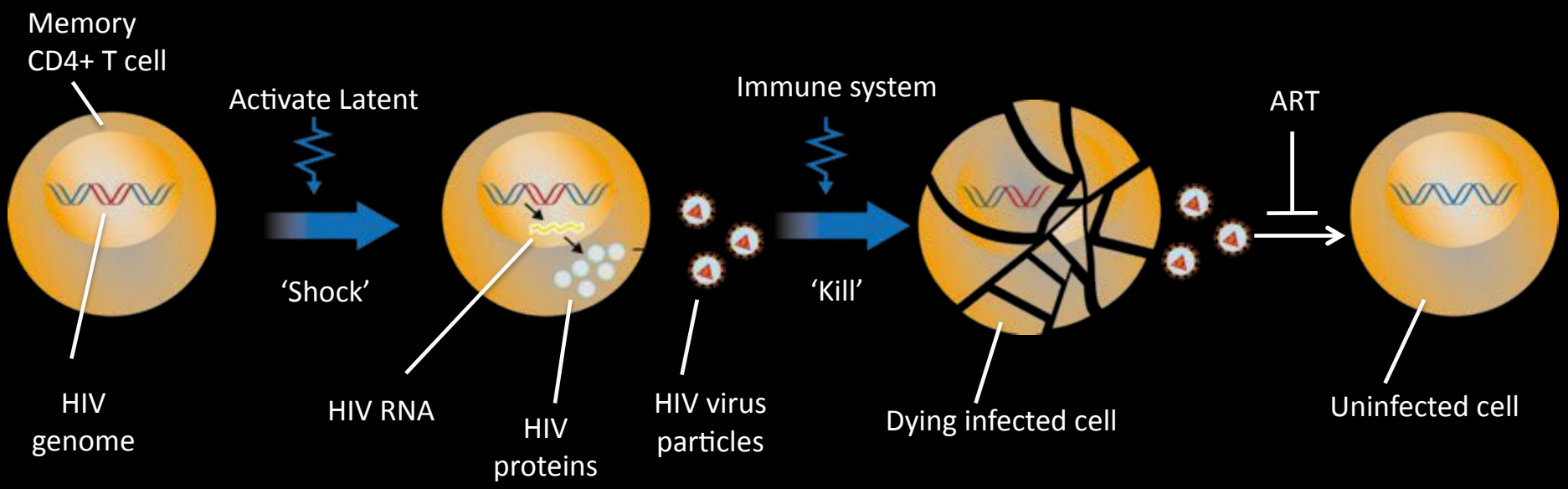
EraMUNE-01

- Intensification of current cART with the addition of raltegravir (RAL)/maraviroc (MVC), with or without IL-7, failed to significantly reduce the total HIV DNA reservoir in peripheral blood monocytes (PBMCs) after 56 weeks of treatment



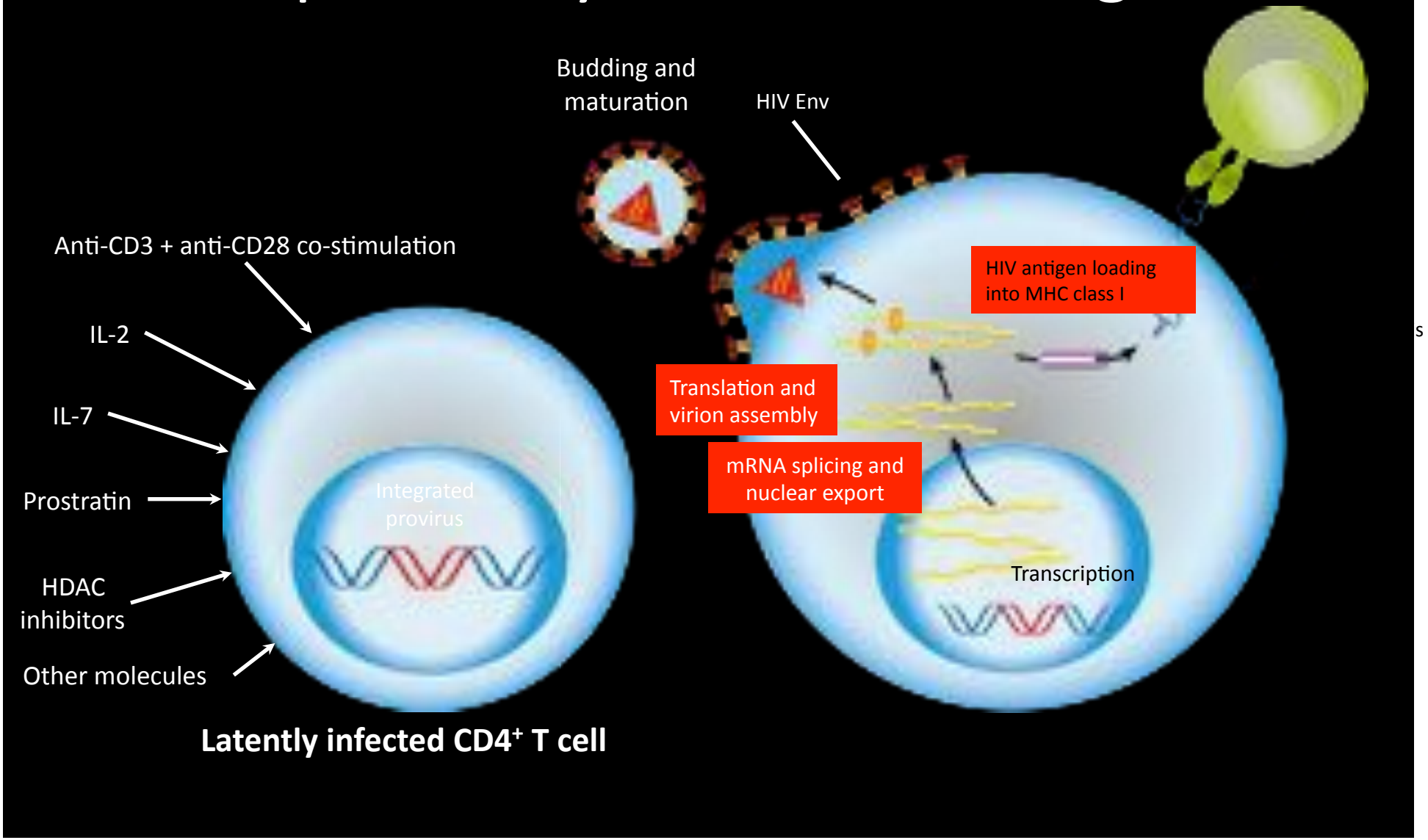

SHOCK
KILL BILL
VOL 2

HIV ‘Shock and kill’

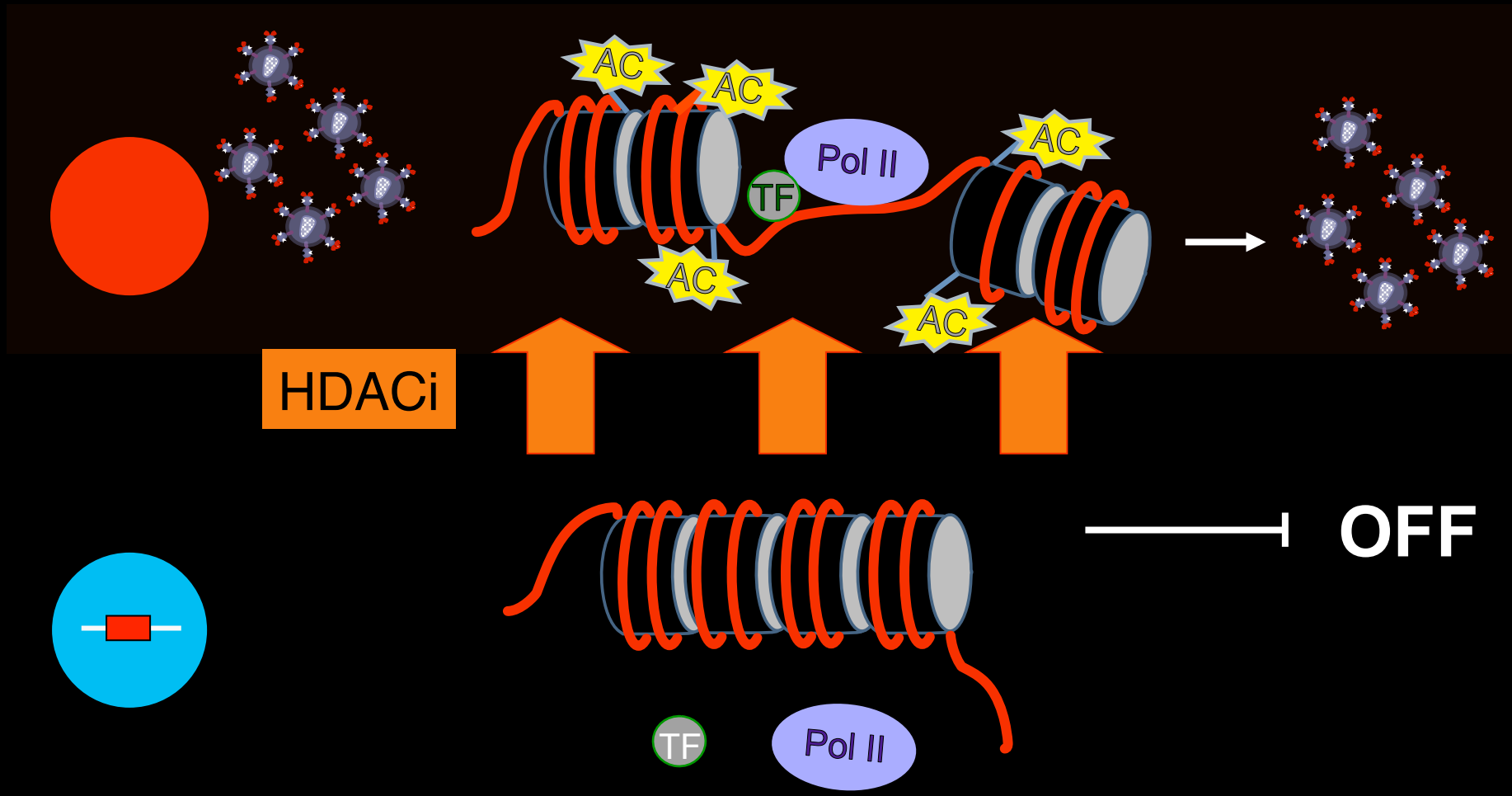


HDACi, histone deacetylase inhibitor
Adapted from Deeks SG. Nature 2012;487:439–40.

Activating latent virus is a necessary step in many HIV cure strategies



HDACi turn HIV genes “on”



HDACs are recruited to the LTR by various transcriptional regulators and deacetylate lysine residues on histones, inducing chromatin condensation, thereby repressing proviral transcription


FISKARS

Activating latent HIV: in vitro

- Histone deacetylase (HDAC) inhibitors[1, 2] ✓
- Cytokines ✓
  - IL-7[3,4]
  - IL-15[5]
- Anti-alcohol agent ✓
  - Disulfuram[6]
- Methylation inhibitors
  - 5-aza-dC[7]
- Immune modulation
  - Anti PD1
- NF-kB activators
  - Prostratin, PMA, TNFα[4]
- Akt/HEXIM-1 modulators
  - HMBA[8]
- Histone Methyltransferase inhibitors (HMTI)[9]
  - Chaetocin, BIX-01294
- Other
  - Quinolines[10]
- Combination enhances potency[4,9,11]

[1]Contreras, *J Biol Chem*. 2009;284(11):6782-9; [2]Wightman., *Immunol Cell Biol* 2012; [3]Wang, *J Clin Invest* 2005; 115:128; [4]Saleh, *Retrovirology* 2011;8:80; [5]Chomont, 6th *IAS* Rome 2011; [6]Xing, *J Virol*; 2011;85(12):6060-4; [7]Friedman, *J Virol*;2011 85:9078-8; [8]Contreras *PLoS Pathog*. 2007 3(10):1459-69 ; 466-72; [9]Bouchat, AIDS 2012; [10]Xing et al., *J Antimicrob Chemother*. 2012;67(2):398-403; [11]Reuse et al., *PLos One* 2009;4:e6093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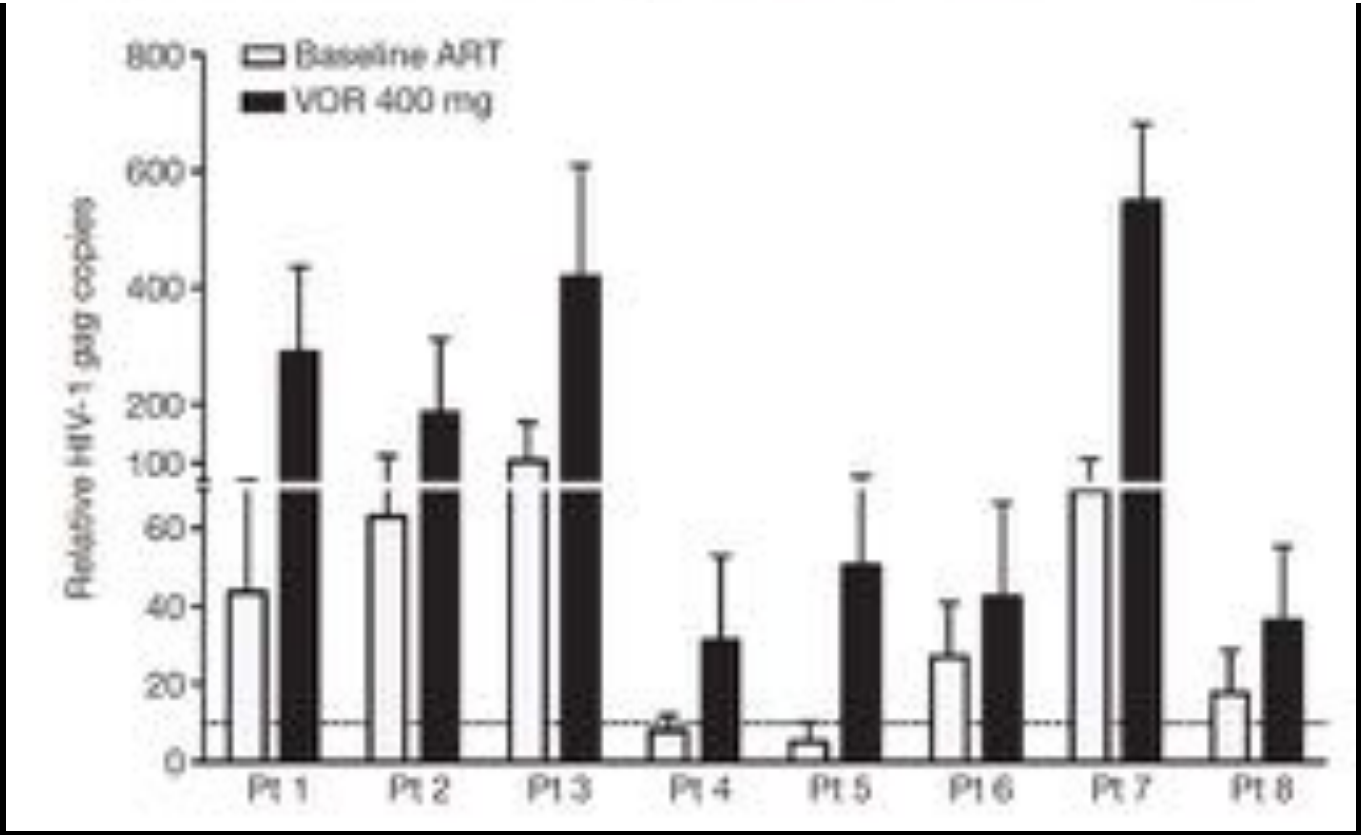
LETTER

doi:10.1038/nature11286

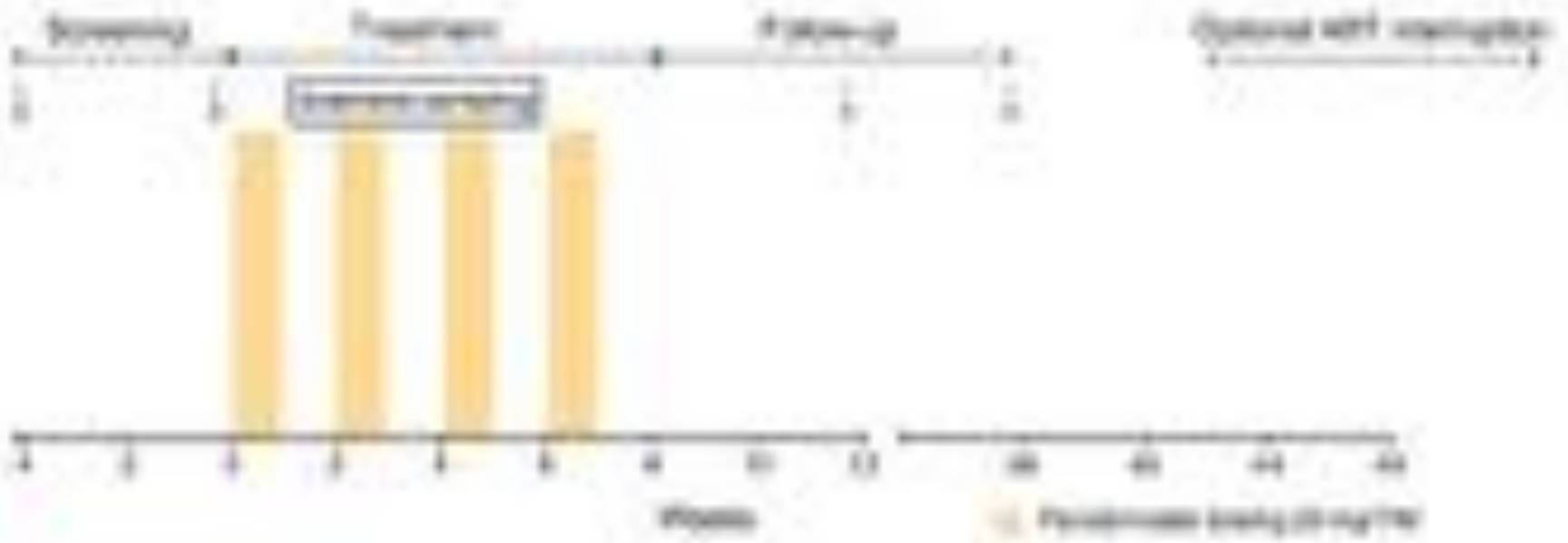
Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy

N. M. Archin[1], A. L. Liberty[2], A. D. Kashuba[1], S. K. Choudhary[1], J. D. Kuruc[1], A. M. Crooks[1], D. C. Parker[1], E. M. Anderson[2], M. F. Kearney[2], M. C. Strain[3], D. D. Richman[3], M. G. Hudgens[1], R. J. Bosch[4], J. M. Coffin[2], J. J. Eron[1], D. J. Hazuda[5] & D. M. Margolis[1]



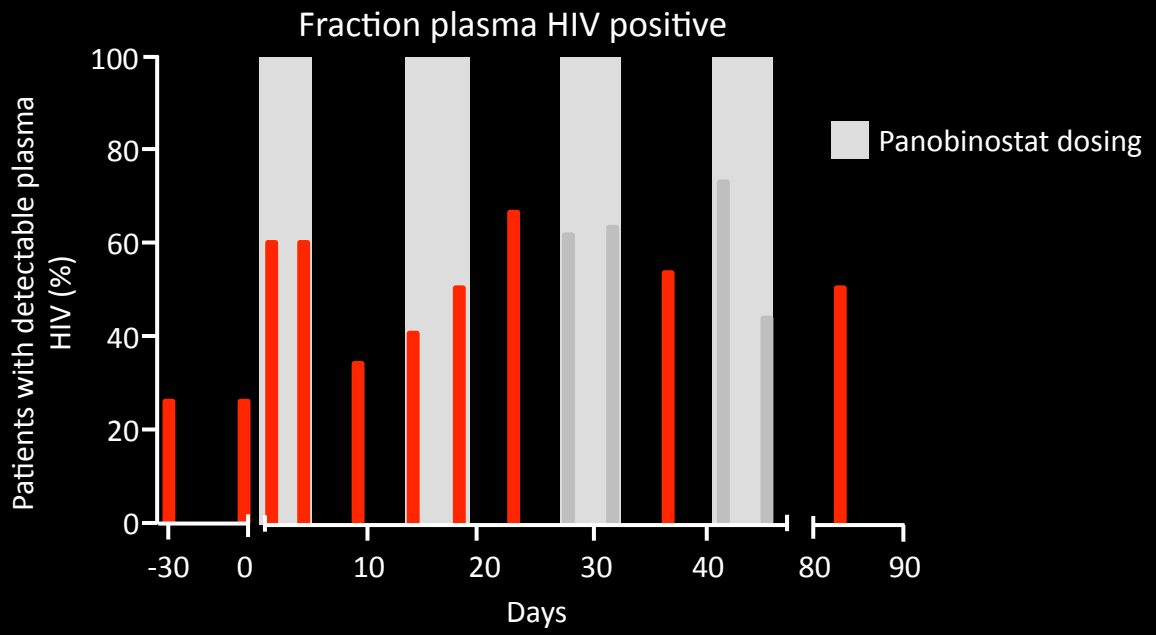
Study design Overall

- Oral tablet 20 mg three times pr week every other week
- Repeated 4 times for a total of 8 weeks
- Total of 12 doses



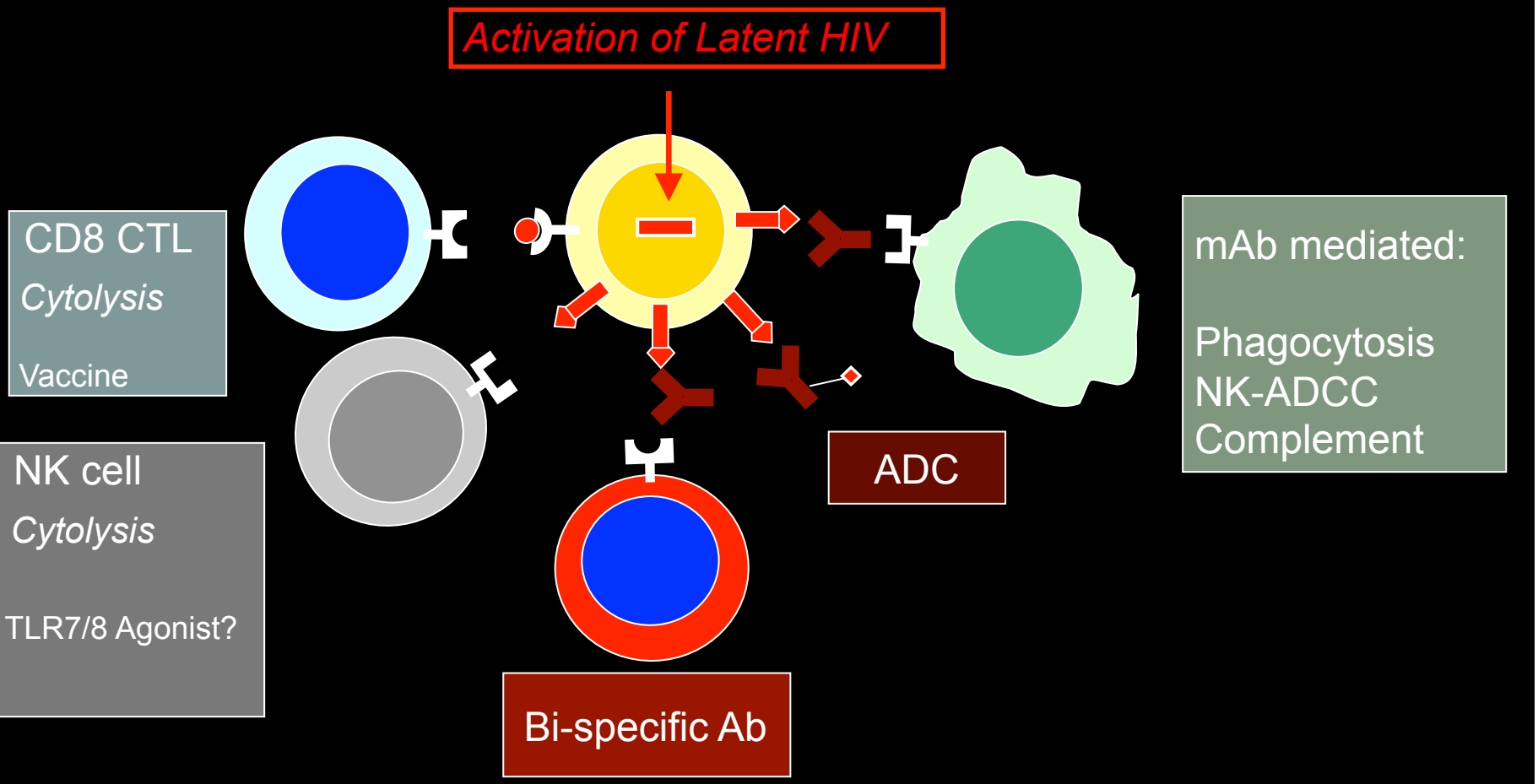
CLEAR study: HDAC inhibitor panobinostat in vivo

- Panobinostat (20 mg) was administered 3 times per week, every other week (n = 15)
- Only 1 patient had undetectable plasma HIV at all time points
- 3 patients had detectable plasma HIV at all time points



Tolstrup M. Cyclic Panobinostat (LBH589) dosing in HIV-1 patients: findings from the CLEAR trial. Towards an HIV Cure Symposium, IAS 2013.

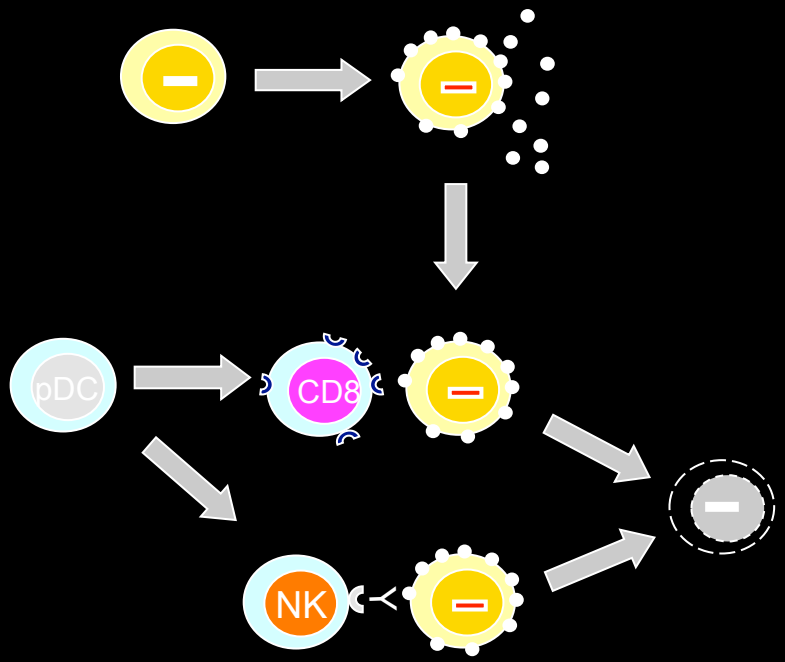
Potential Strategies to Kill Cells Expressing Reactivated HIV



Combination of RMD and TLR7 Agonist

Activate HIV Expression
Romidepsin

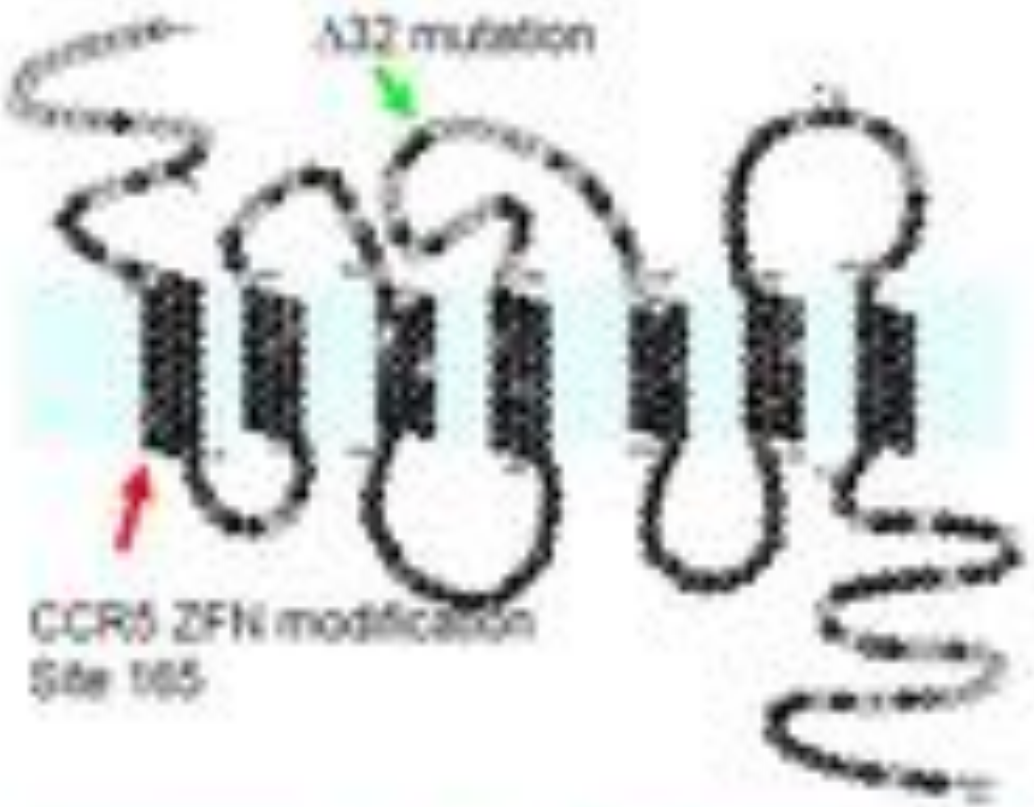
Cell-mediated Killing
via immune modulation
TLR7 agonist



Can activation of DCs help prime HIV-specific immune responses?
Can activated CD8+ CTLs and NK cells help clear cells expressing reactivated HIV?

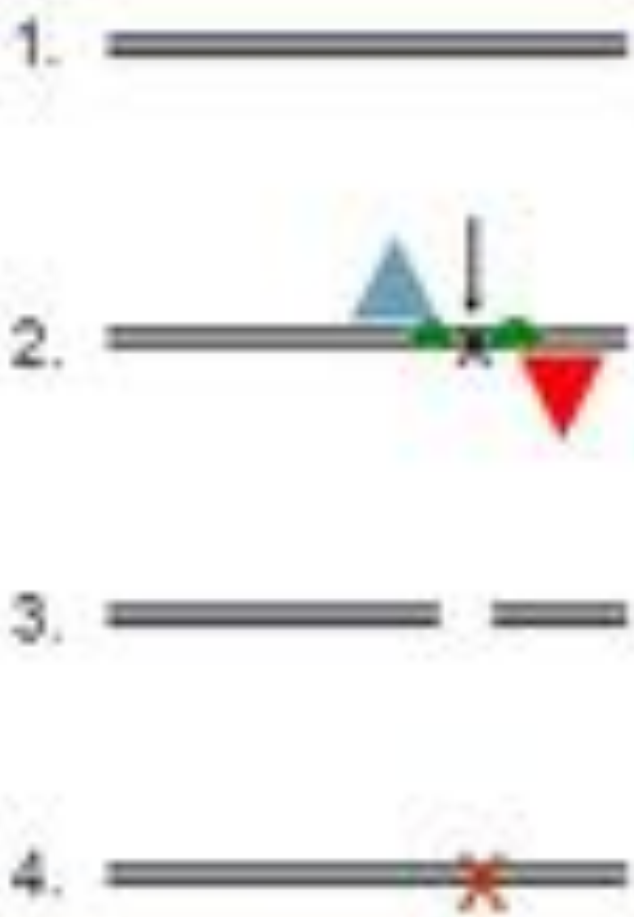
Study in SIV-infected rhesus macaques on ART underway

Targeting the *CCR5* Locus with ZFNs



ZFN pairs targeted to region upstream of the Δ32 mutation

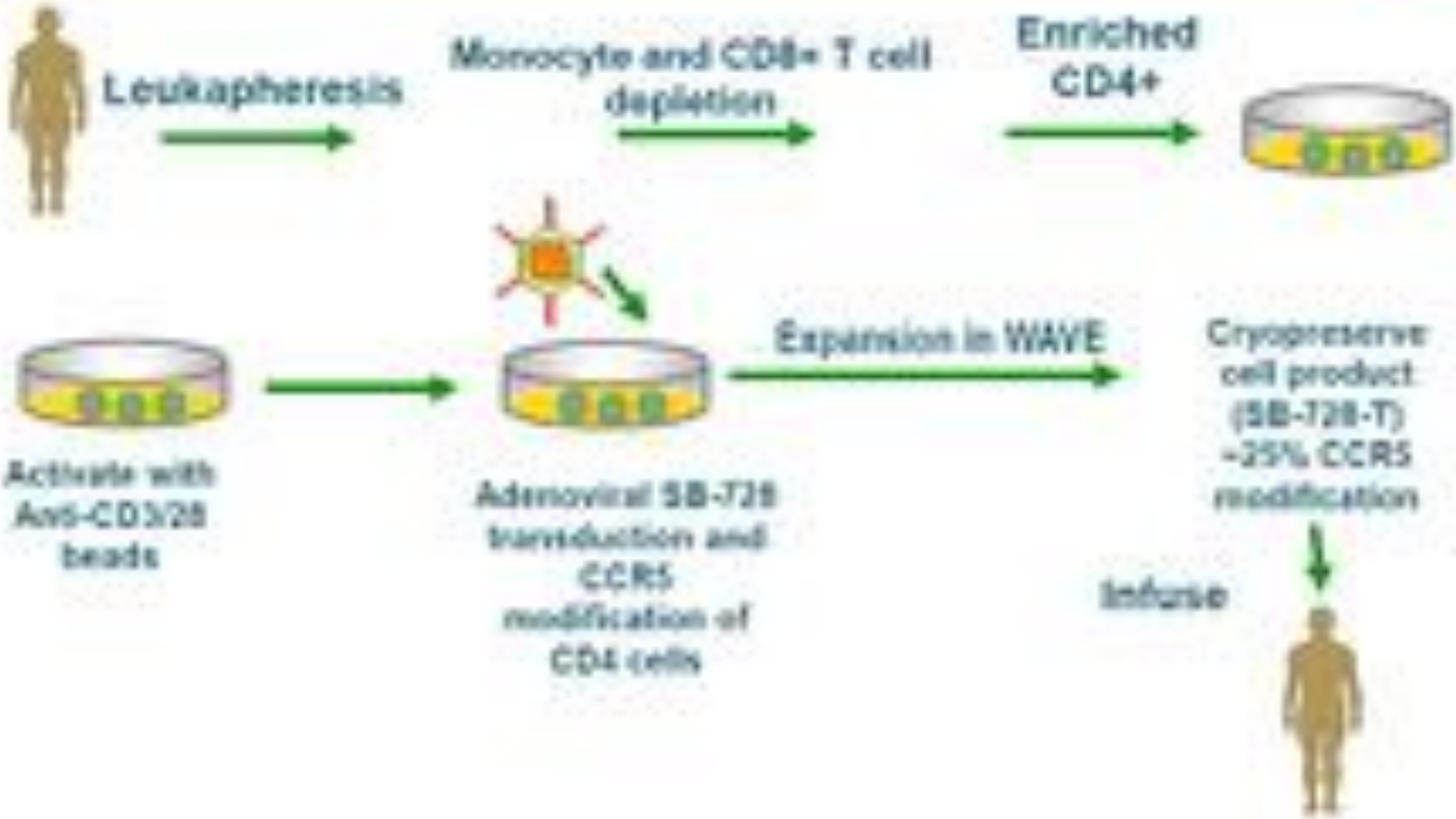
Mechanism of ZFN-mediated Targeted CCR5 Gene Disruption



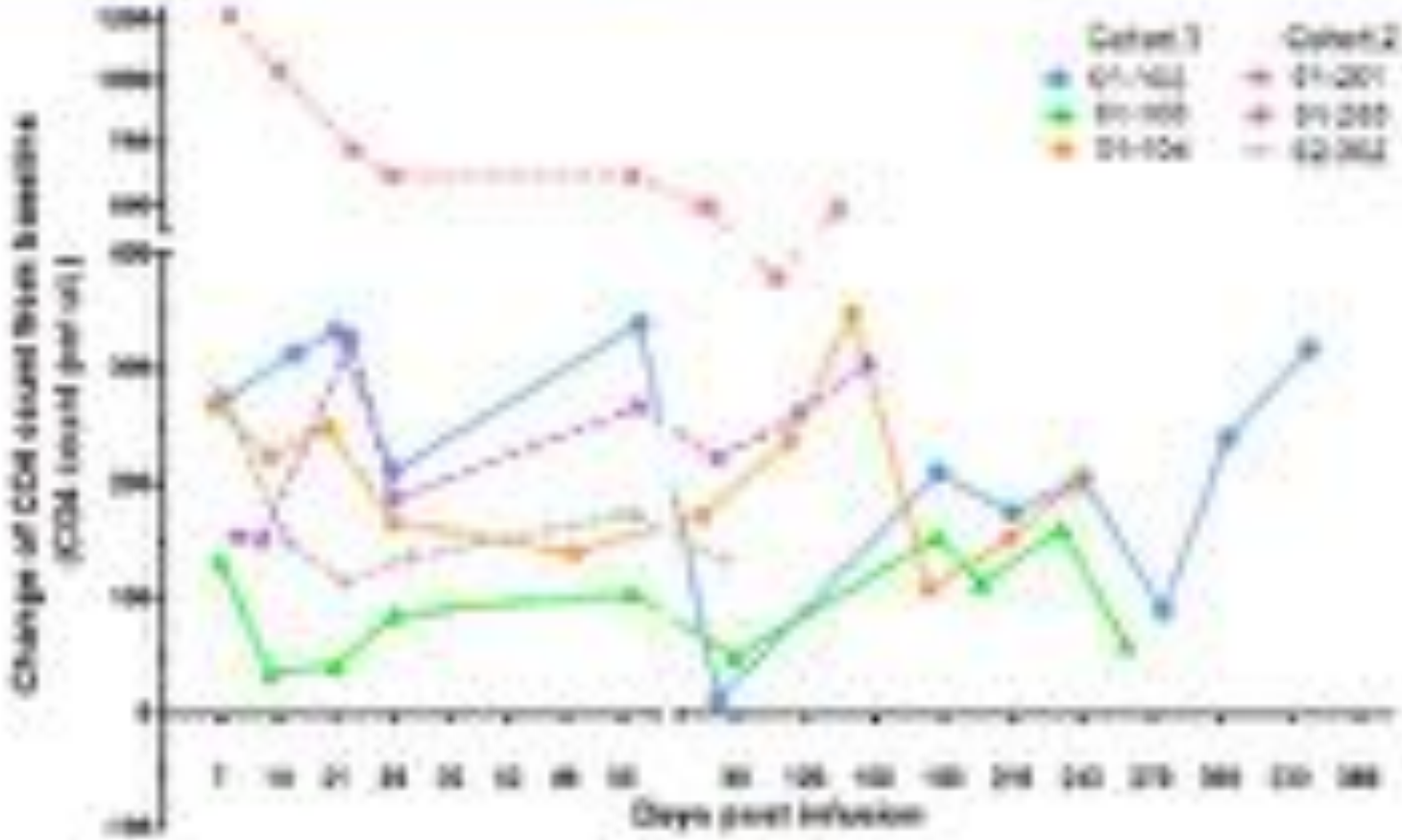
A 5-bp duplication (Pentamer) occurs in 25% of modified cells at target site allowing PCR quantification


Harry Potter
and the
Prisoner
of Azkaban

SB-728-T GMP Manufacturing Process: Autologous ZFN CCR5-Disrupted CD4+ T-cells

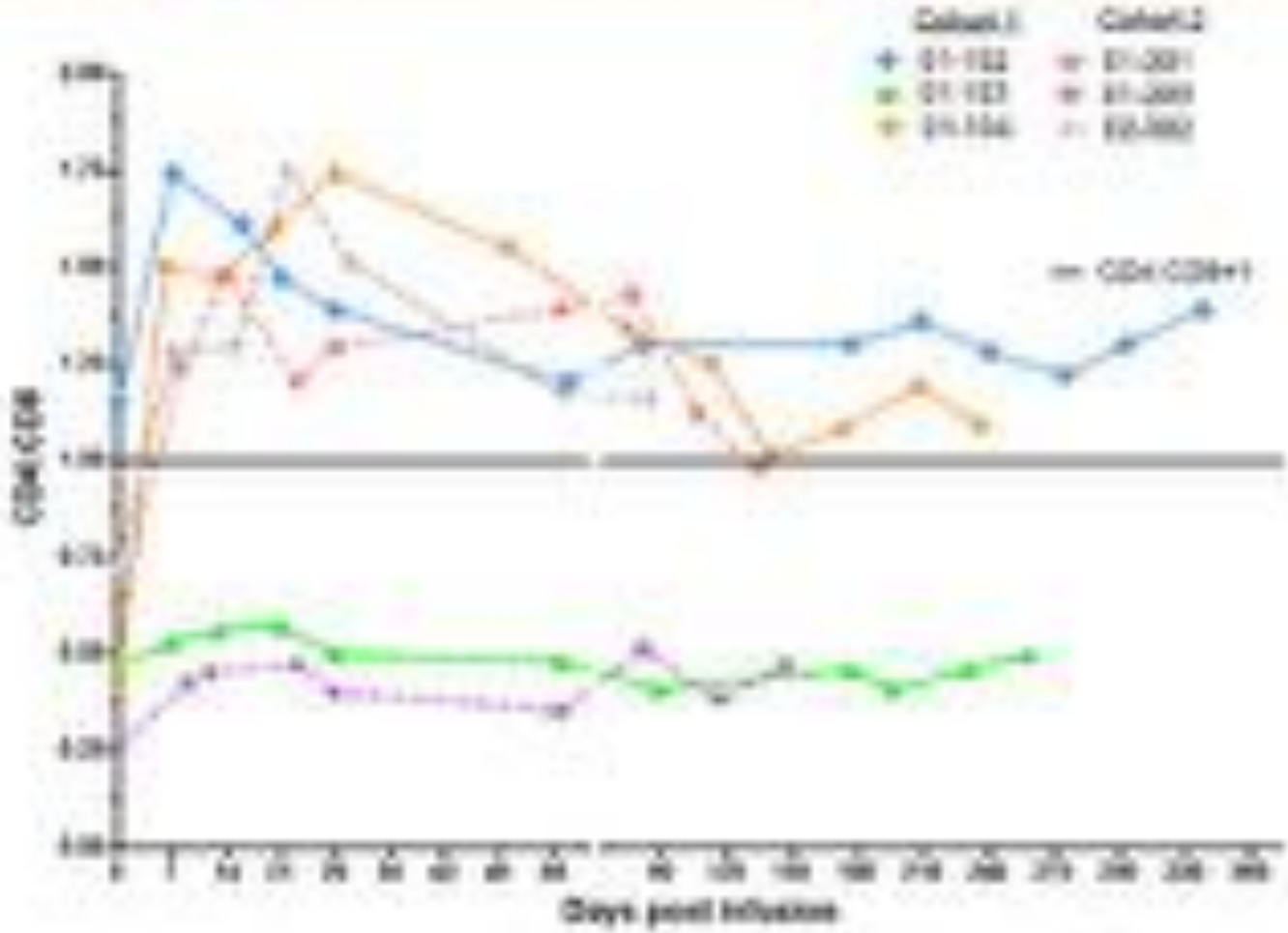


Increased CD4 T-cell Counts from Baseline after Single SB-728-T Infusion

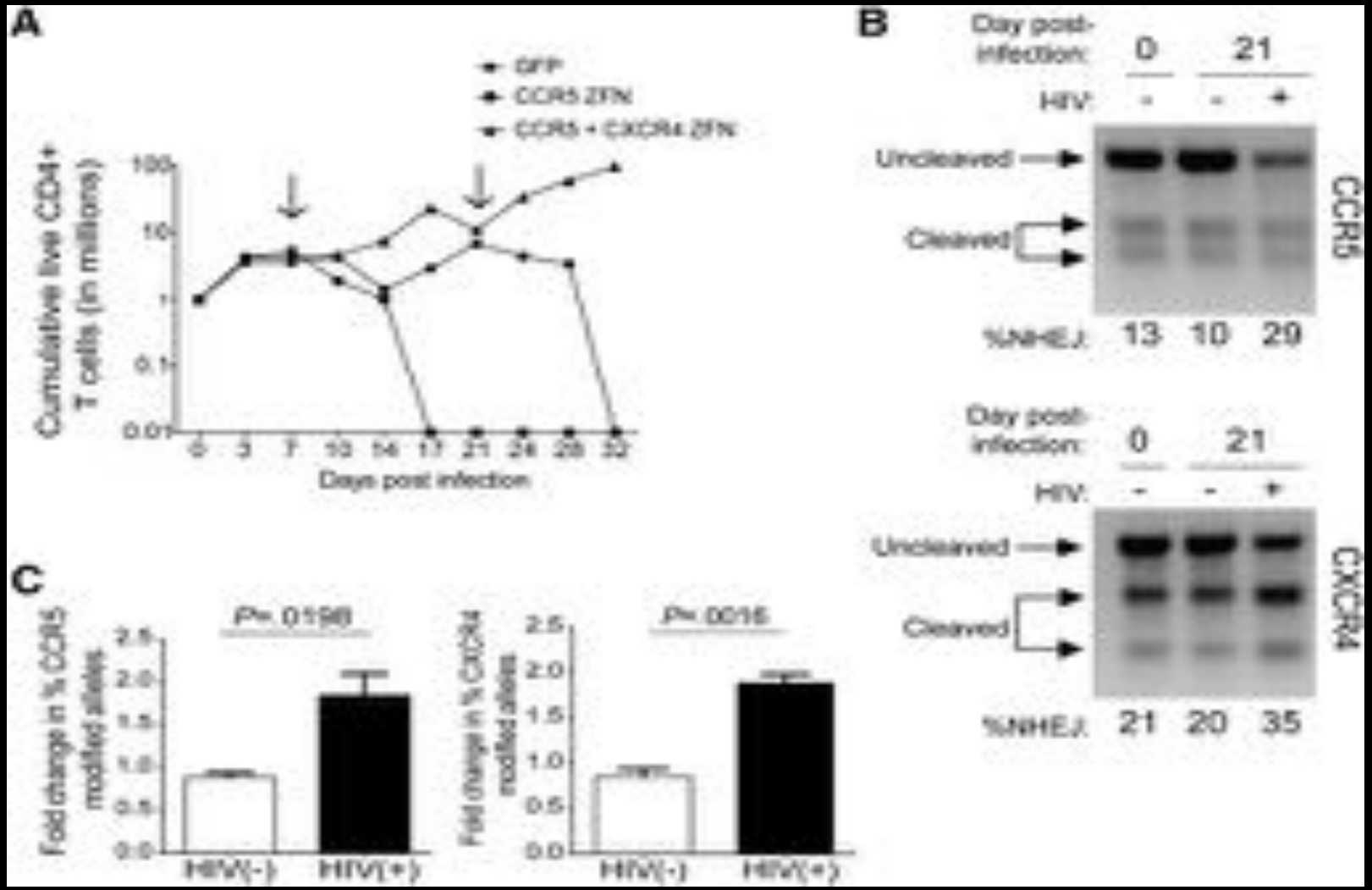


Sustained increase from baseline observed in 5 of 6 subjects at most time points

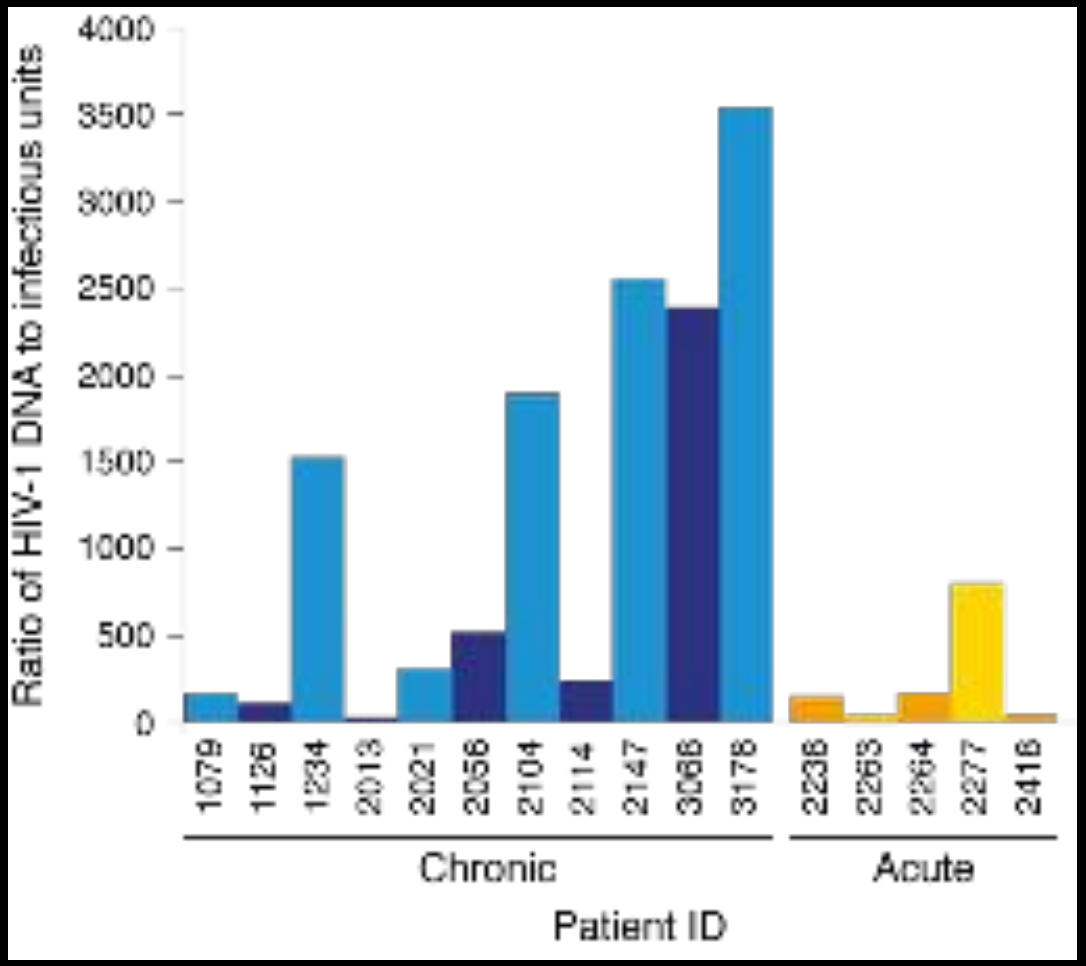
Normalization of CD4:CD8 T-cell Ratio after Single SB-728-T Infusion



CD4:CD8 reversal (from <1 to >1) in 3 of 5 subjects

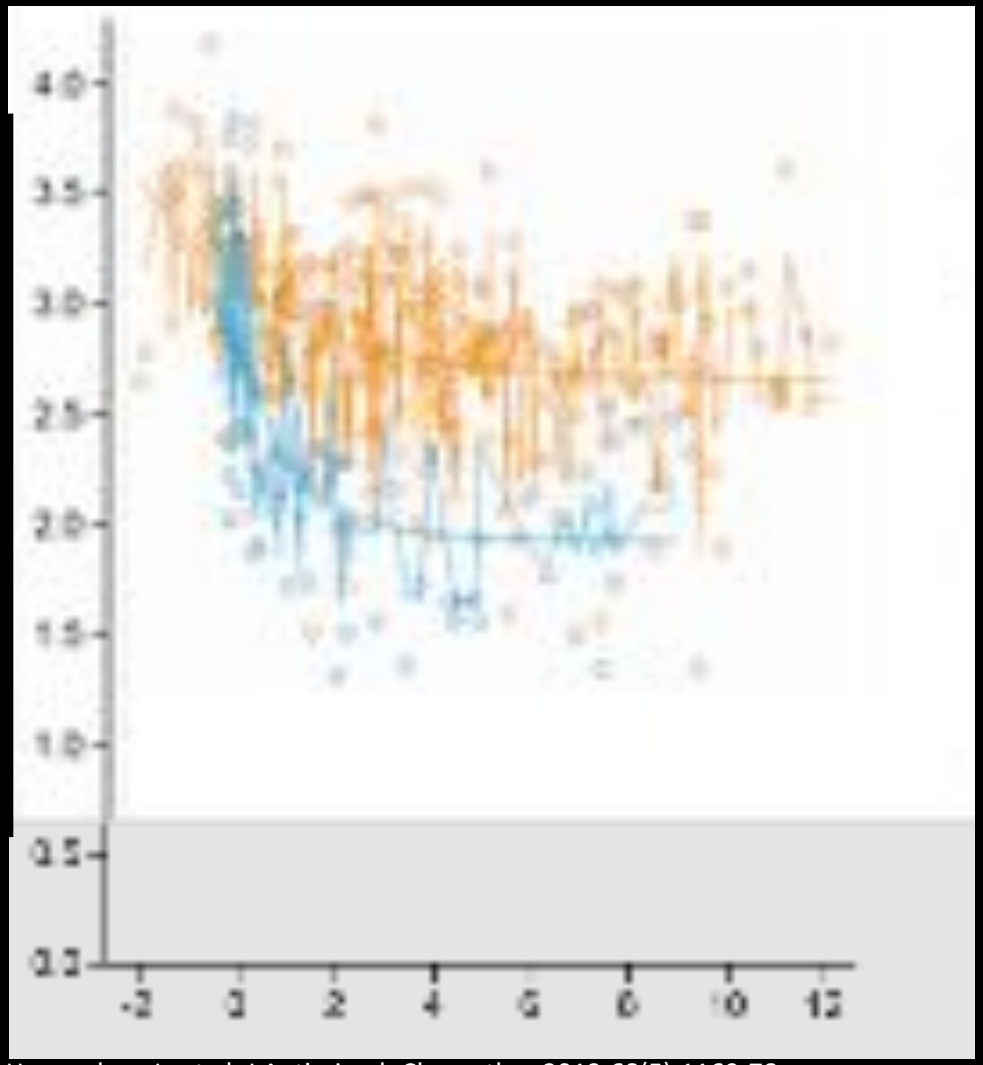

A
GFP
CCR5 ZFN
CCR5 + CXCR4 ZFN
Cumulative live CD4+ T cells (in millions)
100
10
1
0.1
0.01
0
3
7
10
14
17
21
24
28
32
Days post infection
B
Day post-infection:
0
21
HIV:
-
-
+
Uncleaved
Cleaved
CCR5
%NHEJ:
13
10
29
Day post-infection:
0
21
HIV:
-
-
+
Uncleaved
Cleaved
CXCR4
%NHEJ:
21
20
35
C
Fold change in % CCR5 modified alleles
P= 0198
2.5
2.0
1.5
1.0
0.5
0.0
HIV(-)
HIV(+)
Fold change in % CXCR4 modified alleles
P= 0016
2.5
2.0
1.5
1.0
0.5
0.0
HIV(-)
HIV(+)

Reservoir of HIV is less in acutely infected individuals



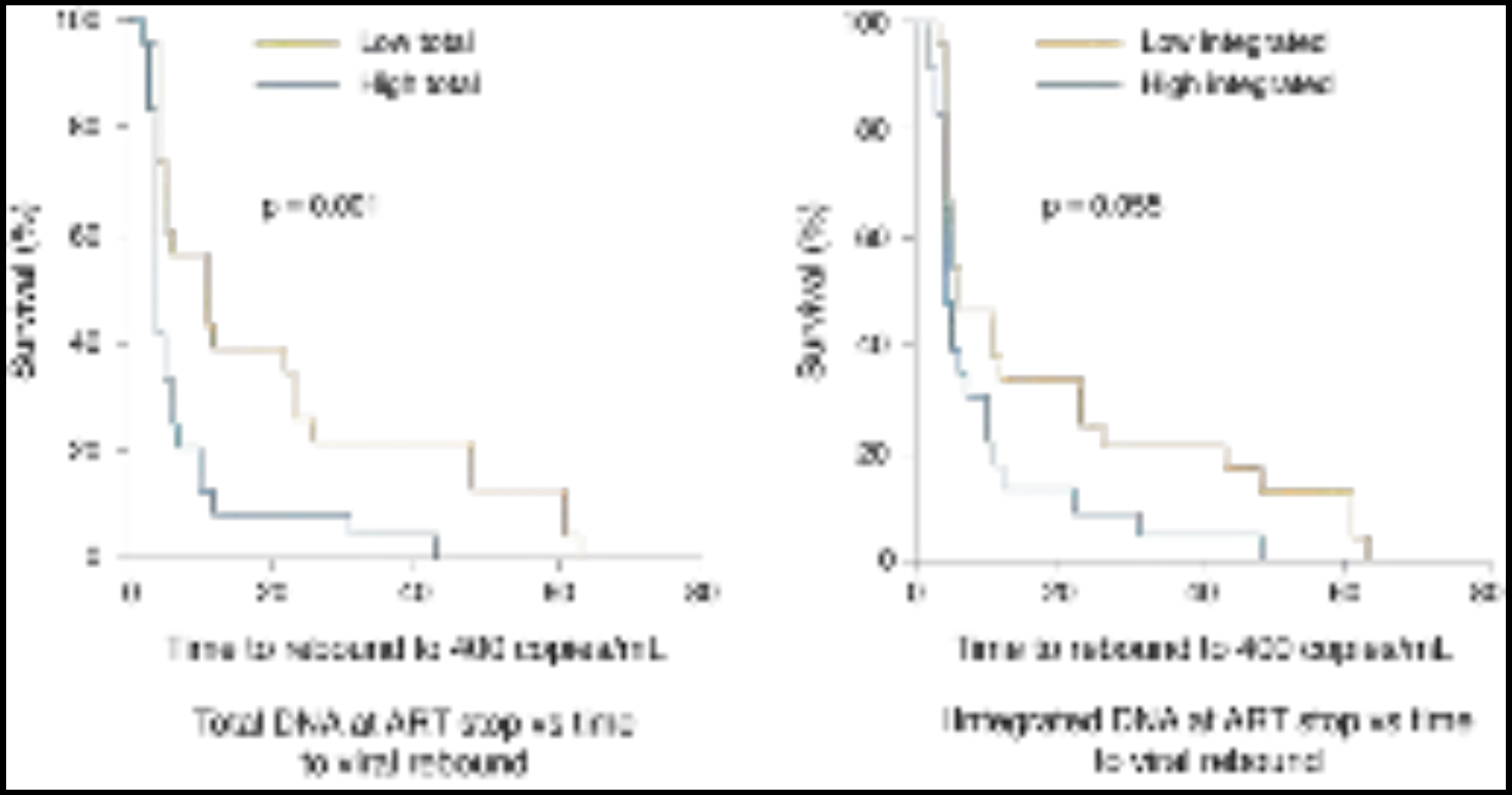
* Indicates maximum values in cases in which the HIV-1 DNA level was below the limit of detection (2 copies/ml).
Eriksson et al. PLoS Pathog 2013;9:e1003174.

Reservoir reduced with early treatment



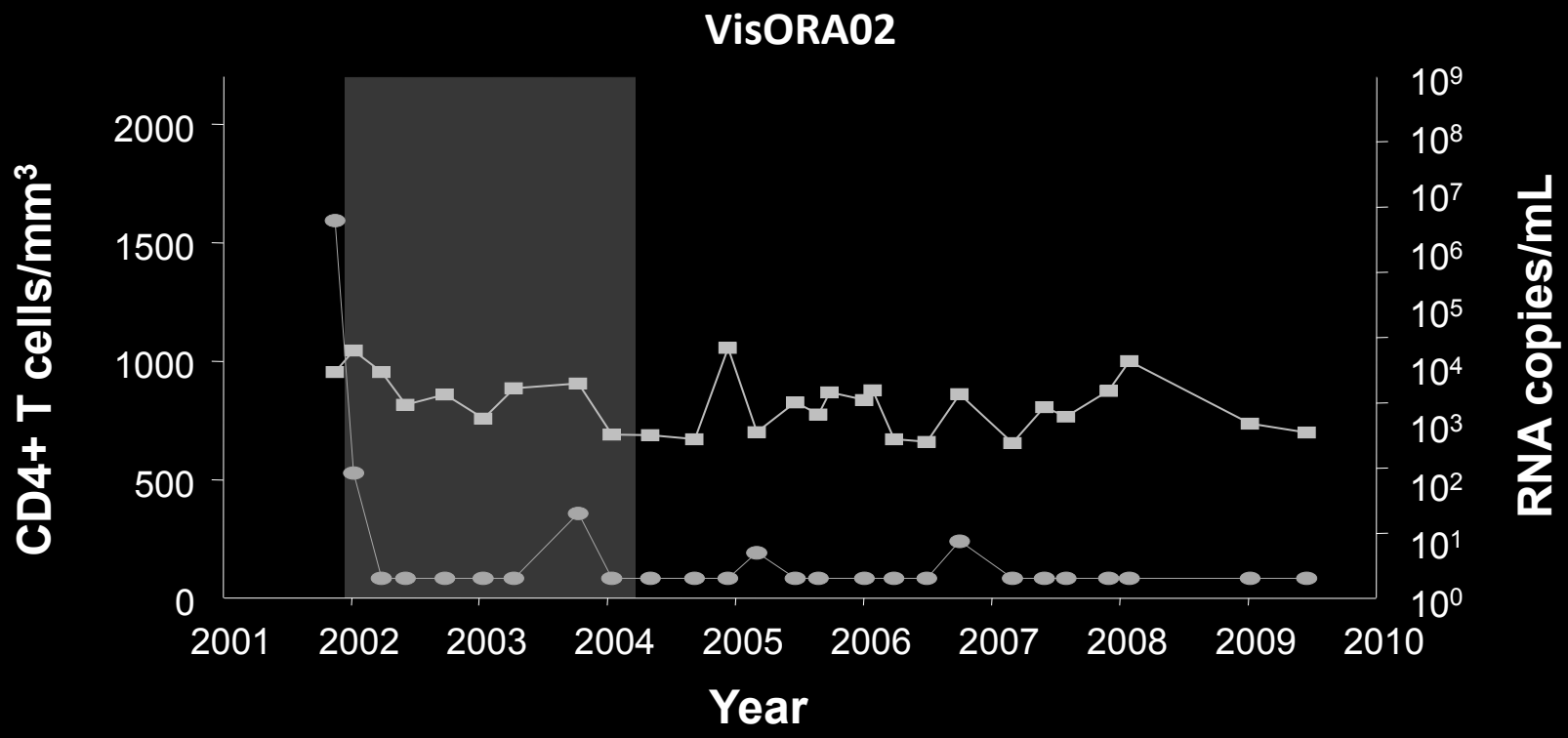
Adapted from Hocqueloux L, et al. J Antimicrob Chemother 2013;68(5):1169-78.

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



Hurst et al. CROI 2014 Abstract 403LB.

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. IAS 2013. ANRS Satellite Symposium. Natural and induced control of HIV infection: differences and similarities.

Have other trials of transient ART at PHI found post-treatment control?

Trials	VL < 50 after no ART	AHI stage	Time at ART	ART duration before interruption
VISCONTI[1,2]	15.6%	Fiebig II–V	2.2 months from diagnosis	**5 years**
Swiss 1[1,3]	9%	Fiebig I–VI	≤ 4 months from infection onset	1.5 years
Primo-SHM[1,4]	5%	70% Fiebig I–IV 30% Fiebig V–VI	2 months from diagnosis	0.5 or 1.5 years
ANRS CO6 PRIMO[1,5]	11%	Fiebig I–VI	3.1 months from infection onset	1.5 years
CASCADE[1]	8.2%	Fiebig I–VI	≤ 3 months from seroconversion	1 year
Trials without post-treatment controllers SPARTAC[1]		Fiebig I–VI	2–6 months from diagnosis	1+ year

AHI, acute HIV infection; VL, viral load.

1. Personal communication, Jinatant Arananowich.
2. Hocqueloux et al. AIDS 2010;24:1598–601. 3. Gianella et al. Antivir Ther 2011;16:535–45.
4. Grijsen et al. PLoS Med 2012;9:e1001196. 5. Goujard et al. Antivir Ther 2012;17:1001–9.

Early ART: Reducing the Size of Initial Reservoir?

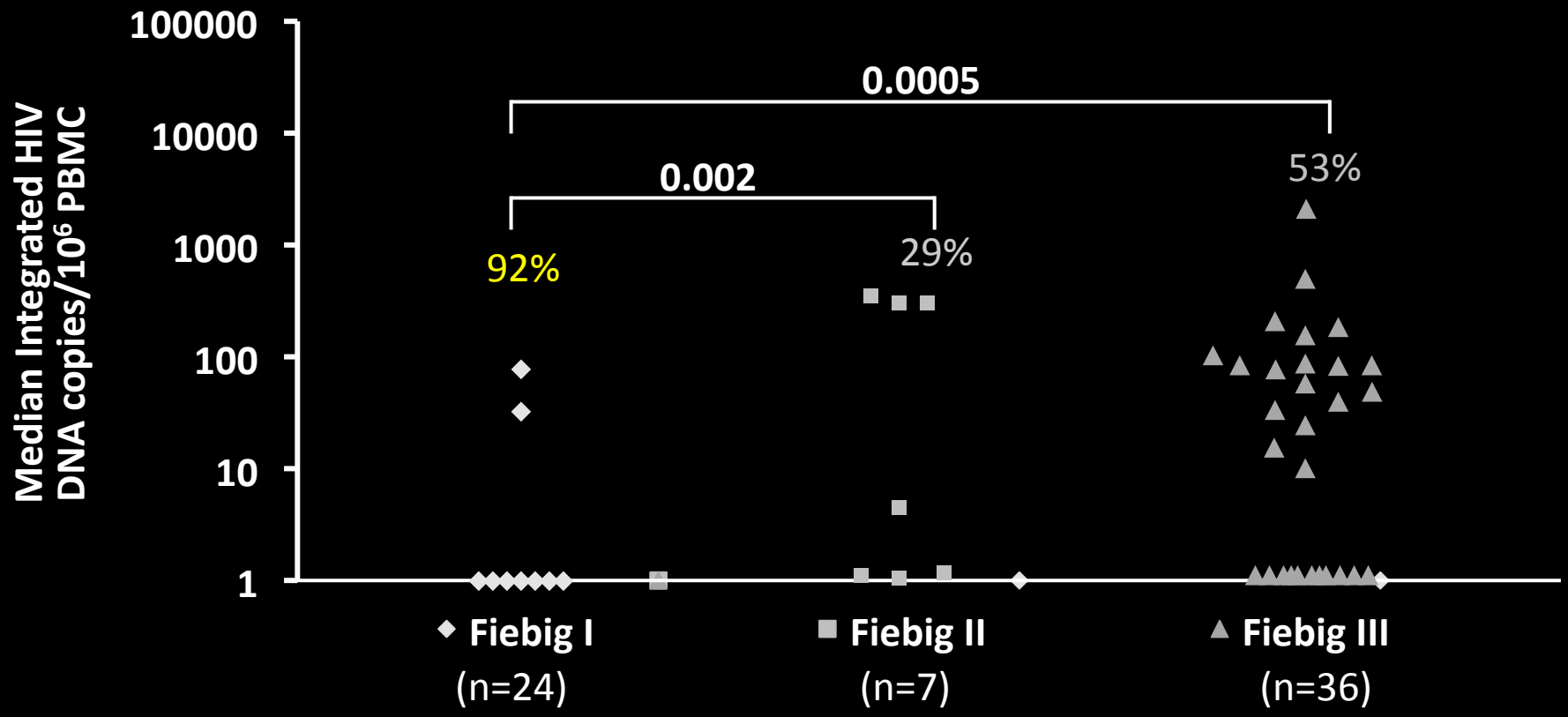
Screening NAT/EIA **52,767 samples → 89 AHI identified**
3 days
75 enrolled into Main Protocol
Optional procedures: Sigmoid biopsy Leukapheresis
Within 2 days → optional ART

Fiebig Classification System of Early Infection:

				% enrolled
Fiebig I	RNA +	p24-	3rd Gen EIA -	37%
Fiebig II	RNA+	p24+	3rd Gen EIA -	10%
Fiebig III	RNA+	p24+	3rd Gen EIA + WB neg	53%

Ananworanich J, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 47.

Almost all Fiebig I Subjects had Undetectable Integrated HIV DNA in PBMC



Ananworanich J, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 47.

HIV-1 Reservoirs Reduced in HIV-Positive Children With Early ART and Viral Control

- Cross-sectional study of 144 perinatally HIV-infected pts with long-term (median: 10.2 yrs) virologic suppression on ART
- Higher proviral burden with increasing age at virologic suppression[1]
- In perinatally infected baby treated early (at 4 hrs of age) with triple ART, noninduced proviral genomes detected by PCR at 1 mo but not at 3 mos of age[2]

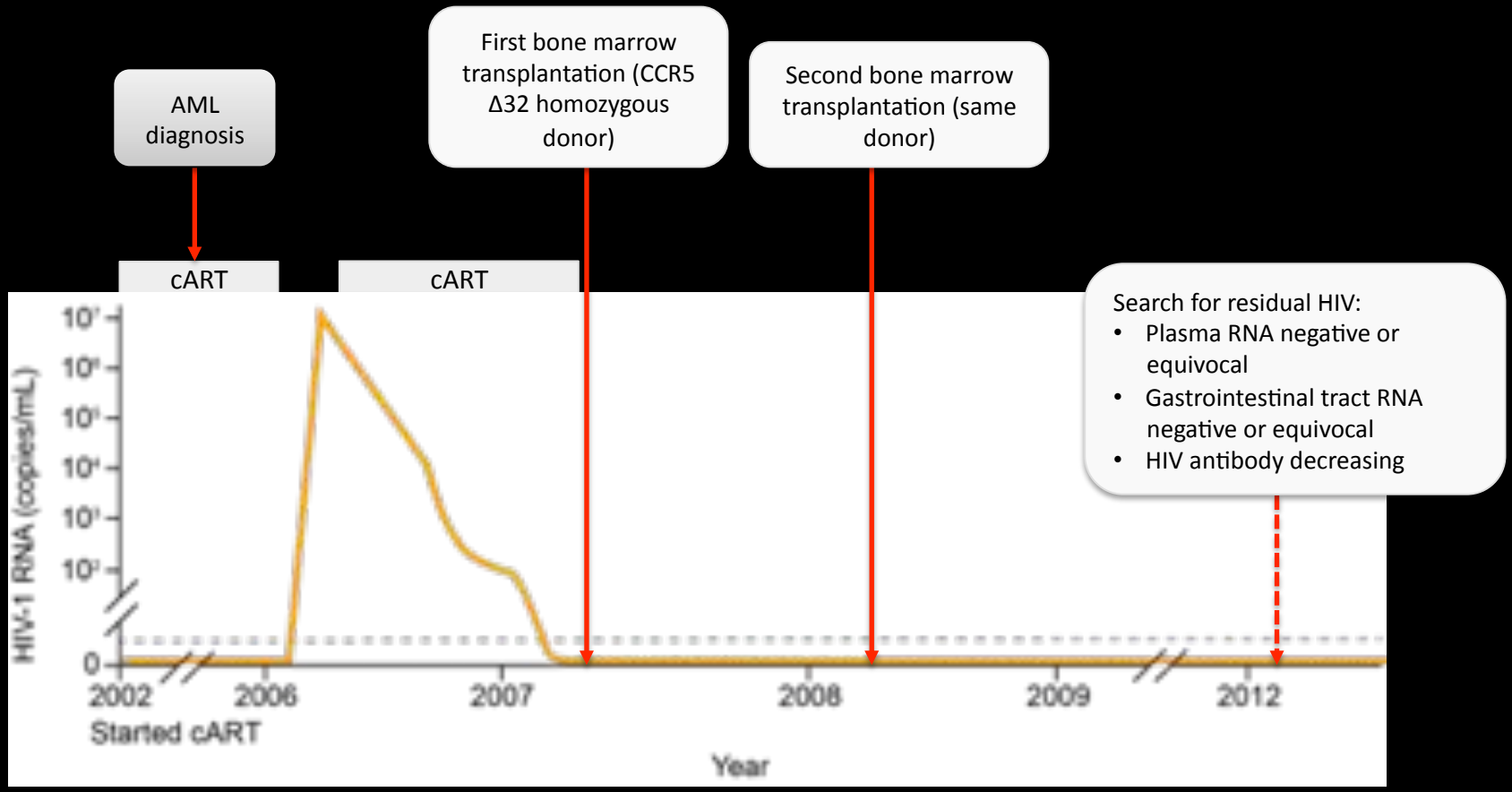
Proviral Reservoir Size by Age of Virologic Control[1]	
Age, yr	**Median HIV-1 DNA copies/ 10^6 PBMCs (IQR)**
< 1 (n = 14)	4.2 (2.6-8.6)
1-5 (n = 53)	19.4 (5.5-99.8)
> 5 (n =77)	70.7 (23.2-70.7)*

*P < .001 compared with < 1 yr

The Emerging Race To Cure HIV Infections

Timothy Ray Brown's startling fate has pushed to the front a daunting research challenge that long seemed a fool's errand

Transplant may lead to functional cure (1)



HIV Rebound After Treatment Interruption in 2 BMT Pts

- 2 HIV+ persons treated with allogeneic hematopoietic stem cell transplantation from CCR5 wild-type donors
- HIV-1 remained undetectable in blood and rectal tissue while pts on ART
- ART withdrawn and pts followed with weekly or biweekly monitoring of viral load (VL) and proviral DNA by clinical assays

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- HIV-1 remained undetectable in blood and rectal tissue while pts on ART
- ART withdrawn and pts followed with weekly or biweekly monitoring of viral load (VL) and proviral DNA by clinical assays
- Pt A: no detectable plasma HIV-1 RNA or cell-associated HIV-1 DNA for 3 mos after ART cessation, then rebound
- Pt B: no detectable virus (including negative PBMC HIV DNA and HIV-1 RNA by ultrasensitive assays) for 8 mos after ART cessation, then rebound
- Both pts developed symptoms of acute retroviral syndrome, including aseptic meningitis
- Symptoms rapidly resolved with ART initiation and viral suppression in both pts

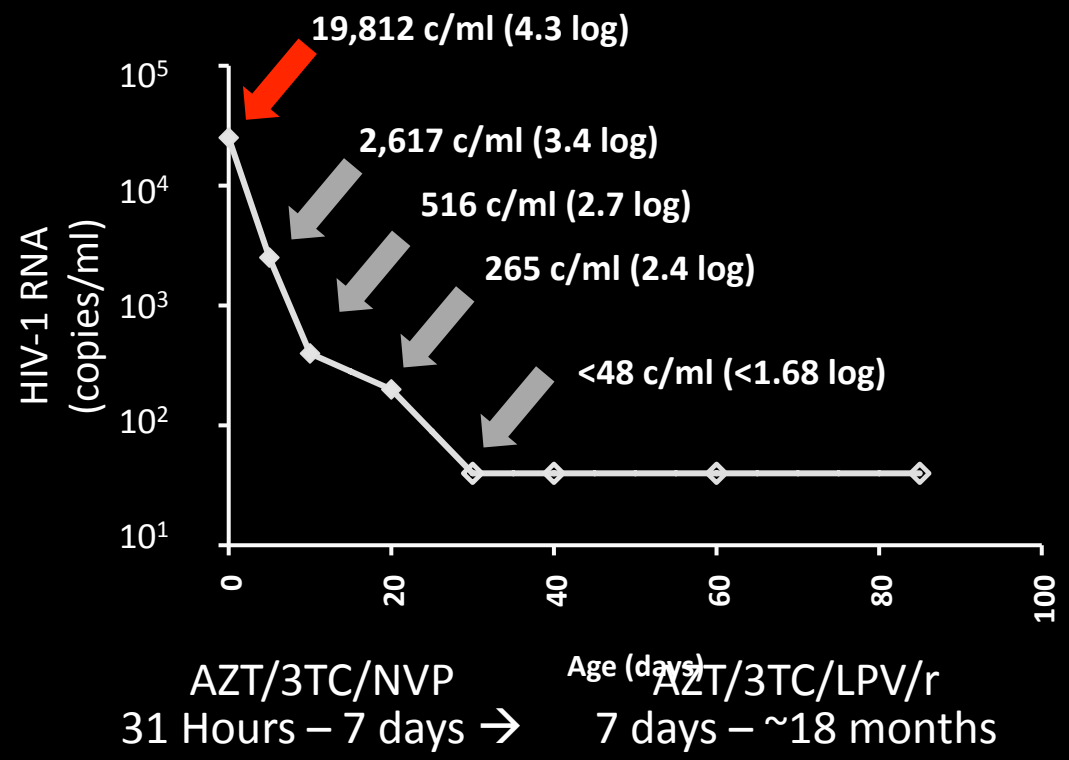
The Second Cure?

- Infant born at U. Miss Medical Center
- Mother HIV+ (EIA, WB); no prenatal care
- Maternal VL: 2423 c/mL, CD4 644/mm^3
  - Infant born 35 weeks; NSVD
  - Rapid test HIV+ in neonate
- Standard testing of exposed infants:
  2 HIV+ tests from 2 samples

Sample	Age	Test	Result
Blood	30 hours	HIV DNA	positive
Blood	31 hours	HIV RNA	19,812 c/mL

Persaud D, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 48LB.

Virologic Response to HART Regimen



- Mother stops ART about month 18 – LTFU until month 23
- HIV testing of infant done before restarting ART

Persaud D, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 48LB.

Virologic Studies to Detect Residual HIV

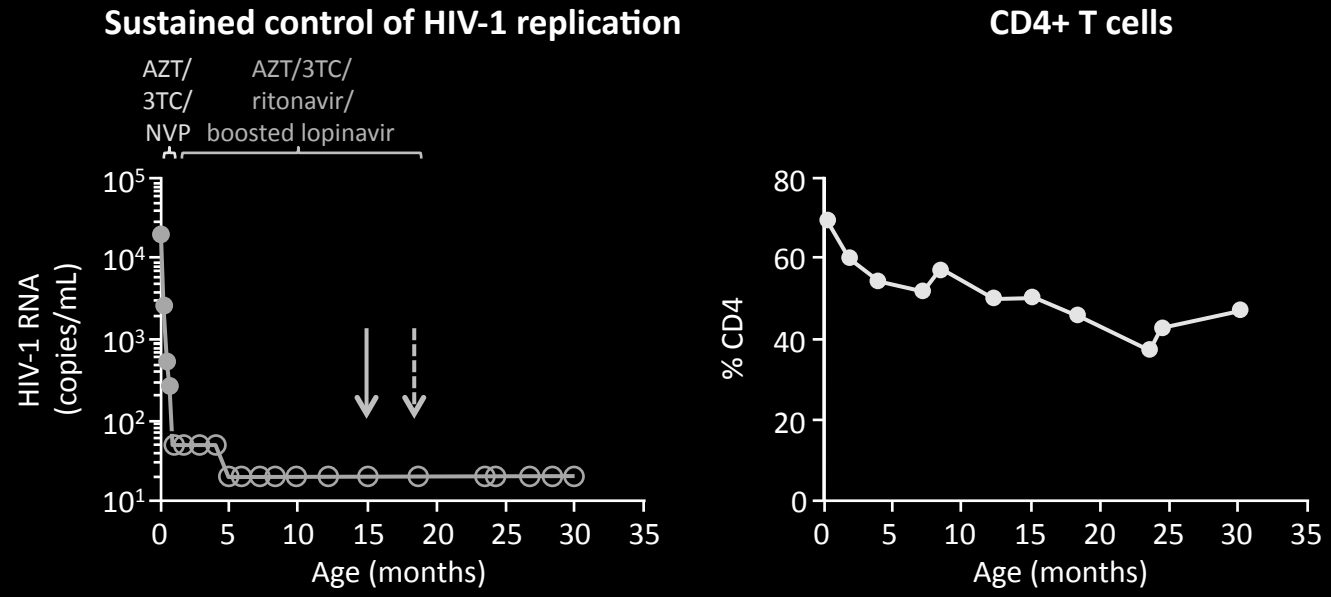
Virologic Studies to Detect Residual HIV in this Very-Early Treated Child

Measurement	Sample Type (amount of sample)	Age at Testing	Quantity (per 1 x 10^6 cells)	Number Cells Tested per well/ (No. Replicates positive)
Total Proviral DNA				
	PBMC	24-months	<2.7 [0]	122,000 (0/2)
		26-months	4.2 [0]	113,000 (1/6)
	Resting CD4+ T cells	24-months	<3.5 [0]	96,500 (0/3)
		26-months	<2.5 [0]	134,000 (0/6)
	Enriched for activated CD4+ T cells	24-months	<2.2 [0]	154,000 (0/6)
		26-months	<2.6 [0]	130,000 (0/6)
	Monocyte-derived adherent cells	24-months	37.6 [0]	14,300 (1/3)
		26-months	<11.5 [0]	29,000 (0/6)
Residual Viremia				
	Plasma	24-months	1- copy/ml	NA
		26-months	<2- copies/ml	NA
Infectious Virus Recovery	Resting CD4+ T cells	24-months	<1/ 22x10^6 IUMP (No HIV recovered)	NA

Persaud D, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 48LB.

Recent updates

- At 30 months of age, the patient had still not received ART since discontinuing at 18 months[1]
- HIV-RNA remains undetectable[1]
- An update at IAS 2013 also confirmed the absence of HIV-RNA at 33 months of age[2]

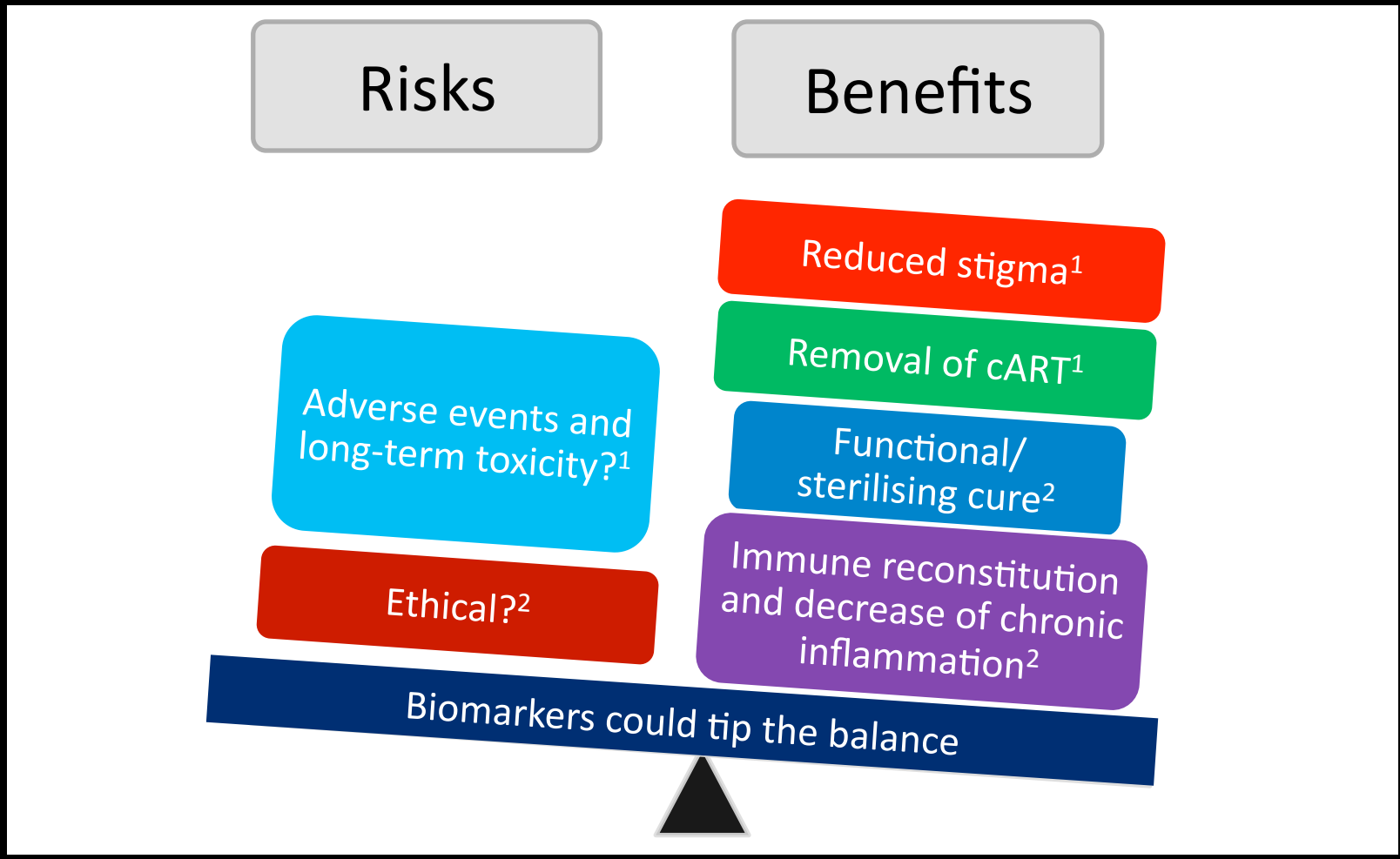


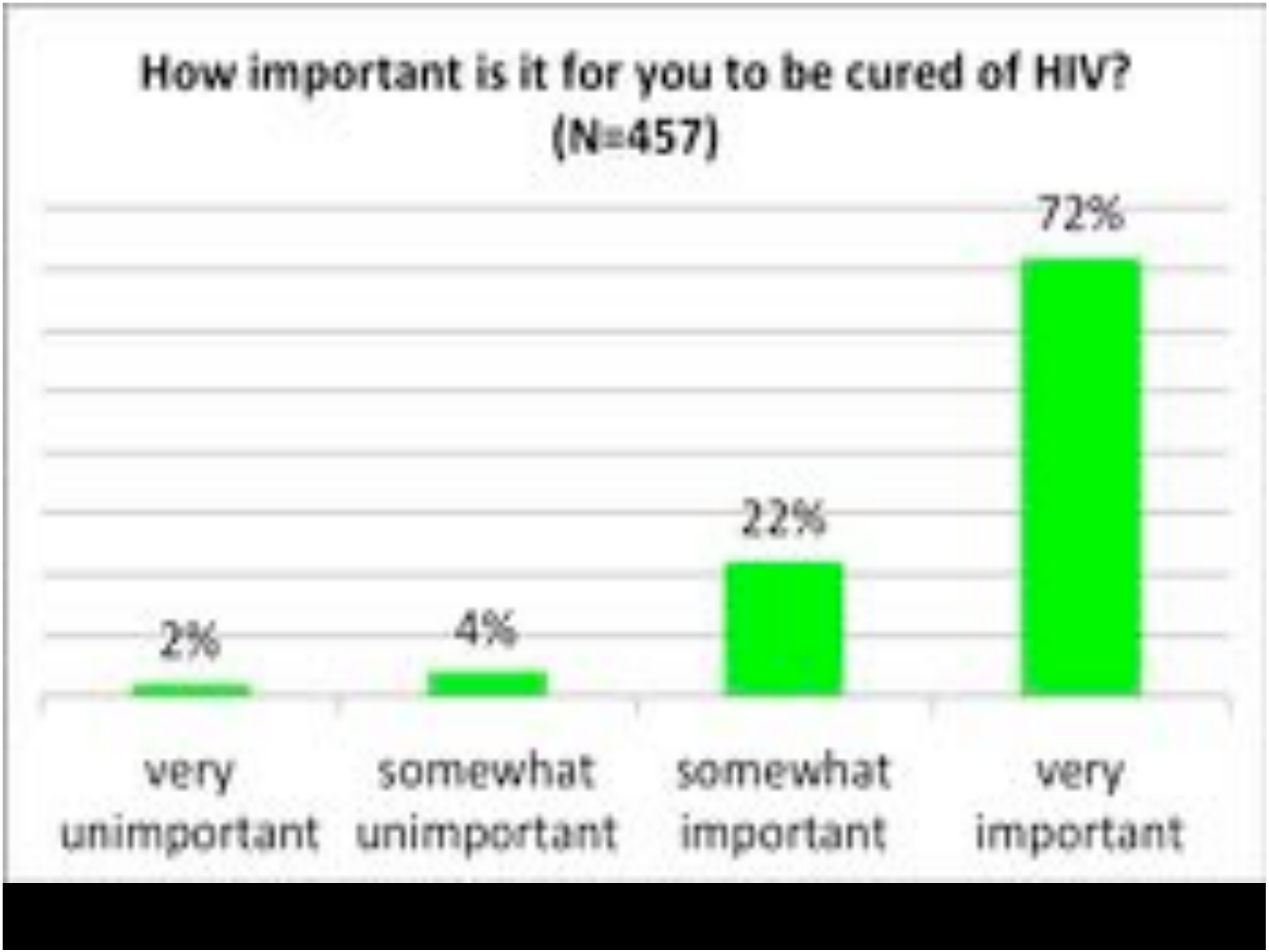
1. Persaud D, et al. N Engl J Med 2013;3691828-35. 2. Purcell D, et al. Retrovirology. 2013;10(1):134


HIV
CASE CURED

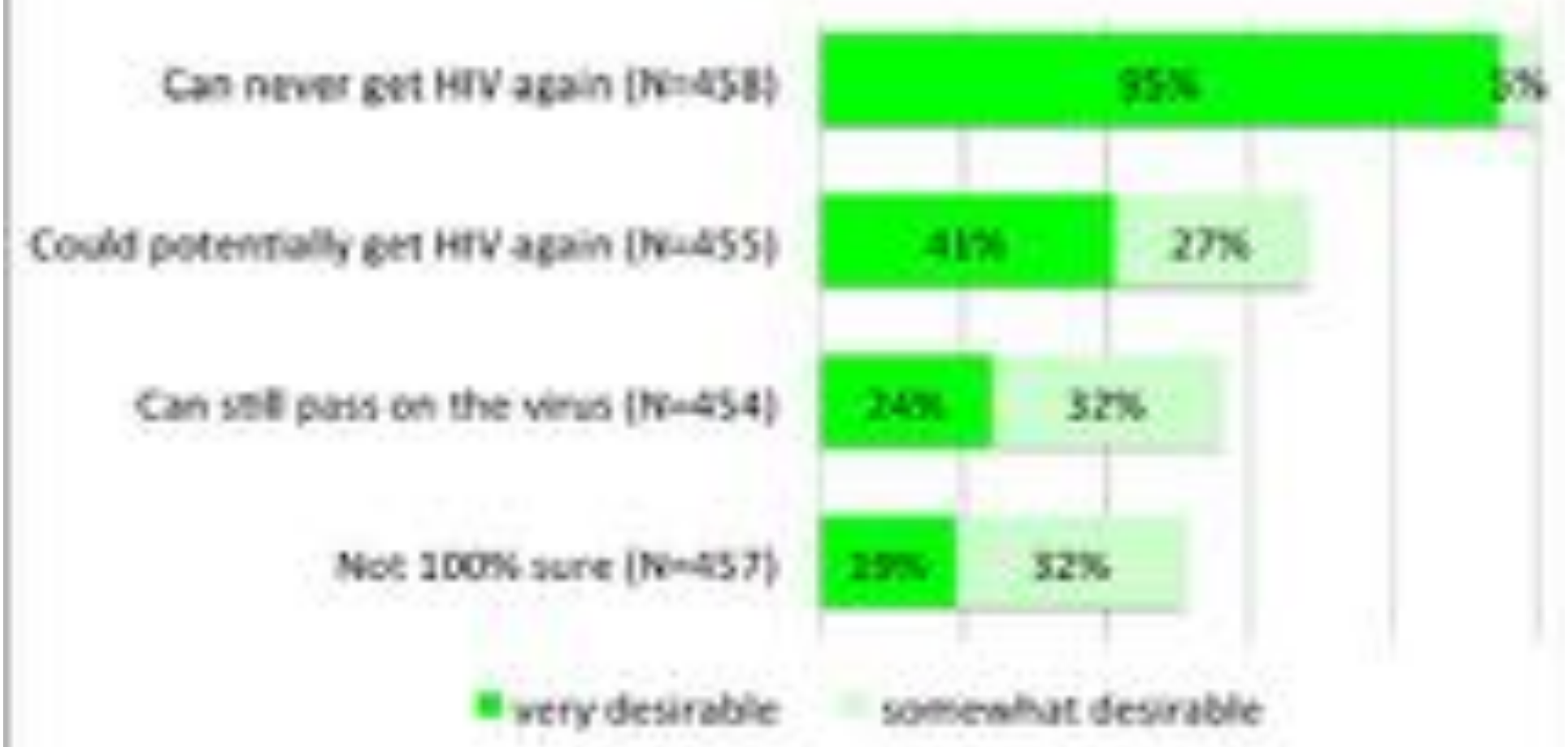

HERMAN BRIX
IN
A MILLION TO ONE
AN ELECTRIFYING DRAMA OF THE WORLD'S GREATEST SPORTS EVENT!

Cure research in HIV: risk and benefit




How important is it for you to be cured of HIV?
(N=457)
72%
22%
4%
2%
very unimportant
somewhat unimportant
somewhat important
very important

Desirability of HIV Cure?



Available Antiretrovirals 2015

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

- Efavirenz
- Nevirapine
- Etravirine
- Rilpivirine

Protease Inhibitors

- Atazanavir
- Darunavir
- Fos-Amprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Other Classes

Fusion inhibitors

- Enfuvirtide

R5 Inhibitors

- Maraviroc

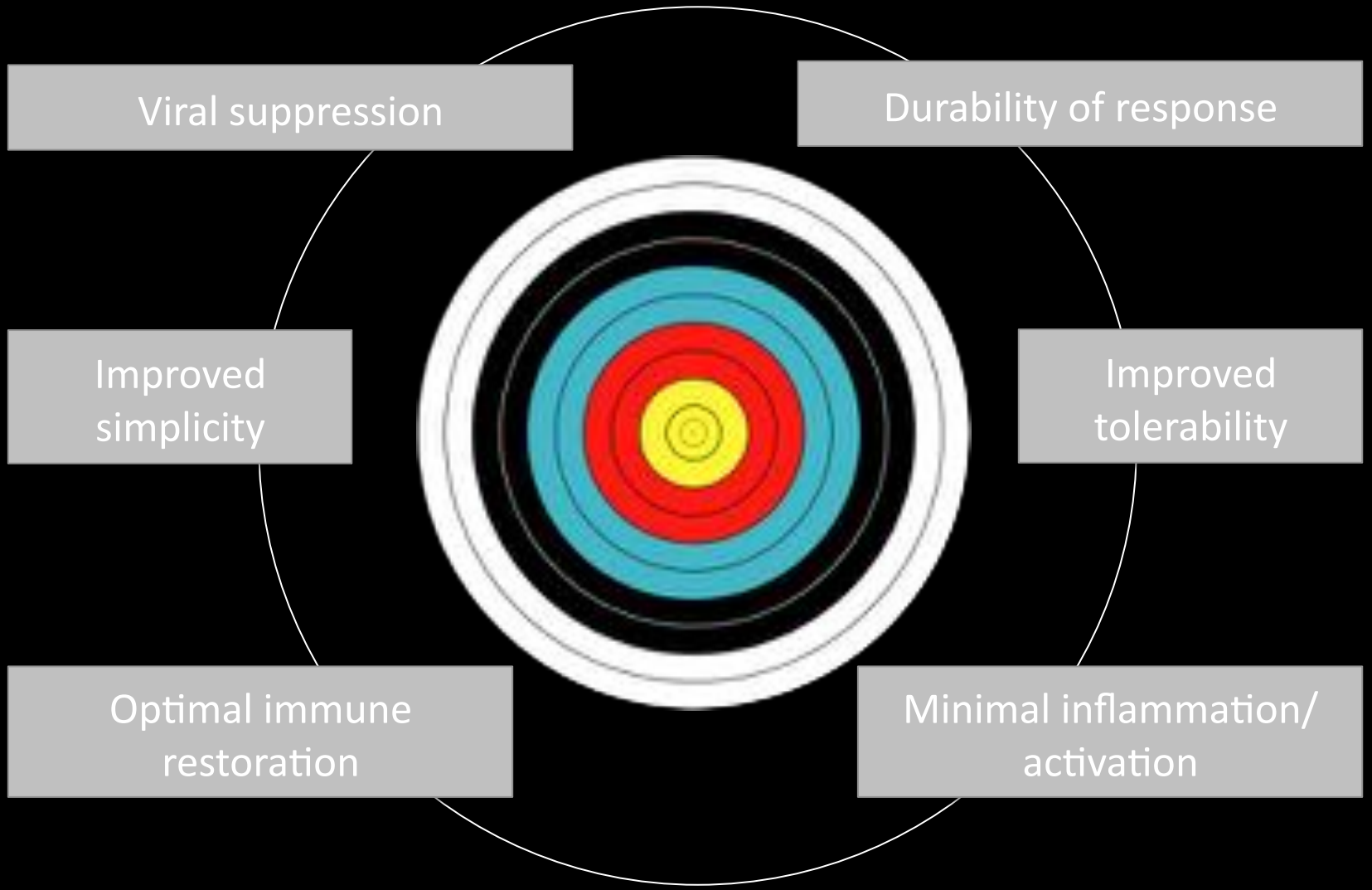
Integrase Inhibitors

- Raltegravir
- Elvitegravir
- Dolutegravir

STR

- TFV/ftc/EFZ
- TFV/ftc/EFZ
- TFV/ftc/cELV

Moving forward with cART: What is the target?



towards an
HIV
cure
people focused
science driven

Thank you

For further information please contact :

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