K|RITH KWAZULU-NATAL RESEARCH INSTITUTE FOR TUBERCULOSIS AND HIV

HPP
HIV Pathogenesis Programme
Doris Duke Medical Research Institute
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Acute HIV infection and HIV elite control: pathways to a vaccine and cure?

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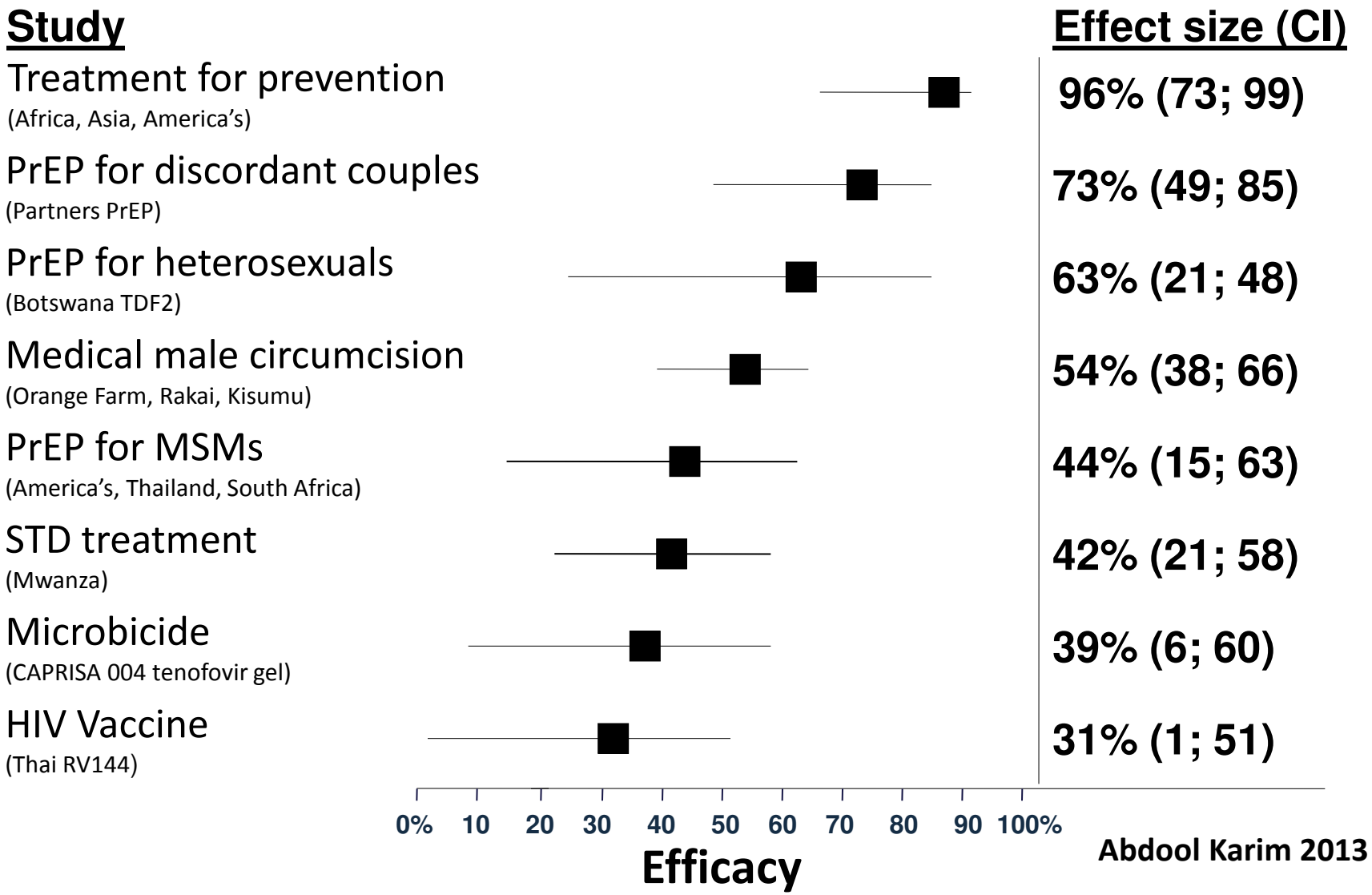
Advanced Workshop on AIDS Clinical Care (AWACC), 27 September 2013, Durban, South Africa

Overview of presentation

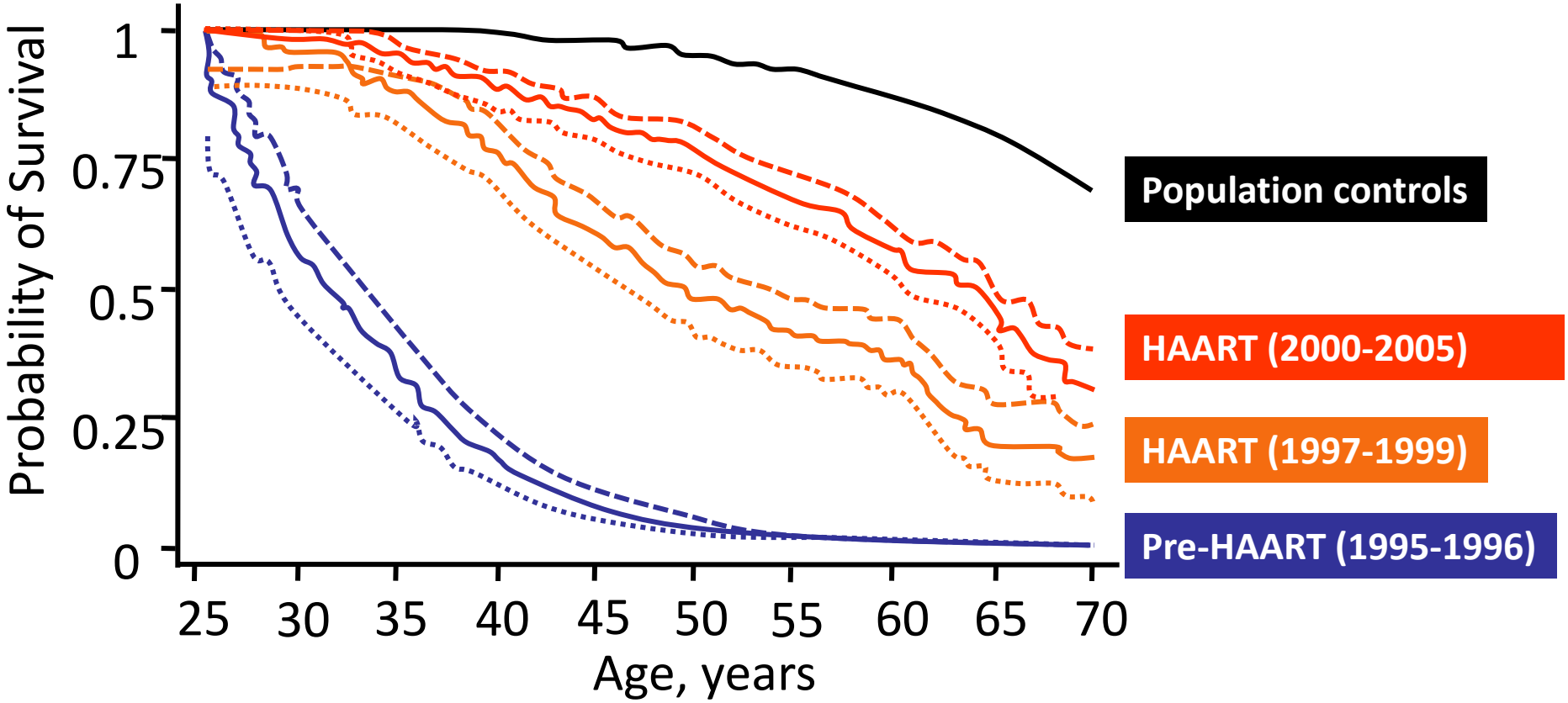
- Rationale for vaccine and cure strategies research
- Challenges and opportunities in vaccine and cure research
- Acute HIV infection
- Elite controllers (Dr Zaza Ndhlovu)

Clinical trial evidence for preventing sexual HIV transmission – July 2011



Abdool Karim 2013

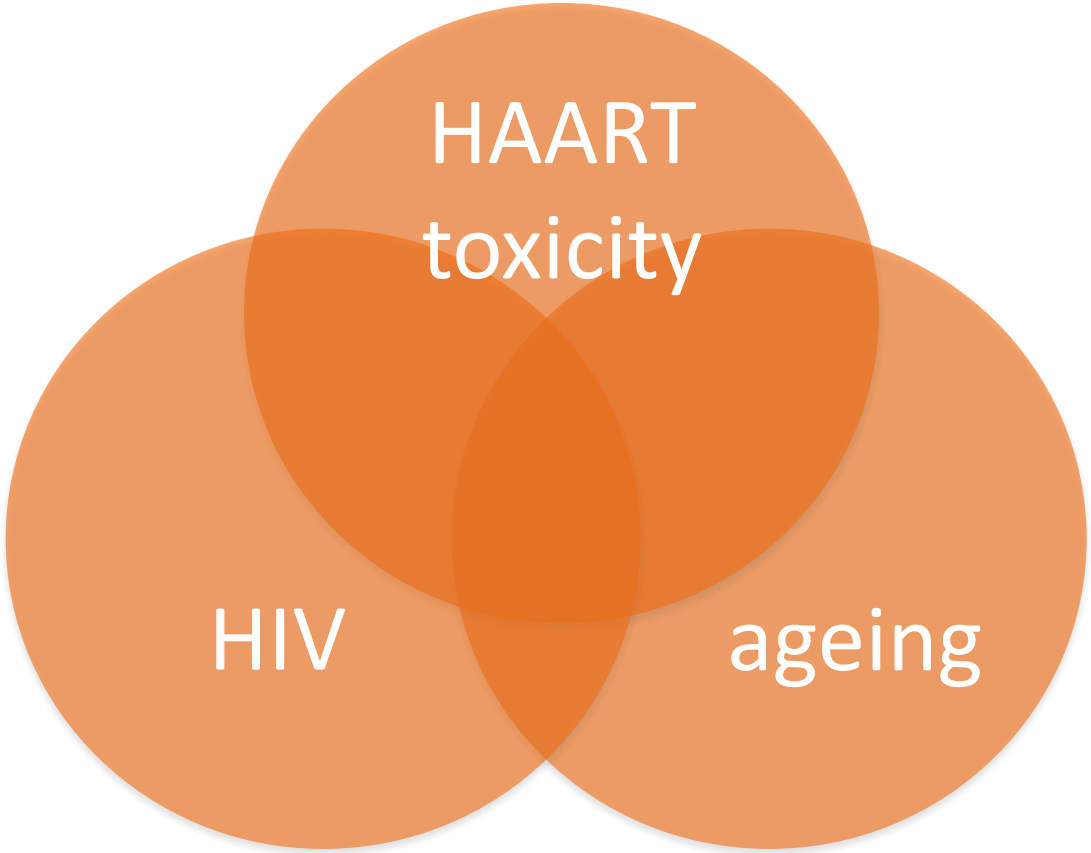
Full life expectancy not restored by HAART



Danish HIV Cohort study n=3,990; HIV neg controls n=379,872

Lohse et al., *Ann Int Med* 2007: 146: 87

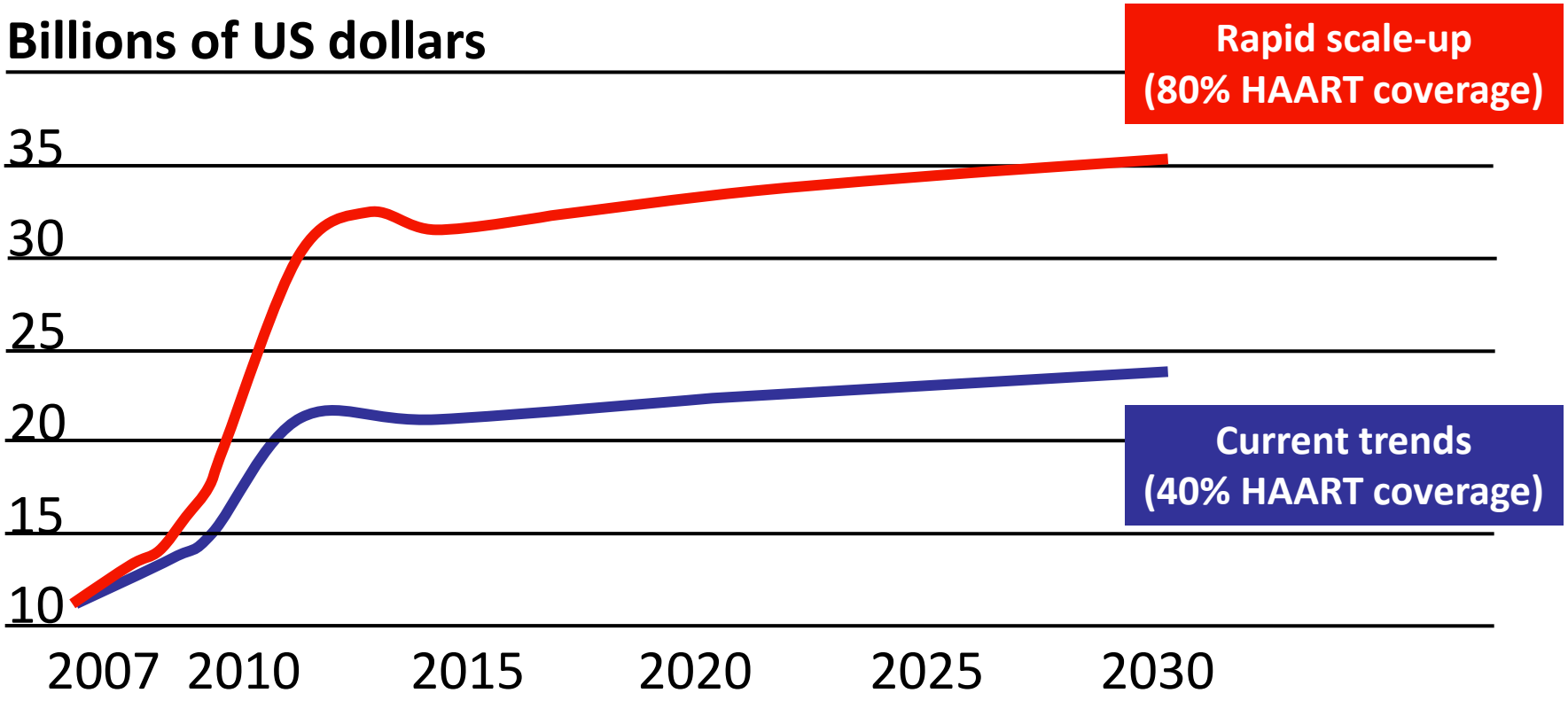
Significant morbidity persists on HAART



- Cardiovascular disease
- Metabolic disorders
- Neurocognitive abnormality
- Liver disease
- Renal disease
- Bone disorders
- Malignancy
- Frailty

Volberding PA and Deeks SG, *Lancet*. 2010; 376(9734):49-62.
ART cohort collaboration, *Clin Infect Dis* 2010; 50(10):1387–1396.

Total projected annual AIDS resource requirements



AIDS treatment costs alone will account for half the the US foreign aid budget by 2016

Hecht et al., *Health Affairs* 2009; 28: 1591; Bongaarts et al., *Science* 2010; 328: 1359

Major Infectious Disease Cases in U.S. before and after Vaccine Availability

Disease	Total Cases	Year	Cases in 1994	% Change
Diptheria	206,939	1921	2	-99.9%
Measles	894,134	1941	963	-99.9%
Mumps	152,209	1968	1537	-99.9%
Pertusis	265,269	1934	4617	-99.9%
Polio	12,269	1952	0*	100%
Rubella	57,686	1969	227	-99.9%
Tetanus	1,560	1923	51	-99.9%

Duration between discovery of microbiologic cause of selected infectious diseases and development of a vaccine

Disease	Years to develop vaccine
Typhoid	105
Haemophilus influenzae	92
Pertussis	89
Polio*	47
Measles	42
Hepatitis B	15
HIV	30…

*In the 1930s, two experimental polio vaccines failed because they were determined to be unsafe, and polio vaccines were almost abandoned.

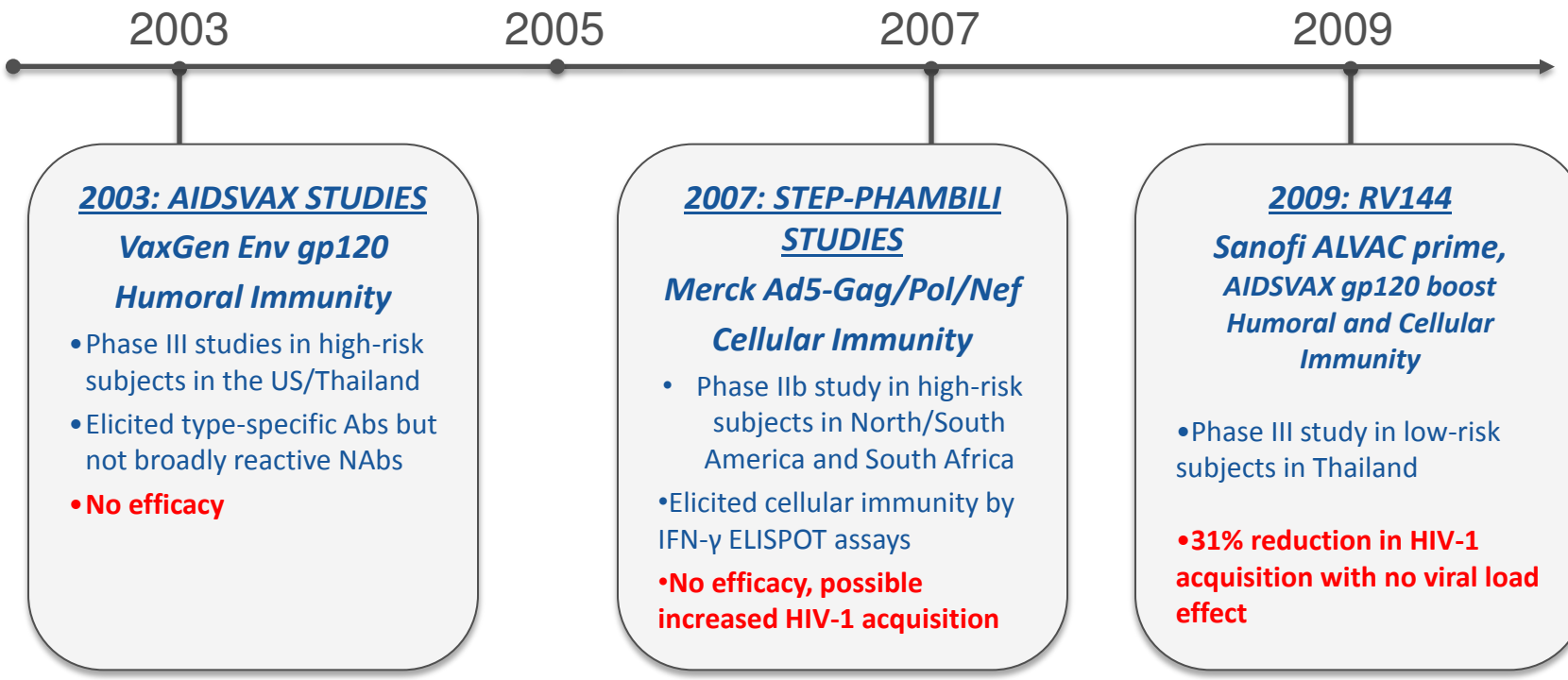
Source: Modified from H. Markel, NEJM, August 25, 2005

Vaccines in brief

- Effective disease prevention strategies
- Used for decades around the world, most commonly in children
- Very safe when manufactured and used properly
- Very cost-effective compared to treatment
- Eliminated smallpox worldwide, almost polio…

Past HIV Vaccine Concepts

Although only three concepts have undergone clinical efficacy testing to date, each HIV vaccine efficacy trial has yielded unexpected outcomes that have transformed the HIV landscape.



Advancing HIV vaccine candidates to efficacy trials will accelerate progress in the field, bringing us closer to an effective global vaccine.

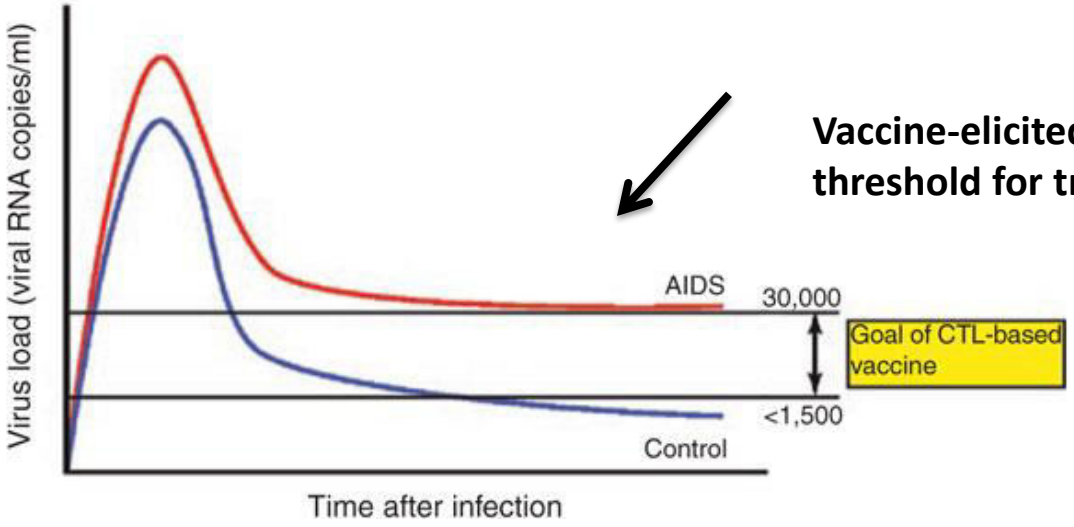
from Nelson Michael and Jerome Kim

June 2010

Why haven't these vaccines worked?-Scientific Obstacles

- The natural immune response to HIV infection does not eliminate the virus
- The natural immune response to HIV infection does not protect against superinfection
- Enormous sequence variability. We do not know how to construct an immunogen to cover this sequence variability
- We do not know what constitutes a protective immune response

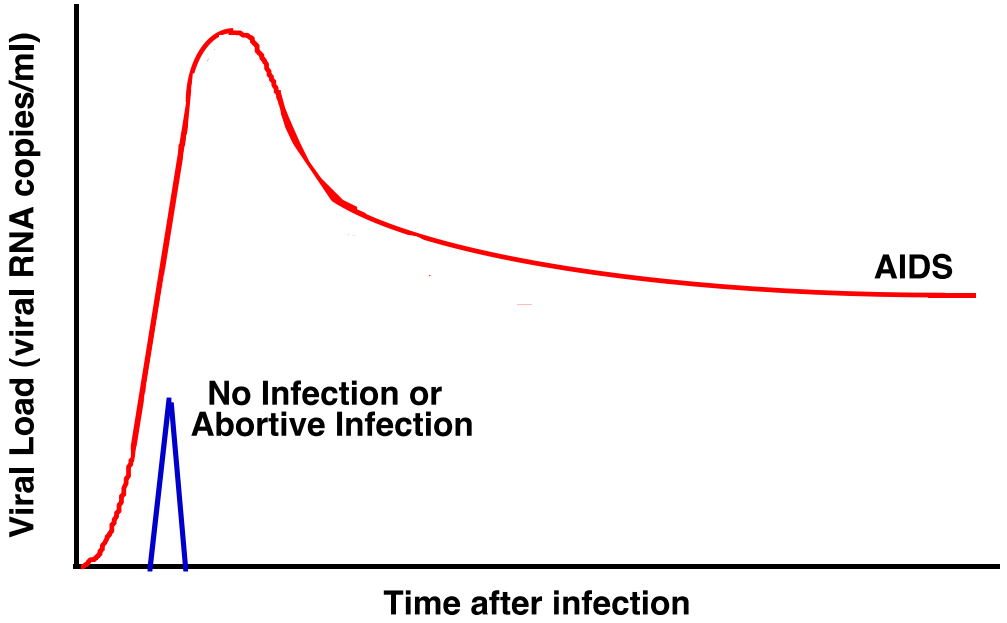
Evolution of a T cell HIV/AIDS Vaccine Paradigm



Vaccine-elicited immunity controls infection below threshold for transmission

New Paradigm:

Vaccine-elicited immunity prevents or aborts infection, or provides early complete control.



So, are we closer to developing a vaccine against HIV?

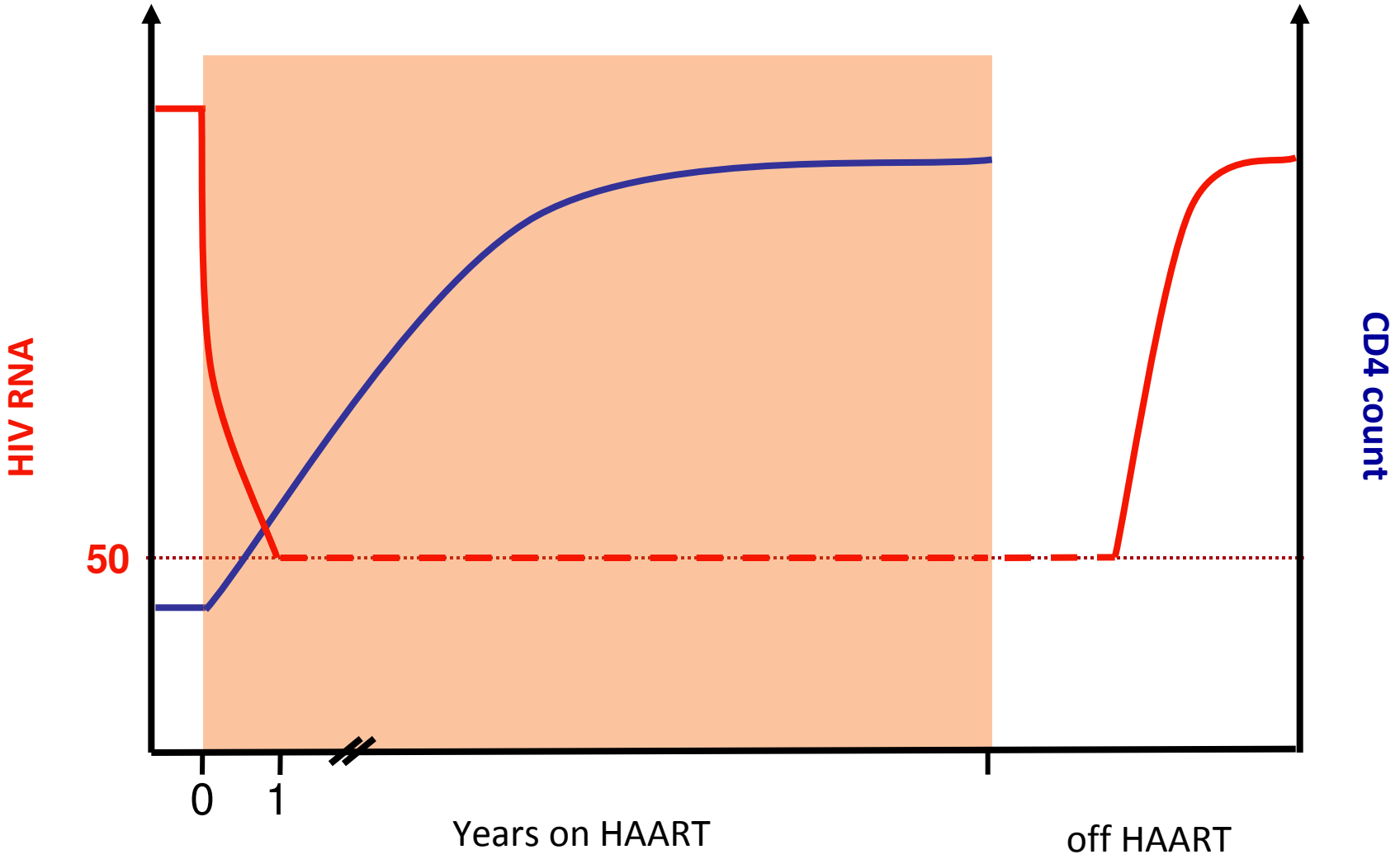
Most certainly YES...

- **First sign of protection in humans**
- **Significant advances in basic sciences**

BUT……

- **We probably need to expect more failures than successes**
- **A vaccine is NOT around the corner**
- **It will NOT be a magic bullet**
- **We need to do more basic and clinical research**
- **This effort needs public and government support**

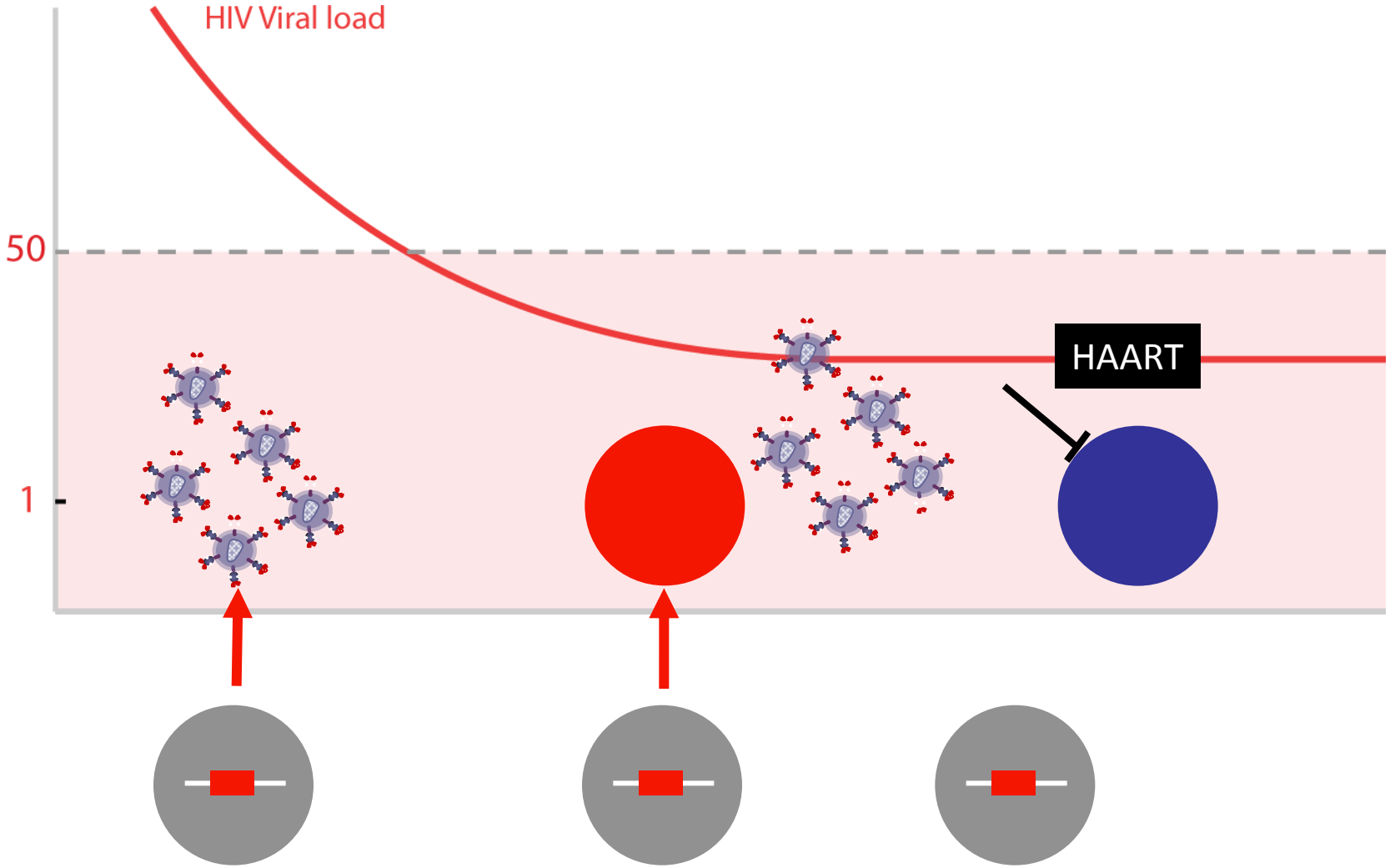
cART does not clear the virus even after many years



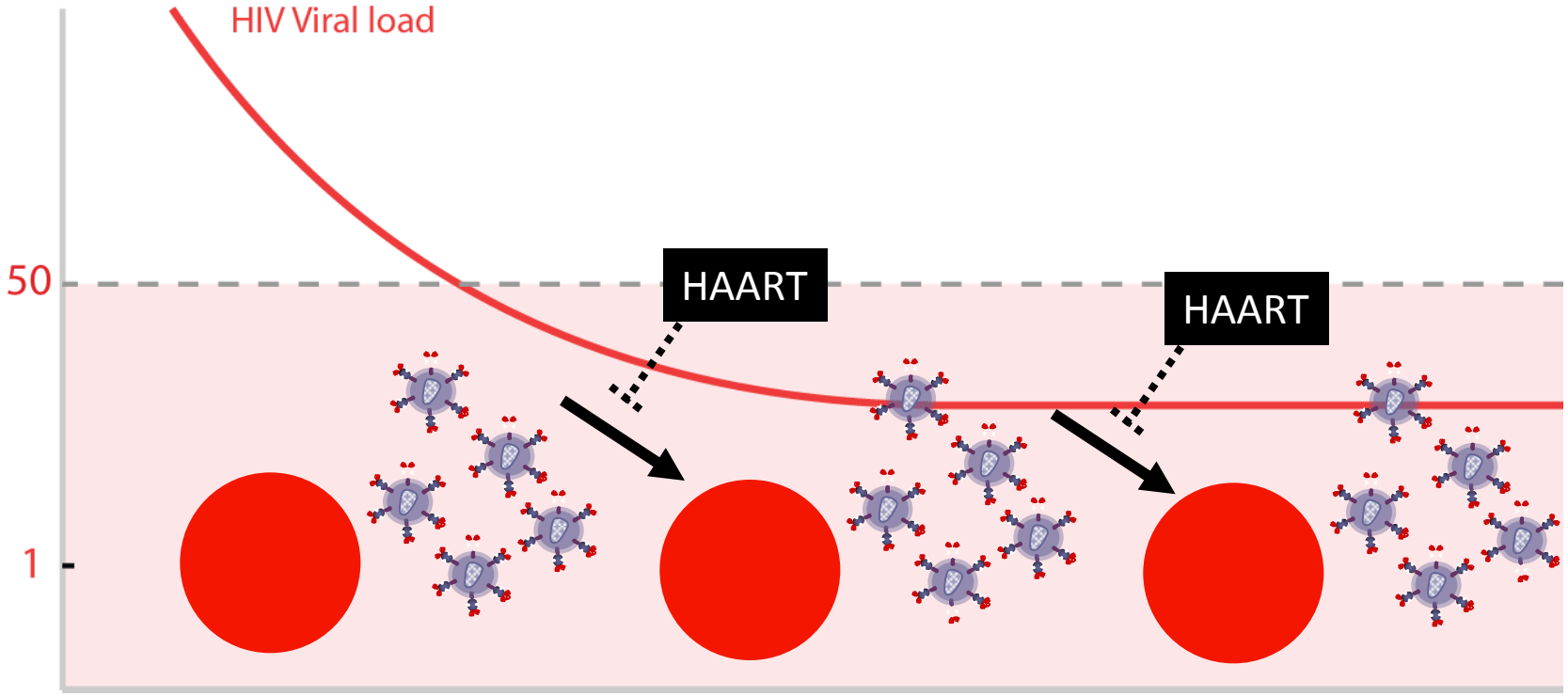
Barriers to cure

- Latently infected T-cells
- Residual viral replication
- Anatomical reservoirs

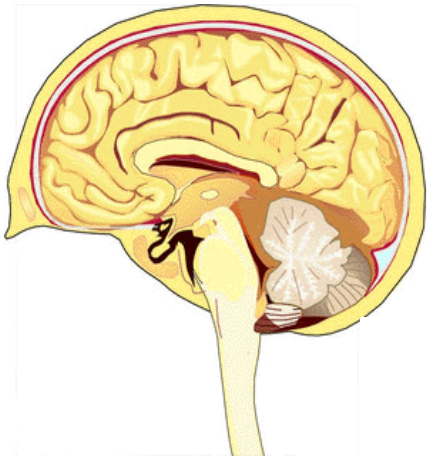
Latently infected T-cells

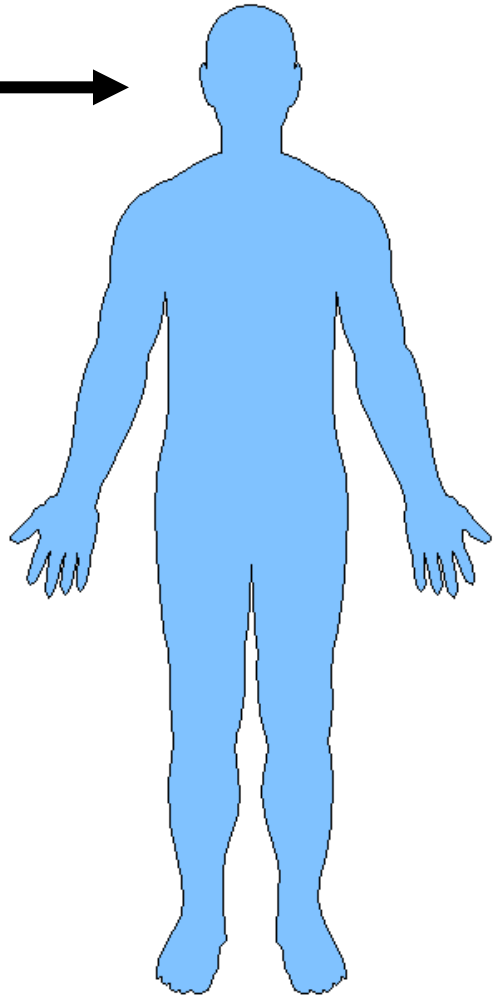


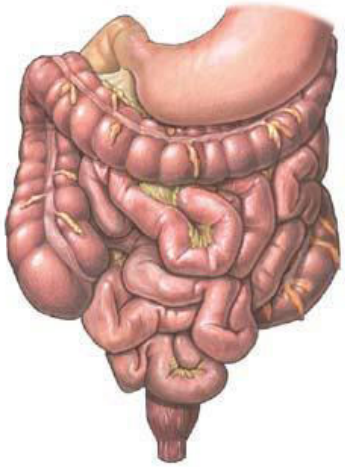
Residual viral replication

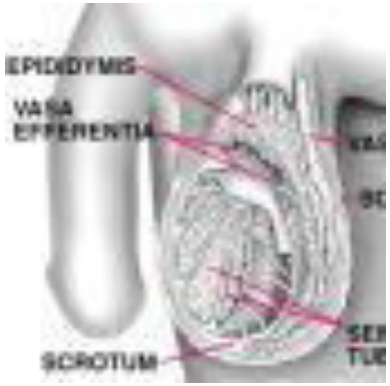


Anatomical reservoirs









Sterilising cure: lessons learned

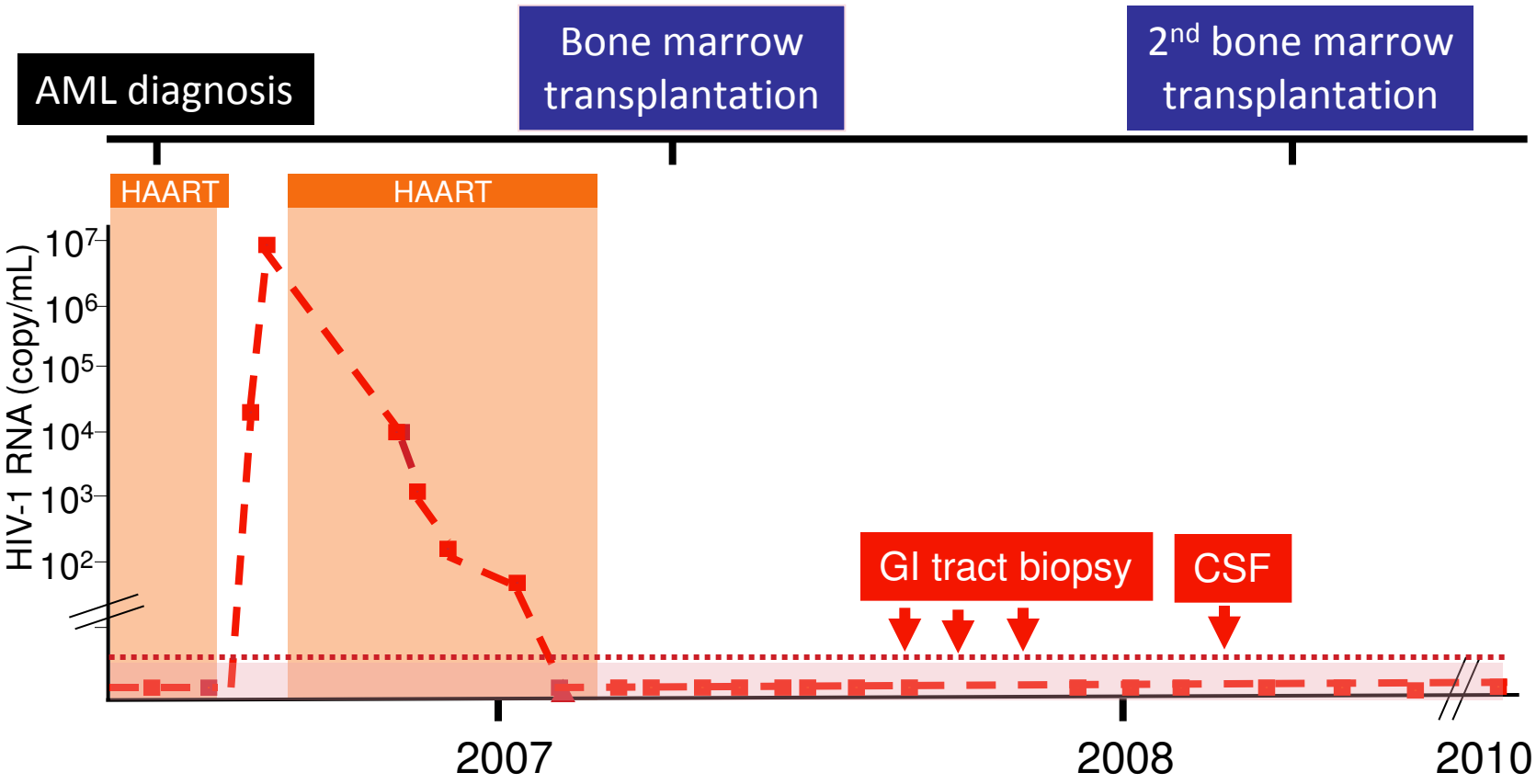
BRIEF REPORT

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

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

Hutter et al., *N Engl J Med*, 2009; 360:692

Sterilising cure: lessons learned



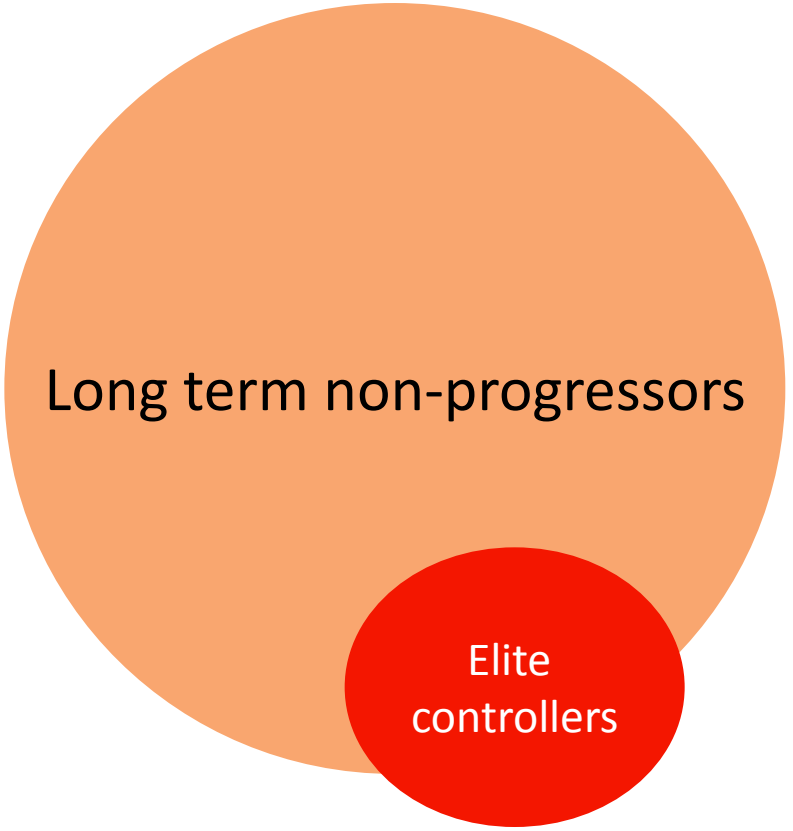
- Latently infected cells can be eliminated
- Anatomical reservoirs can decay
- Complete viral suppression without HAART is possible

Hutter et al., *N Engl J Med*, 2009; 360:692

Functional cure: elite controllers

- Strong HIV-specific CD4+ and CD8+ responses

- Long term effects
  - Loss of CD4 (7%)
  - Ongoing virus replication and evolution
  - Immune activation increased



Martinez V et al., J Infect Dis 2005; 191: 2053; Deeks and Walker, *Immunity* 2007; 27:406; Hunt et al., *J Infect Dis* 2008 ;197:126; Hatano et al., *J Virol* 2009; 83: 329; Pereyra et al., *J Infect Dis* 2009; 200:984; O'Connell et al., *J Virol* 2010: May 5 (epub)

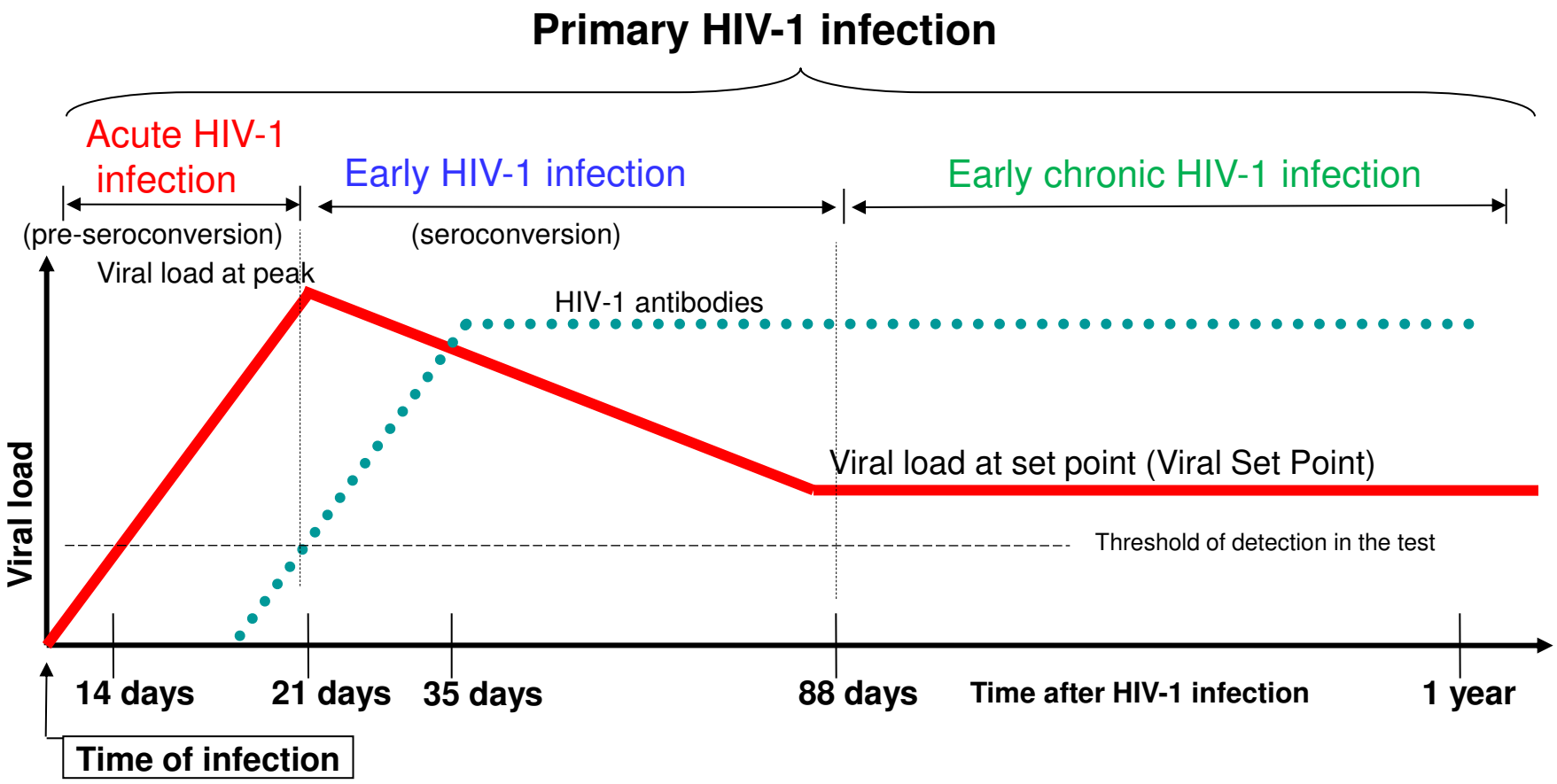
Strategies for cure

- Optimise HAART
  - Intensification
  - Early treatment
- Eliminate latently infected cells
- Make cells “resistant” to HIV

Reasons for hope for a cure

- Berlin patient- functionally cured after CCR5Δ32 homozygous bone marrow transplant
- Mississippi baby
- Two Boston patients- cure after “normal” bone marrow transplants

Acute, early and primary HIV-1 infection

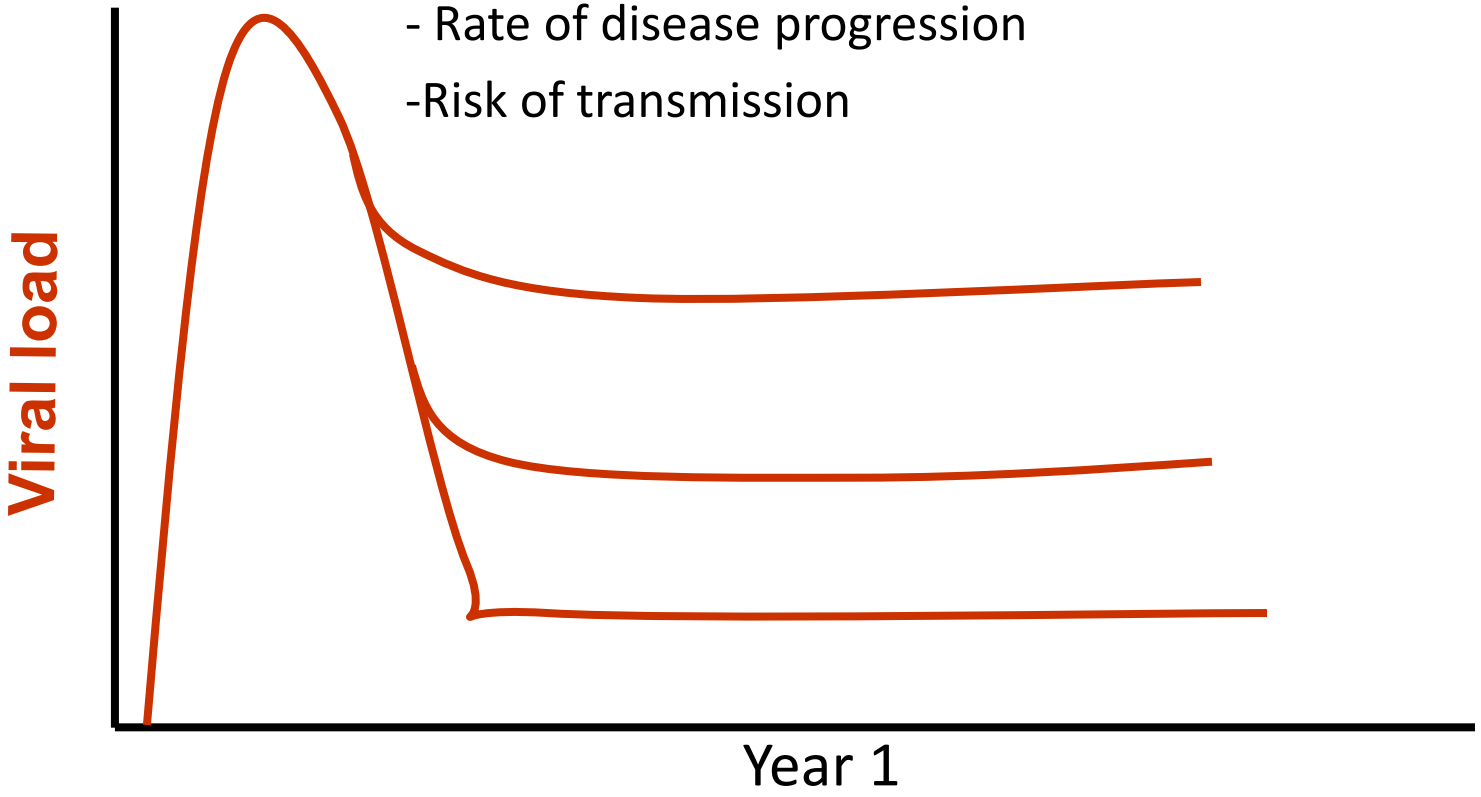


Immune responses, viral factors, host factors?

There is heterogeneity in viral load set point following acute HIV-1 infection

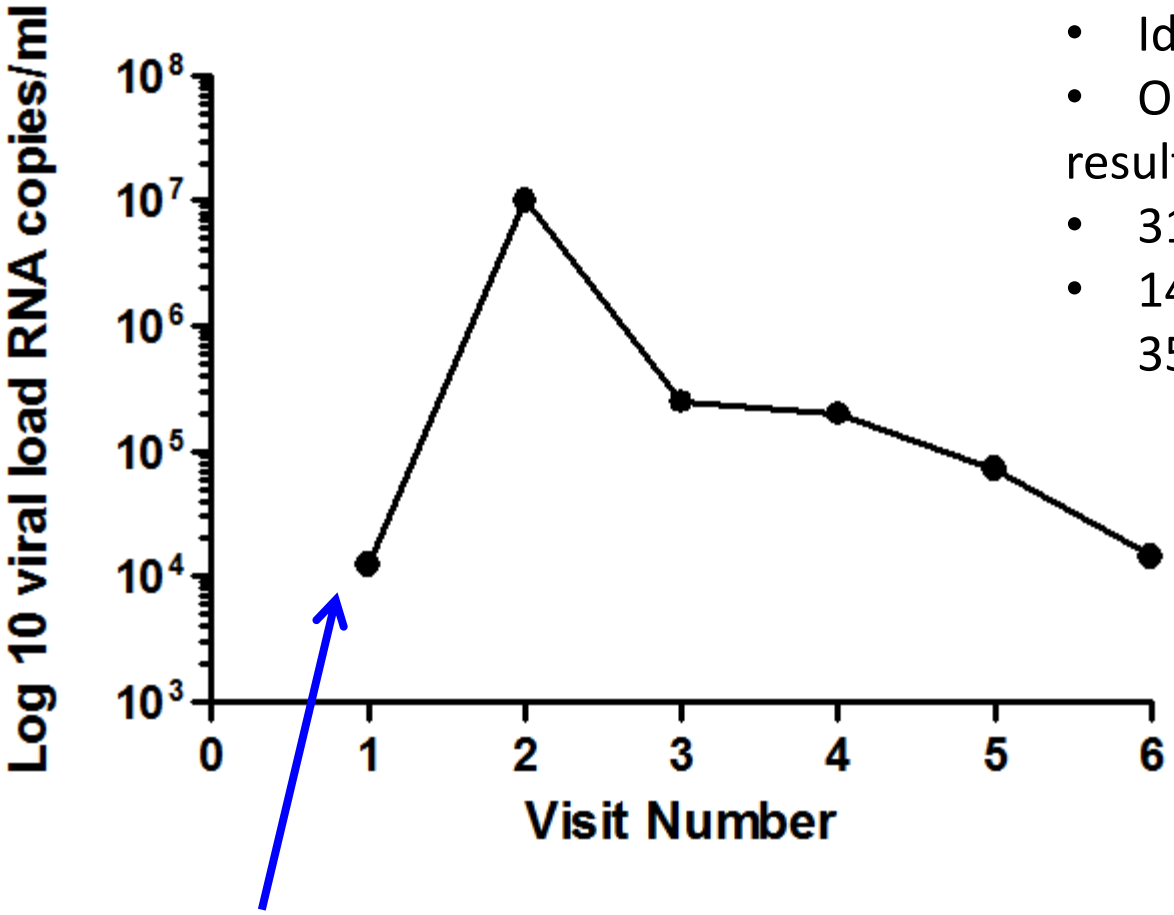
Viral set point is a predictor for:

- Rate of disease progression
-Risk of transmission



Key questions: What factor or combination of factors determines viral load set point?

Typical patient recruited with acute HIV infection



- Screened 12, 425 cases
- Identified 106 cases
- Only 65 cases returned for results
- 31 in longitudinal follow-up
- 14/31 CD4 count less than 350 cells/ml within 2 years.

Viral RNA positive,
HIV-1 antibody negative

Challenges of acute infection studies

- Very narrow window of opportunity to identify people with acute HIV infection
- Very expensive (RNA screening, very many have to be screened to identify a case)
- Follow-up of cases and retention are a challenge
- Current or upcoming interventions such as post-exposure prophylaxis are challenging for AI studies

What have we learnt?

- In most cases only a single variant of HIV-1 is transmitted
- Early events are very important in determining the subsequent course of disease
- Gag-specific immune responses associate with viral control in early (but not acute) HIV-1 infection
- Limited and ineffective immune responses may partially explain the failure of the immune system to contain the virus. Limited immune responses in acute/early HIV infection are not fully explained by immune escape mutations.
- Replicative fitness of the virus is associated with lower viral load set point but there is high transmission of immune escape variants which could diminish immune responses

Future directions

- Understand the quality and (barriers) of effective immune responses in acute HIV-1 infection
- Consequences and impact of transmission and selection of immune-driven polymorphisms
- Define the precise balance between effective immune responses and viral replicative capacity required for viral containment
- Better understanding of acute or early immune dysfunction may be key to vaccine design
- Early treatment- prevent reservoir formation and possible cure?

Acknowledgements

UKZN

- Jaclyn Wright
- Mopo Radebe
- Kamini Gounder
- Mammekwa Mokgoro
- Fundisiwe Chonco
- Manjeetha Jaggernath
- Saleha Omarjee
- Sinikithemba study team
- HPP acute infection study team

Simon Fraser University

- Mark Brockman
- Zabrina Brumme

Harvard/MGH

- Bruce Walker
- Marcus Altfeld

Microsoft Research

- David Heckerman
- Jonathan Carlson

University of Oxford

- Philip Goulder

Acknowledgements

Funding

- NIH
- Ragon Institute of MGH, MIT and Harvard University
- South African DST/NRF
- International AIDS Vaccine Initiative
- Howard Hughes Medical Institute
- Victor Daitz Foundation

- For more information on the HPP AI study:
- Dr Aveshen Govender: 0842244242