Preventive and therapeutic HIV vaccines

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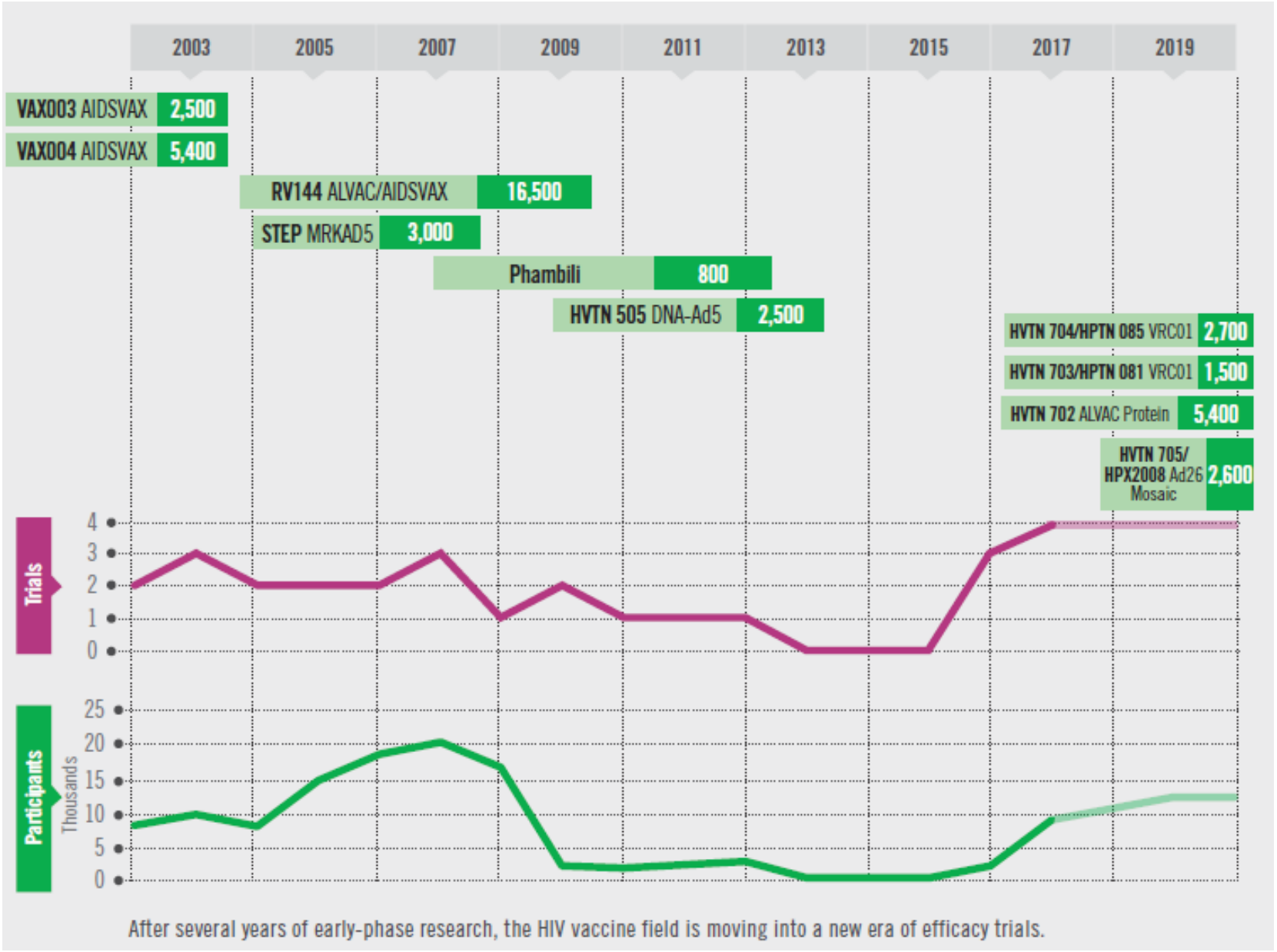
Disclosures

- No conflicts to declare

Background

- FAQ: by patients and colleagues
- Publication about “promising results”, especially in the non-medical press
- Vaccines are by far the most effective weapon in epidemics
- Most clinical vaccine trials were not very convincing, but vaccine trials have a revival



After several years of early-phase research, the HIV vaccine field is moving into a new era of efficacy trials.

Questions

- What would you guess was the effectiveness of the 2017/2018 Influenza vaccine?

A. 20%
B. 40%
C. 60%
D. 80%
E. >90%

Questions

- What would you guess was the effectiveness of the 2017/2018 Influenza vaccine?

A. 20%
B. **40%**
C. 60%
D. 80%
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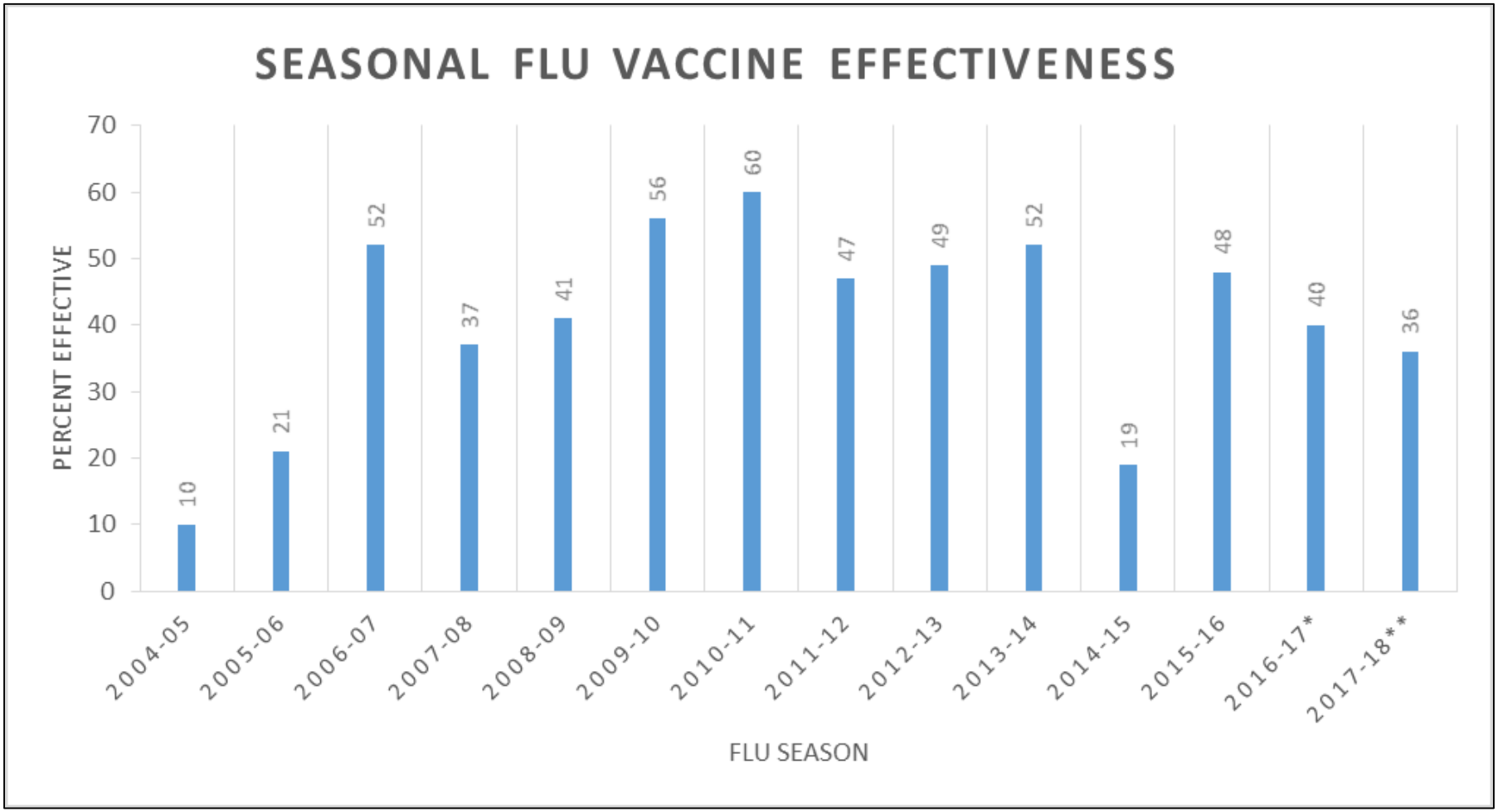

Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD) - www.cdc.gov/flu

Questions

- What would you guess was the **one** year effectiveness of the first, large published HIV vaccine trial in Thailand?

A. 20%
B. 40%
C. 60%
D. 80%
E. >90%

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2009 VOL. 361 NO. 23

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*

Rerks-Ngarm S *et al., N Engl J Med.* 2009 Dec 3;361(23):2209-20

The NEW ENGLAND

4 priming injections of a recombinant canarypox vector vaccine ALVAC-HIV [vCP1521]

+

2 booster injections of a recombinant glycoprotein 120 subunit vaccine AIDSVAX B/E

for the MOPH–TAVEG Investigators*

Rerks-Ngarm S *et al., N Engl J Med.* 2009 Dec 3;361(23):2209-20

The NEW ENGLAND

4 priming injections of a recombinant canarypox vector vaccine ALVAC-HIV [vCP1521]

+

2 booster injections of a recombinant glycoprotein 120 subunit vaccine AIDSVAX B/E

"prime-boost" schedule
based on the dual ability of canarypox viruses to induce cellular responses and **prime** for an antibody responses
that could be **boosted** with recombinant envelope proteins

for the MOPH–TAVEG Investigators*

Rerks-Ngarm S *et al., N Engl J Med.* 2009 Dec 3;361(23):2209-20

A Sound Rationale Needed for Phase III HIV-1 Vaccine Trials

Dennis R. Burton,[1] Ronald C. Desrosiers,[2] Robert W. Doms,[3] Mark B. Feinberg,[4] Robert C. Gallo,[5] Beatrice Hahn,[6] James A. Hoxie,[3] Eric Hunter,[6] Bette Korber,[7] Alan Landay,[8] Michael M. Lederman,[9] Judy Lieberman,[2] Joseph M. McCune,[10] John P. Moore,[11] Neal Nathanson,[3] Louis Picker,[12] Douglas Richman,[13] Charles Rinaldo,[14] Mario Stevenson,[15] David I. Watkins,[16] Steven M. Wolinsky,[17] Jerome A. Zack[18]

"We have a concern about the wisdom of the U.S. government's sponsoring a recently initiated phase III trial in Thailand…"

Burton DR *et al., Science.* 2004 Jan 16;303(5656):316

The NEW ENGLAND

4 priming injections of a recombinant canarypox vector vaccine ALVAC-HIV [vCP1521]

+

2 booster injections of a recombinant glycoprotein 120 subunit vaccine AIDSVAX B/E

26.676 screened ➔ 16.402 enrolled ➔ 12.542 received all doses

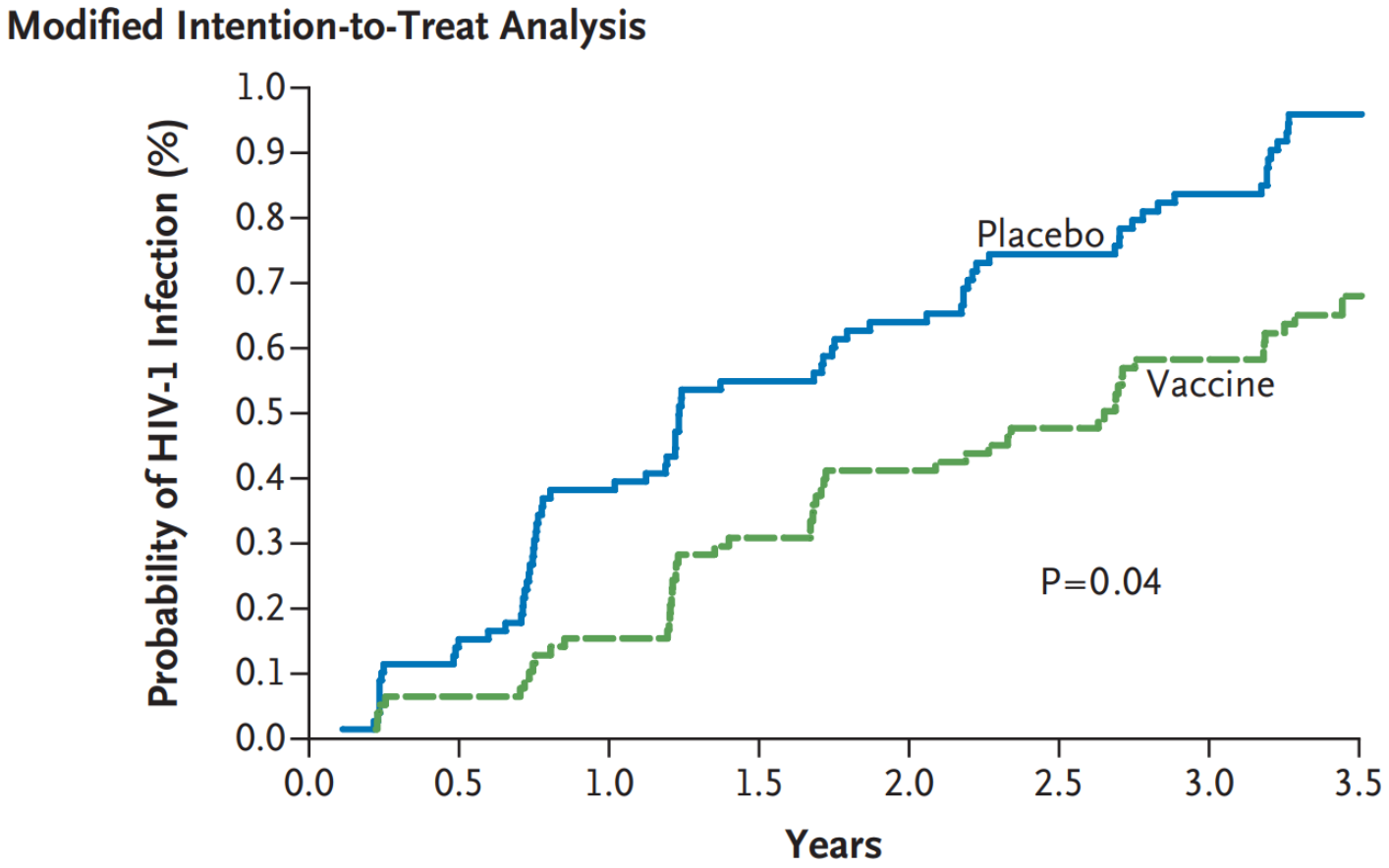
132 HIV seroconversions (56 verum *vs* 76 placebo)

for the MOPH–TAVEG Investigators*

Rerks-Ngarm S *et al., N Engl J Med.* 2009 Dec 3;361(23):2209-20

"Thai-Trial" (RV144)

Phase III: RV144 Sanofi ALVAC prime, AIDSVAX gp120 boost

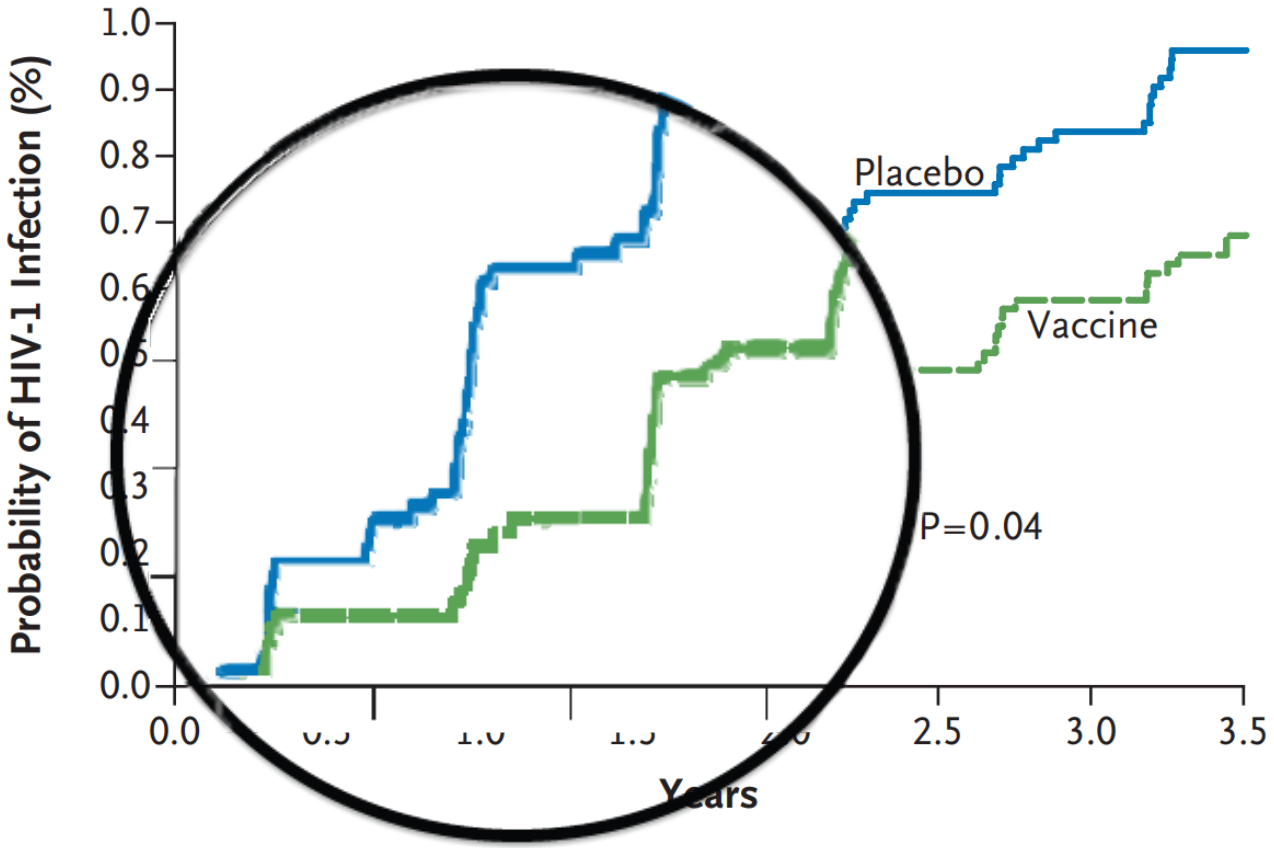


Rerks-Ngarm S *et al., N Engl J Med.* 2009 Dec 3;361(23):2209-20

"Thai-Trial" (RV144)

Phase III: RV144 Sanofi ALVAC prime, AIDSVAX gp120 boost

Modified Intention-to-Treat Analysis

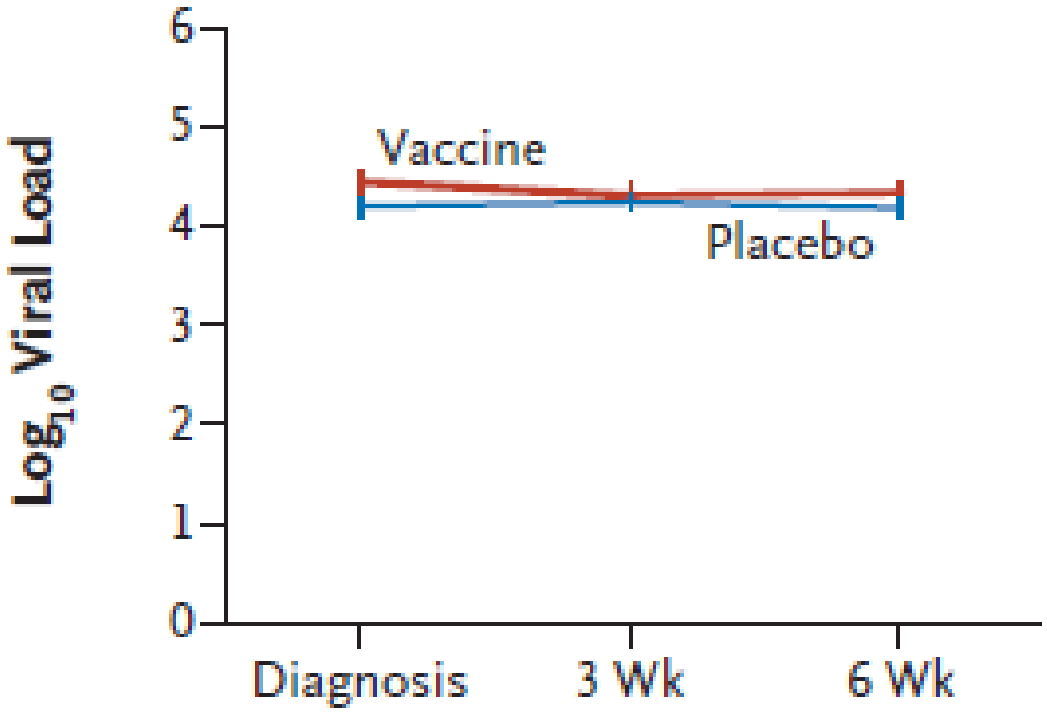


Est. VE = 31.2%; 95% CI 1.1-52.1%

Rerks-Ngarm S *et al., N Engl J Med.* 2009 Dec 3;361(23):2209-20

"Thai-Trial" (RV144)

The receipt of vaccine did not have a significant effect on the viral load in subjects who were found to have early HIV-1 infection



Rerks-Ngarm S *et al., N Engl J Med.* 2009 Dec 3;361(23):2209-20

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 5, 2012 VOL. 366 NO. 14

Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial

Barton F. Haynes, M.D., Peter B. Gilbert, Ph.D., M. Juliana McElrath, M.D., Ph.D., Susan Zolla-Pazner, Ph.D., Georgia D. Tomaras, Ph.D., S. Munir Alam, Ph.D., David T. Evans, Ph.D., David C. Montefiori, Ph.D., Chitraporn Karnasuta, Ph.D., Ruengpueng Sutthent, M.D., Ph.D., Hua-Xin Liao, M.D., Ph.D., Anthony L. DeVico, Ph.D., George K. Lewis, Ph.D., Constance Williams, B.S., Abraham Pinter, Ph.D., Youyi Fong, Ph.D., Holly Janes, Ph.D., Allan DeCamp, M.S., Yunda Huang, Ph.D., Mangala Rao, Ph.D., Erik Billings, Ph.D., Nicos Karasavvas, Ph.D., Merlin L. Robb, M.D., Viseth Ngauy, M.D., Mark S. de Souza, Ph.D., Robert Paris, M.D., Guido Ferrari, M.D., Robert T. Bailer, Ph.D., Kelly A. Soderberg, Ph.D., Charla Andrews, Sc.M., Phillip W. Berman, Ph.D., Nicole Frahm, Ph.D., Stephen C. De Rosa, M.D., Michael D. Alpert, Ph.D., Nicole L. Yates, Ph.D., Xiaoying Shen, Ph.D., Richard A. Koup, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Jaranit Kaewkungwal, Ph.D., Sorachai Nitayaphan, M.D., Ph.D., Supachai Rerks-Ngarm, M.D., Nelson L. Michael, M.D., Ph.D., and Jerome H. Kim, M.D.

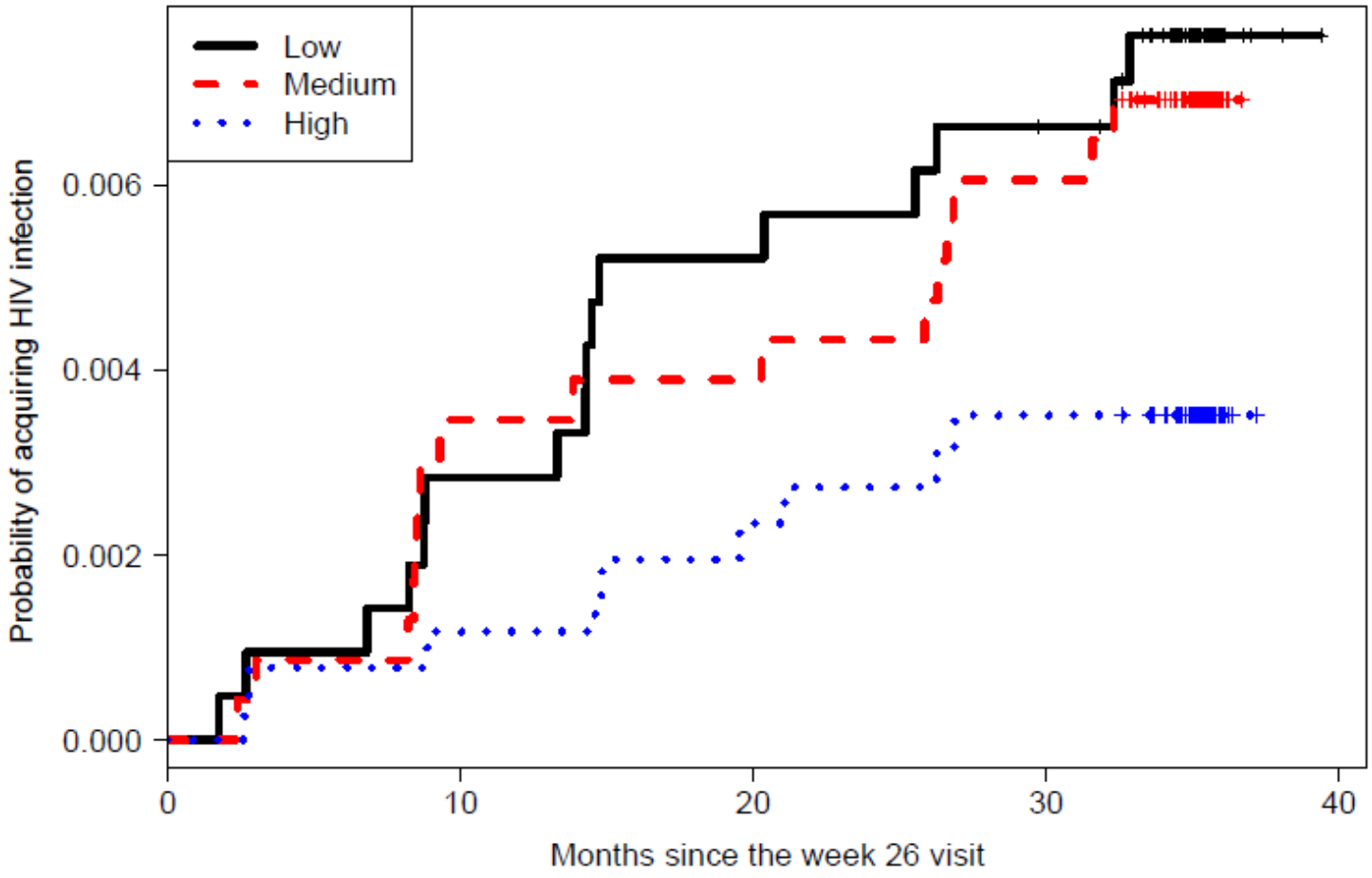
Haynes BF *et al., N Engl J Med.* 2012 Apr 5;366(14):1275-86

The binding of IgG antibodies to variable regions 1 and 2 (V1V2) of HIV-1 envelope proteins (Env) correlated inversely with the rate of HIV-1 infection

Variable	Odds ratio	P-value	Q-value
IgA Binding to Envelope Panel	1.54	0.027	0.08
IgG Avidity A244 gp120	0.81	0.37	0.56
ADCC AE.HIV-1 Infected CD4 Cells	0.92	0.68	0.68
Tier 1 Neutralizing Antibodies	1.37	0.22	0.45
IgG Binding to gp70-V1V2	0.57	0.015	0.08
CD4+ T Cell Intracellular Cytokines	1.09	0.61	0.68

Haynes BF *et al., N Engl J Med.* 2012 Apr 5;366(14):1275-86

The first study showing that a biomarker predicted the outcome



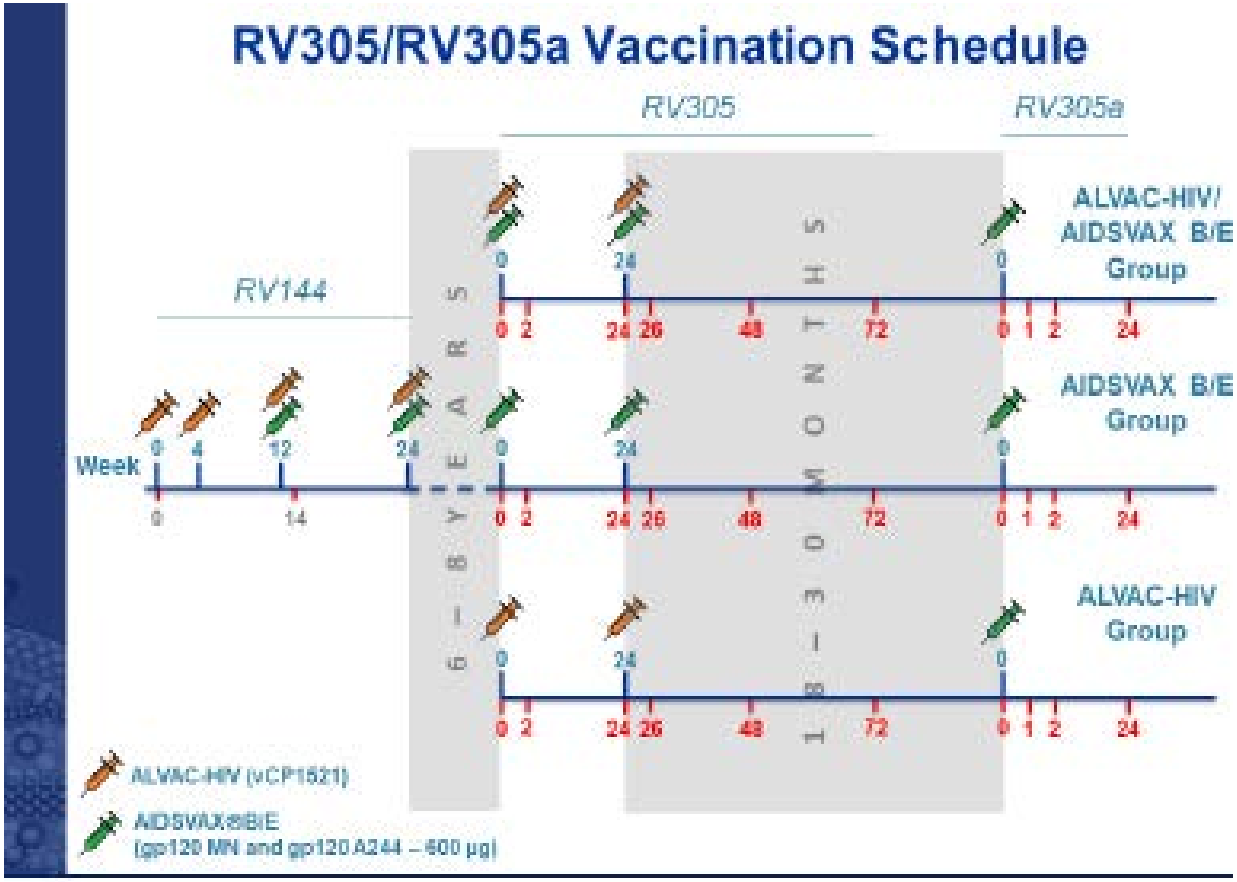
Haynes BF *et al., N Engl J Med.* 2012 Apr 5;366(14):1275-86

#306

Additional Boost of AIDSVAX B/E Further Increased RV305 IgG but not IgA Antibodies

Akapirat S[1], Vasan S[1,2], Rerks-Ngarm S[3], Punnee Pitisuttithum P[4], Smith K S[1], Rittiboongrad S[1], Puangkaew J[1], Phogat S[5], Sinangil F[6], Michael NL[7], Excler JL[8], Kim JH[9], Karasavvas N[9], and O'Connell RJ[1], on behalf of the RV306 Study Group

1) Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; 2) The Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA; 3) Ministry of Public Health, Nonthaburi, Thailand; 4) Mahidol University, Bangkok, Thailand; 5) Novartis Vaccines, Emeryville, CA, USA; 6) Global Solutions for Infectious Diseases, South San Francisco, CA, USA; 7) US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA; 8) International Vaccine Institute, Seoul, Republic of Korea; 9) Virus Diseases Branch, Walter Reed Army Institute of Research, Silver Spring, MD, USA



Akapirat S *et al.* 18th CROI, Boston, March 4–7, 2018

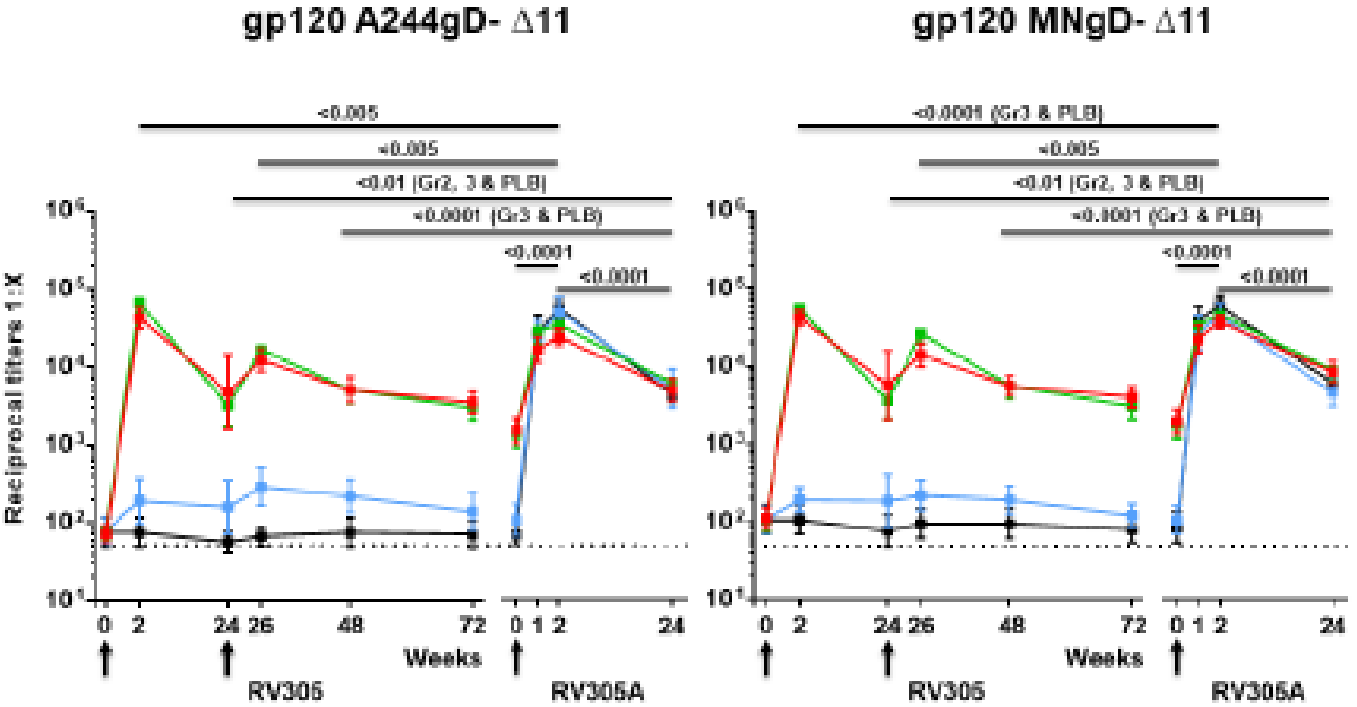
#306

Additional Boost of AIDSVAX B/E Further Increased RV305 IgG but not IgA Antibodies

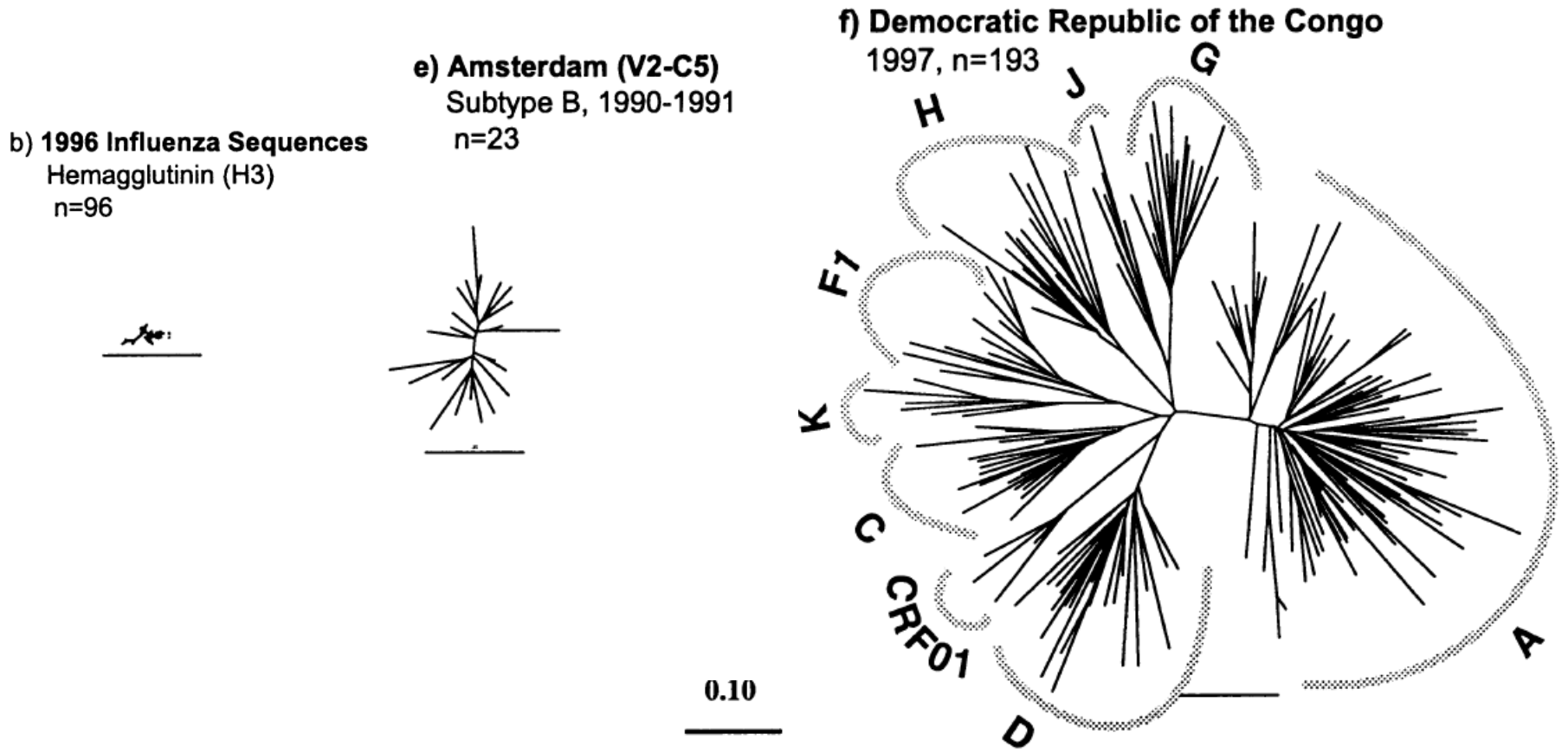
Akapirat S[1], Vasan S[1,2], Rerks-Ngarm S[3], Punnee Pitisuttithum P[4], Smith K S[1], Rittiboongrad S[1], Puangkaew J[1], Phogat S[5], Sinangil F[6], Michael NL[7], Excler JL[8], Kim JH[9], Karasavvas N[9], and O'Connell RJ[1], on behalf of the RV305 Study Group

1) Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; 2) The Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA; 3) Ministry of Public Health, Nonthaburi, Thailand; 4) Mahidol University, Bangkok, Thailand; 5) Merck Research Laboratories, Blue Bell, PA, USA; 6) Global Solutions for Infectious Diseases, South San Francisco, CA, USA; 7) US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA; 8) International Vaccine Institute, Seoul, Republic of Korea; 9) Virus Diseases Branch, Walter Reed Army Institute of Research, Silver Spring, MD, USA

Additional boost of AIDSVAX B/E increased levels of IgG responses to gp120 in all groups



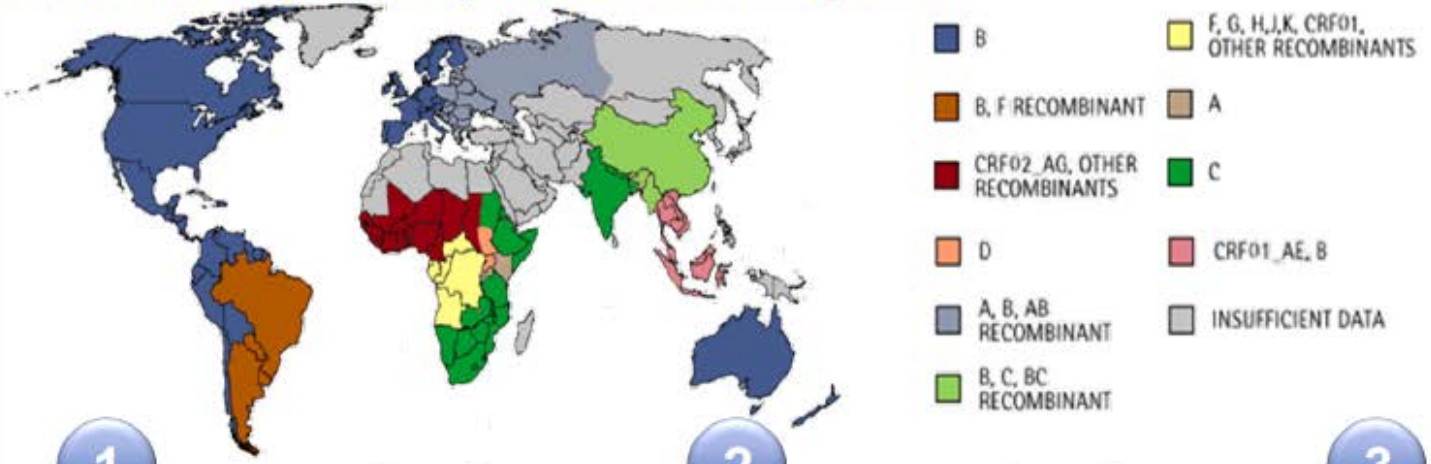
A comparison between HIV and influenza virus illustrates the extraordinary scale of HIV variation, and underscores the importance of exploring innovative HIV vaccine strategies



Modified from Korber B *et al., Br Med Bull.* 2001;58:19-42

High Level Target Product Profile Goal:

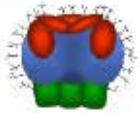
Prophylactic vaccine offering protection against all clades of HIV-1 through an heterologous prime boost regimen



1 Vectors that elicit optimal immune responses

2 Mosaic inserts for global coverage (Gag-Pol-Env)

3 Trimeric env proteins for improved humoral immunity



Theory behind therapeutic vaccines

- Deliver non-infectious HIV antigens
- Antigens processed and presented to CD4-, CD8- and B-cells
- Elimination / reduction of latent HIV reservoir due to enhanced immune response
- Induction of a bnAb

reviewed in Streeck H *et al., Nat Med.* 2013 February ; 19(2): 143–149.

Types of therapeutic vaccines

- DNA and RNA encoding for HIV antigens
- Viral vectors: canarypox (ALVAC), Modified Vaccinia Ankara strain (MVA), adenoviruses, lentiviruses
- HIV protein or peptide vaccines
- Dendritic cell vaccines

reviewed in Fleury H *et al., AIDS Res Hum Retroviruses* 2018 Jan;34(1):27-30.

Problems of therapeutic and preventive vaccinations

- Lots of new, attractive methods (not just in the HIV field), some show very promising results in animal studies

- To prove the efficacy in humans
  - Therapeutic vaccines: treatment interruptions, biomarkers, endpoints?
  - Preventive vaccines: different vaccine in different regions, minimal incidence rate (e.g. 3% per year) required?

HIV reservoir and cure research

Casper Rokx
Erasmus University Medical Center
Rotterdam, the Netherlands

Conflict of interest

- None related to this conference

- Outside this conference:
  - Involved in grants from Gilead, Merck
  - Advisory boards for Gilead, ViiV
  - Travel reimbursement of Gilead, Merck, ViiV
  - Lectures for Gilead, ViiV, Virology Education

The purpose is to understand the factors involved to come to an HIV cure

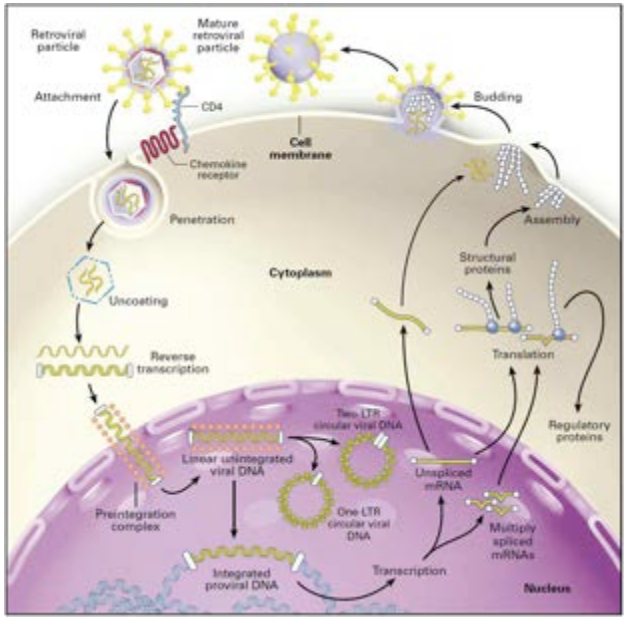
- The answer for cure is in the reservoir

- HIV Reservoir
  - Where is it?
  - How to measure it?
  - What does it?

- Cure strategies
  - How to target the reservoir?
  - Pitfalls? (And challenges for you!)

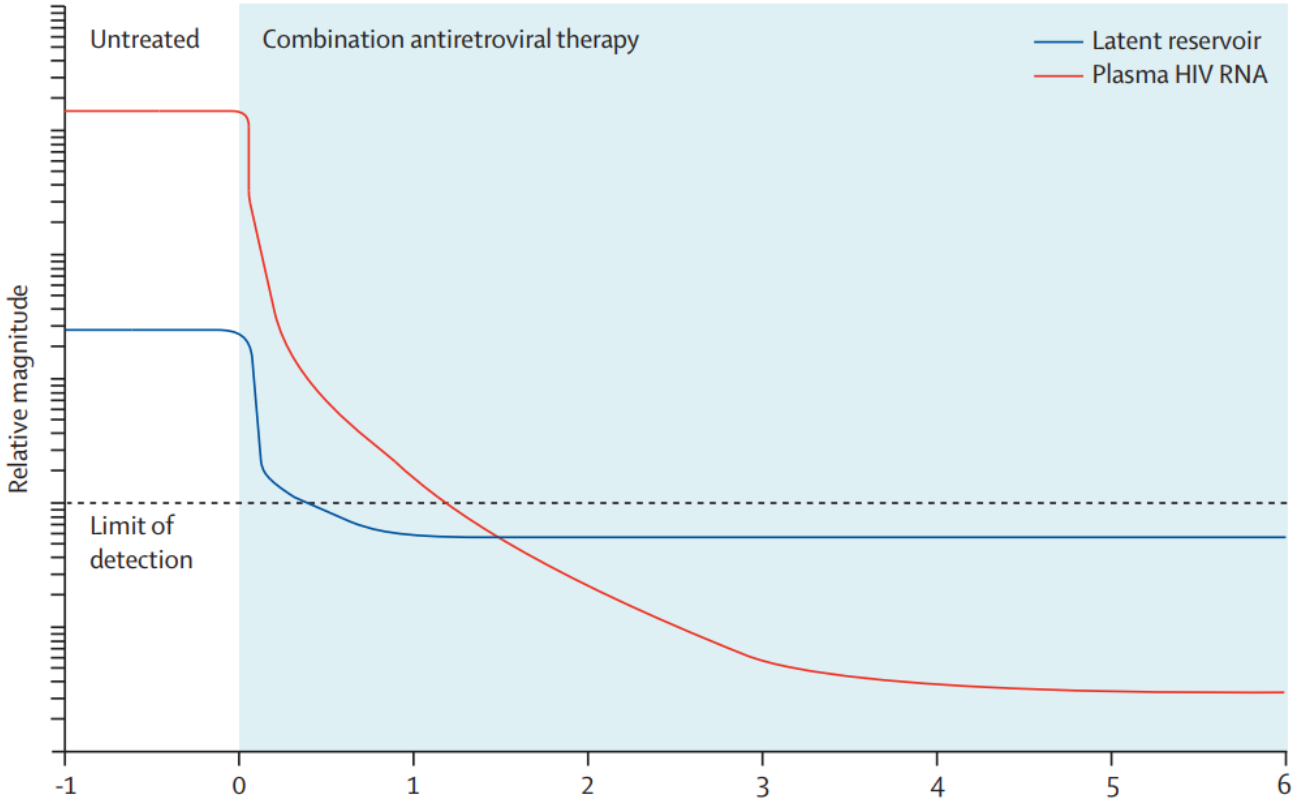
Definition of the HIV reservoir (non peer reviewed)

The integrated HIV-DNA in the host genome of long lived human mononuclear cells that is BOTH capable to produce a virus that is replication competent AND successful in host immunity evasion



Picture from Furtado MR *et al., N Engl J Med.* 1999 May 27;340(21):1614-22

Natural course of the reservoir

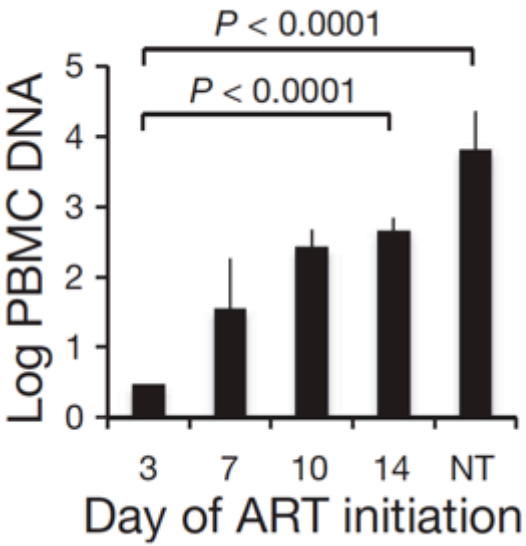


- HIV reservoir:
  - Where is it?
  - How to measure it?
  - What does it?

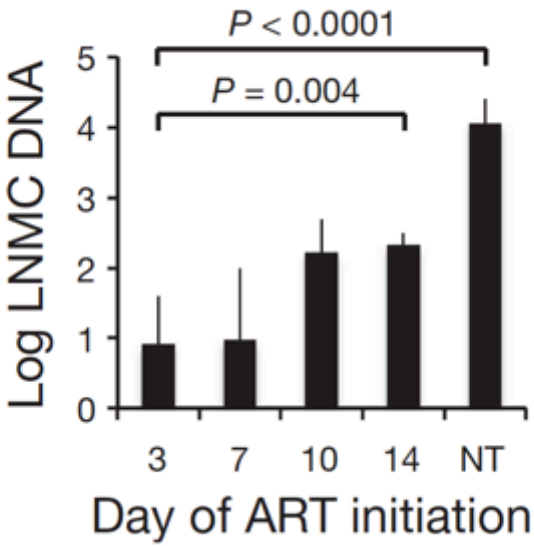
Volberding PA *et al., Lancet.* 2010 Jul 3;376(9734):49-62

Where is it?

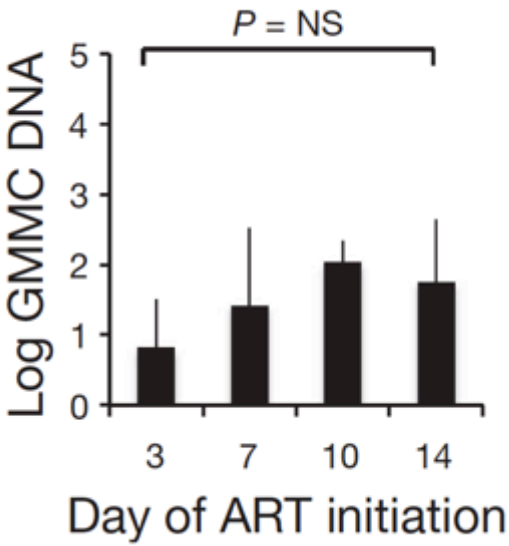
Blood



Lymph node

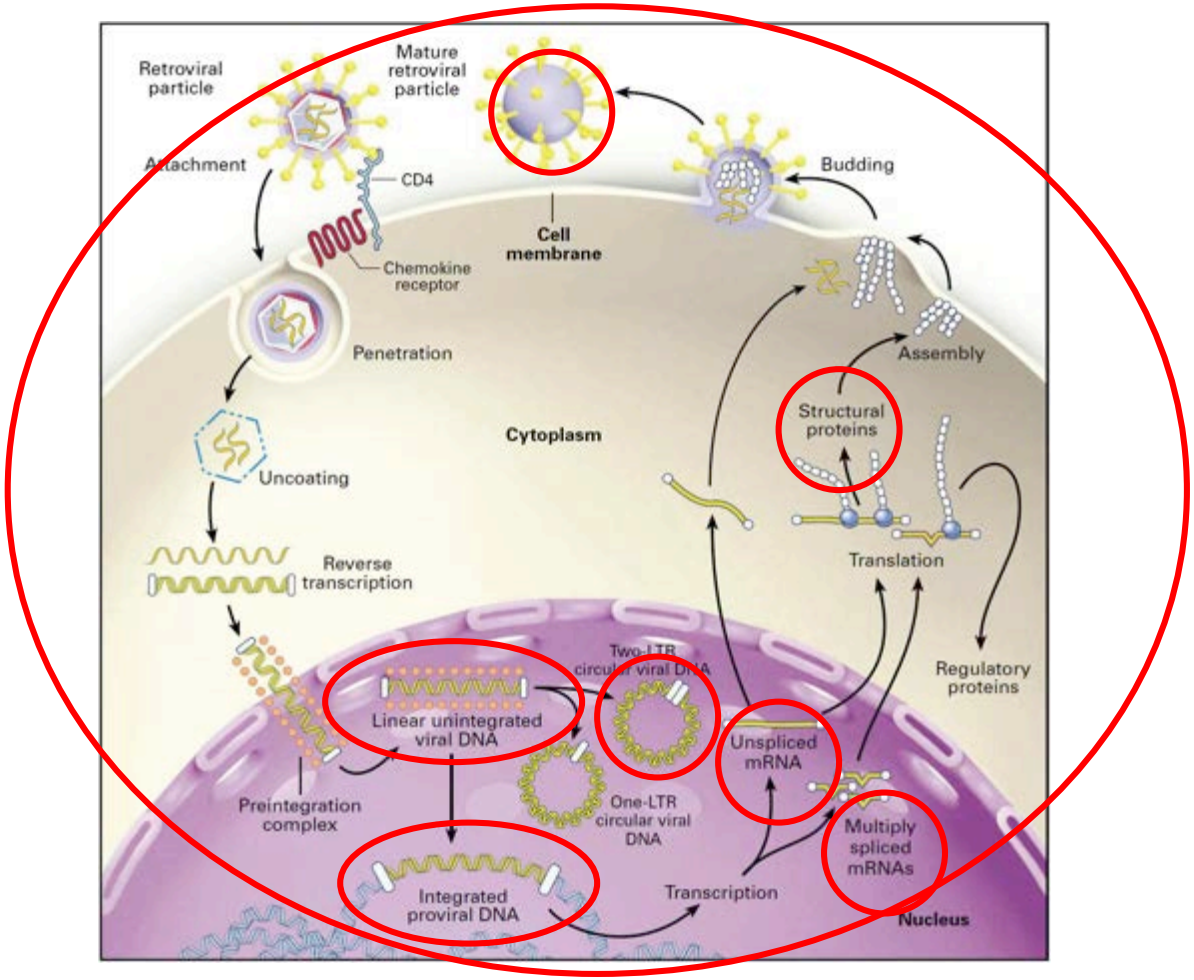


Gut



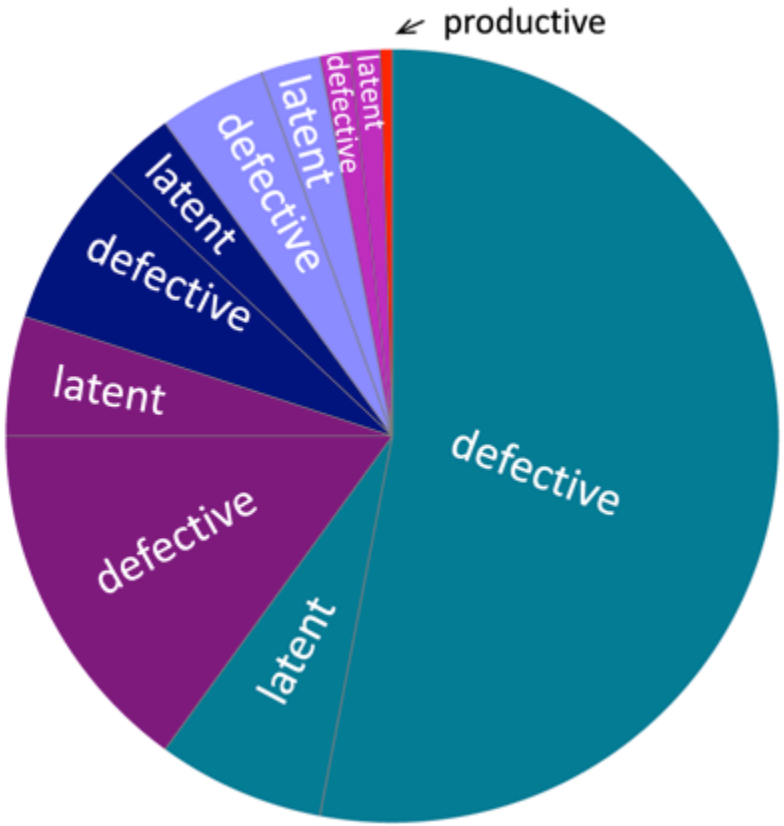
Whitney JB *et al., Nature.* 2014 Aug 7;512(7512):74-7

How to measure it?



Furtado MR *et al., N Engl J Med.* 1999 May 27;340(21):1614-22

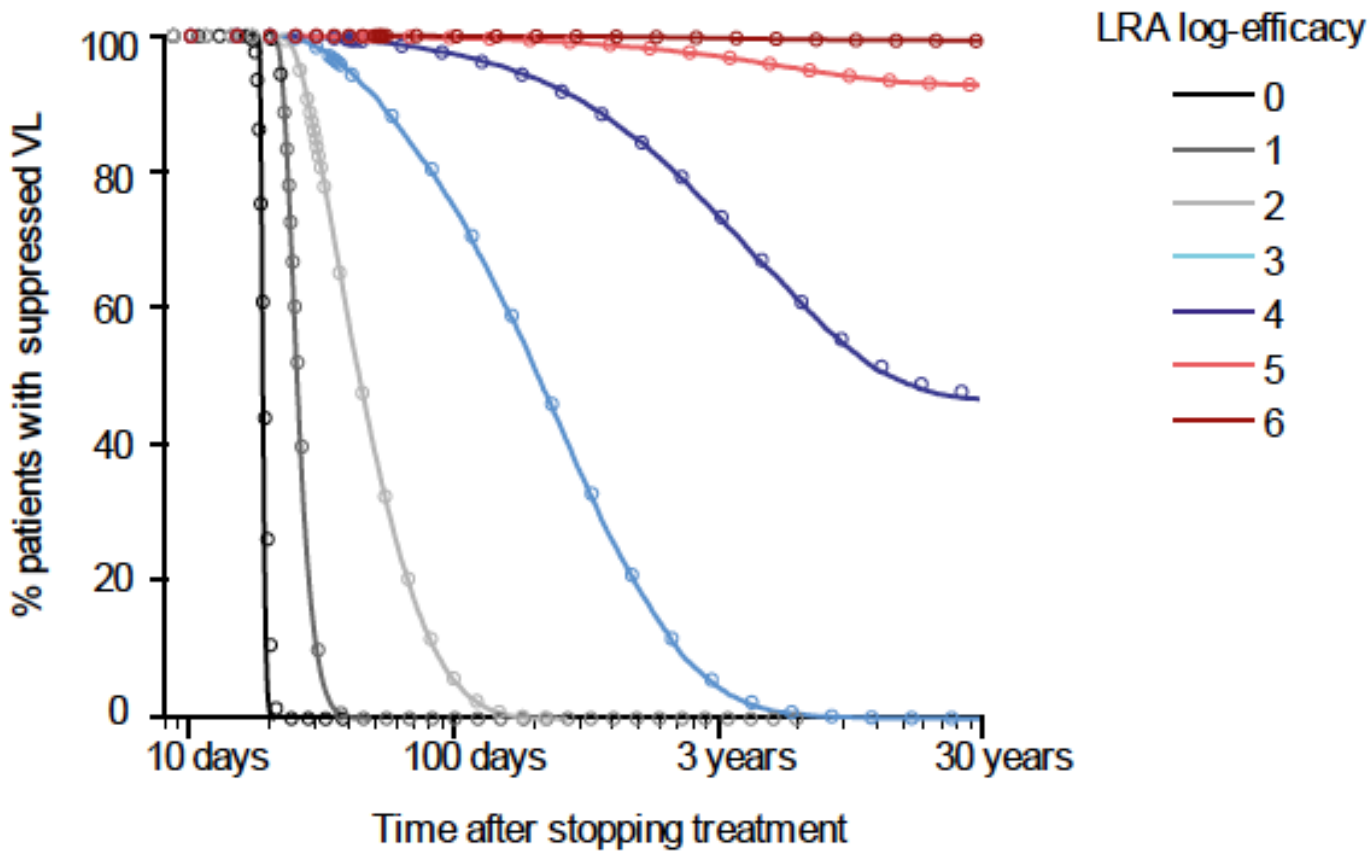
What does it?



class	DNA	US RNA	MS RNA	proteins	particle
A	+	-	-	-	-
B	+	low	-	-	-
C	+	intermediate	low	limited set	-
D	+	high	high	limited set	-
E	+	high	high	complete set	-
F	+	high	high	complete set	+

Pasternak AO *et al., Retrovirology.* 2018 Jan 29;15(1):13

The cure hypothesis

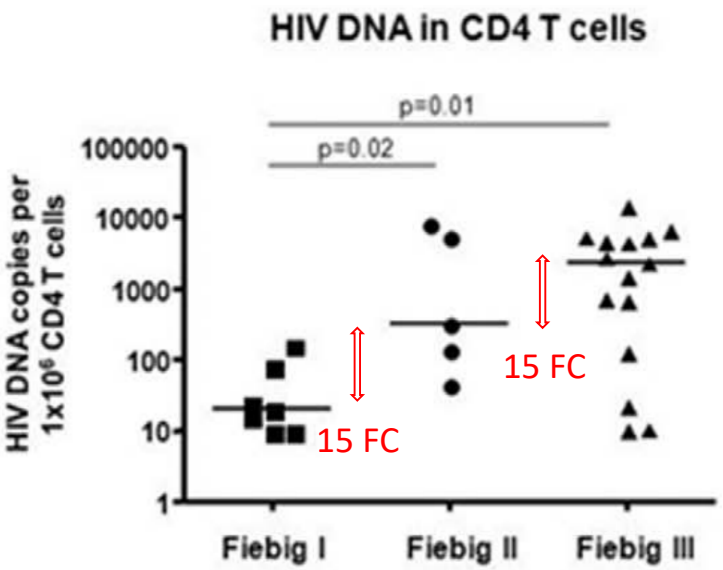


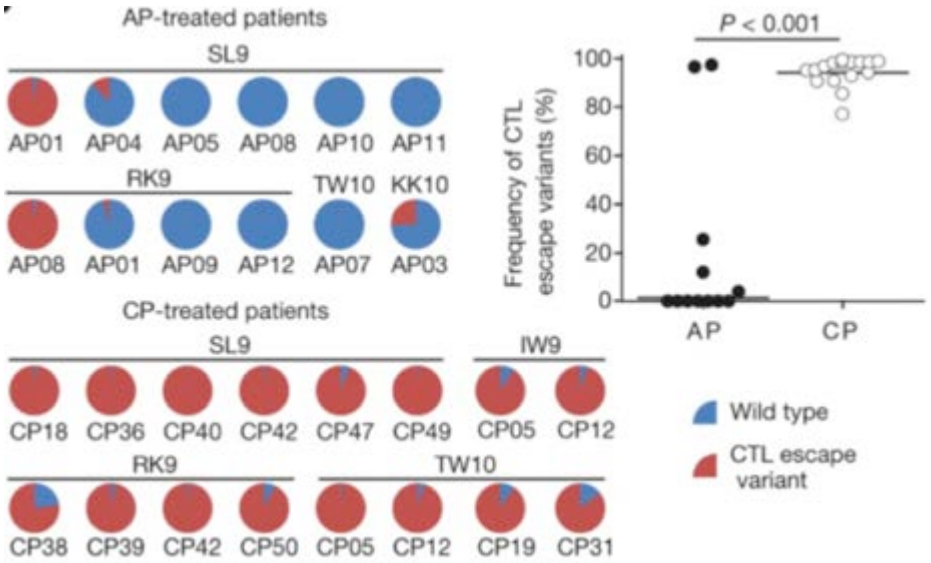
- Manipulation:
  - Decrease reservoir starting point
  - Improve reservoir reduction

Hill AL *et al., Proc Natl Acad Sci U S A.* 2014 Sep 16;111(37):13475-80

From PrEP, TasP and T&T to cure

1. Intervene in acute HIV (up to 6 months from seroconversion)

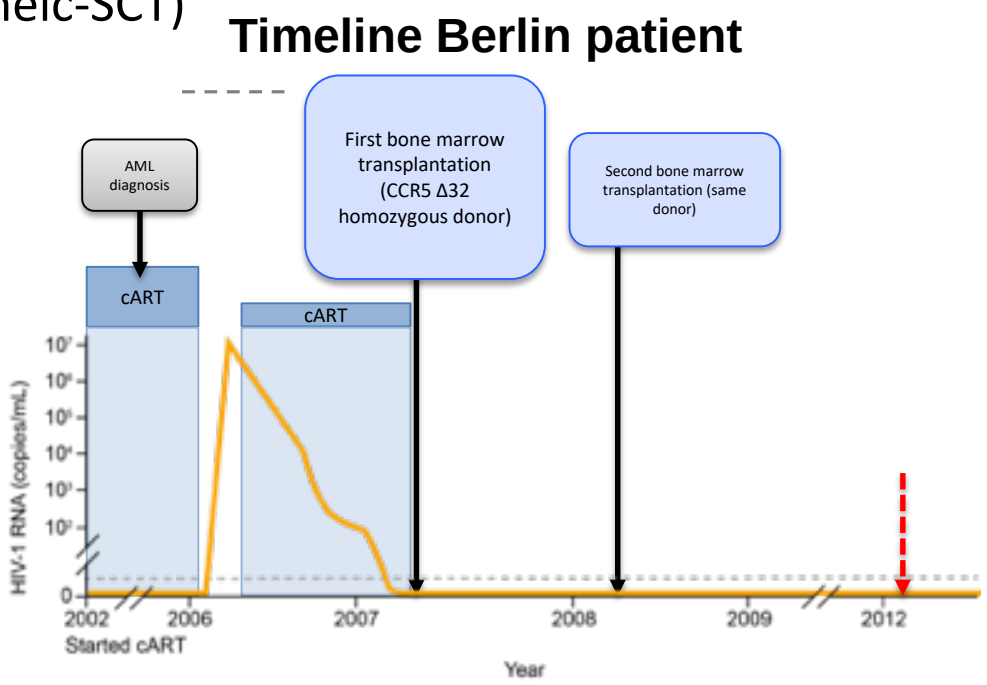




Ananworanich J *et al., PLoS One.* 2012;7(3):e33948
Walker BD *et al.*, abstract #13, CROI 2016

From PrEP, TasP and T&T to cure

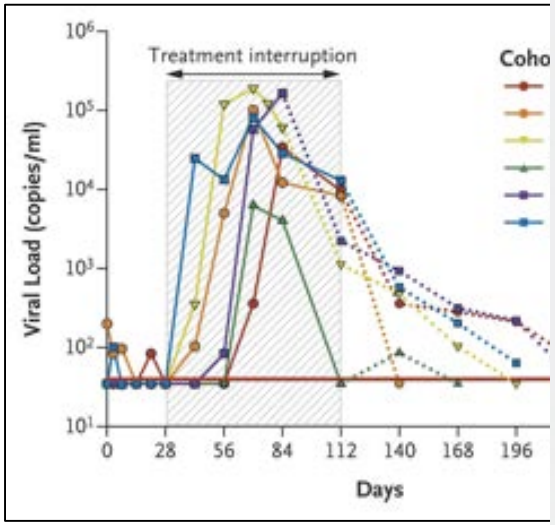
1. Intervene in acute HIV (up to 6 months from seroconversion)
2. Manipulate hiding HIV in the reservoir and target the host
   - Massive interventions (allogeneic-SCT)
   - Genetic interventions
   - Immunological interventions
   - Viral/host interventions



Hütter G *et al., N Engl J Med. 2009 Feb 12;360(7):692-8*
Kent SJ *et al., Lancet Infect Dis.* 2013 Jul;13(7):614-21
Yukl SA *et al., PLoS Pathog.* 2013;9(5):e1003347

Genetic interventions

- Genetic intervent
  - Target host(-virus
  - Target integrated

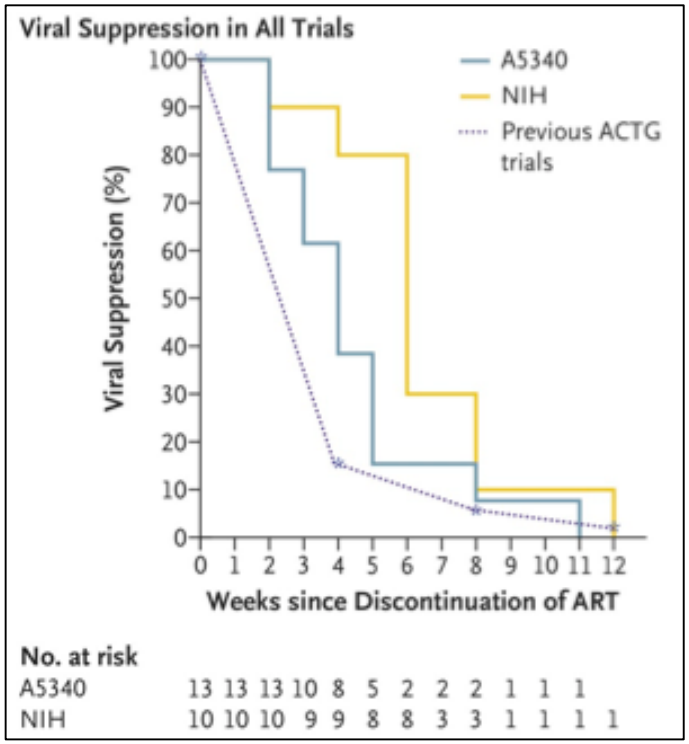


Fear of off target effects in the host genome but also in society

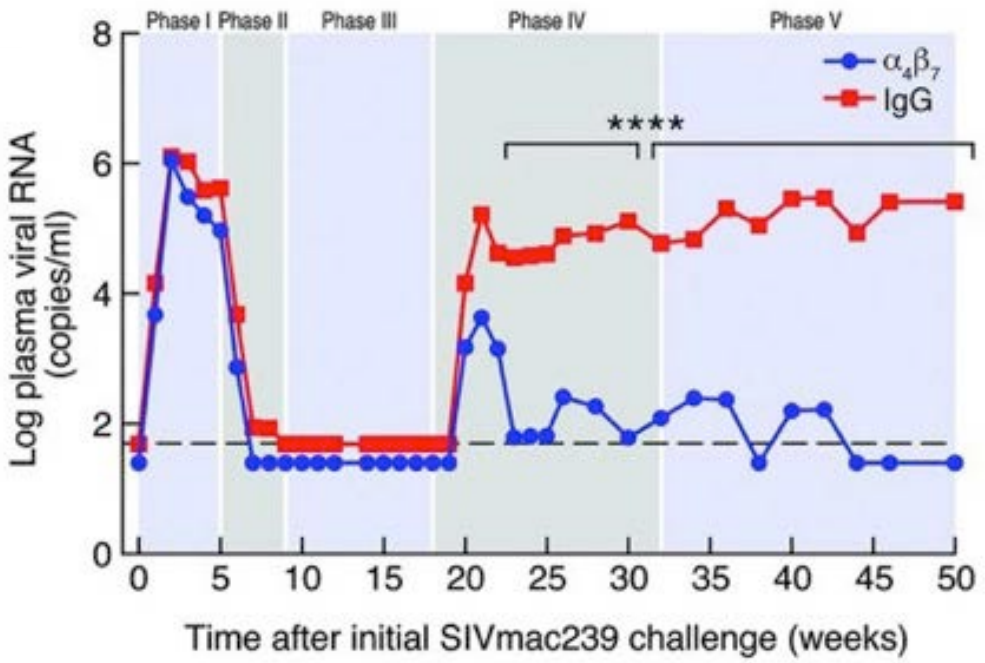
Tebas P *et al., N Engl J Med.* 2014 Mar 6;370(10):901-10

Immune interventions

- Infuse anti-HIV antibodies (VRCO1)

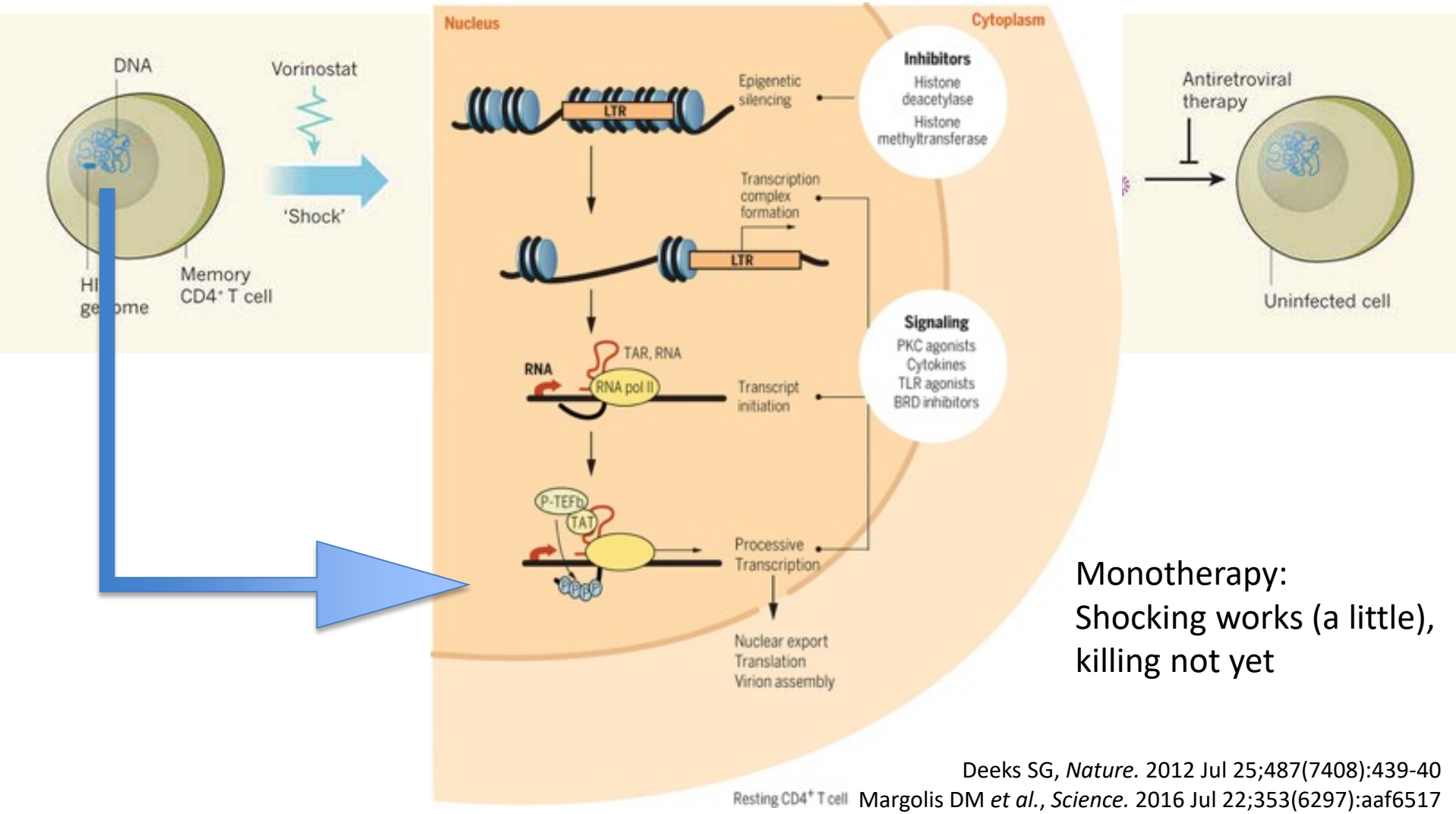


- Monkey studies to the rescue!
- T-cell/innate cell activators or infuse host Abs



Bar *et al., N Engl J Med.* 2016 Nov 24;375(21):2037-2050

Viral/host interaction
Shock and Kill

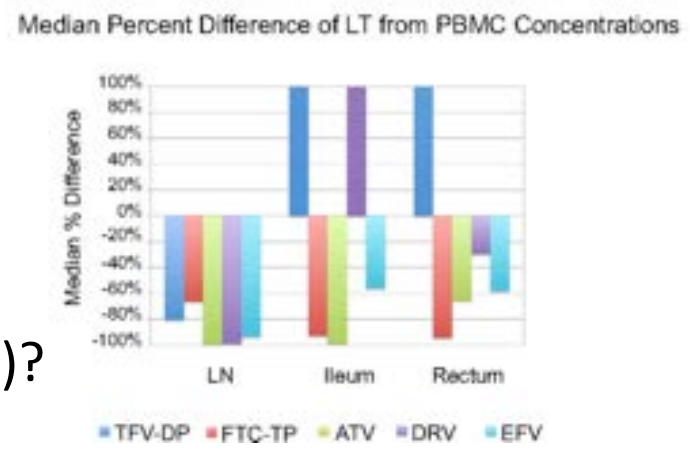


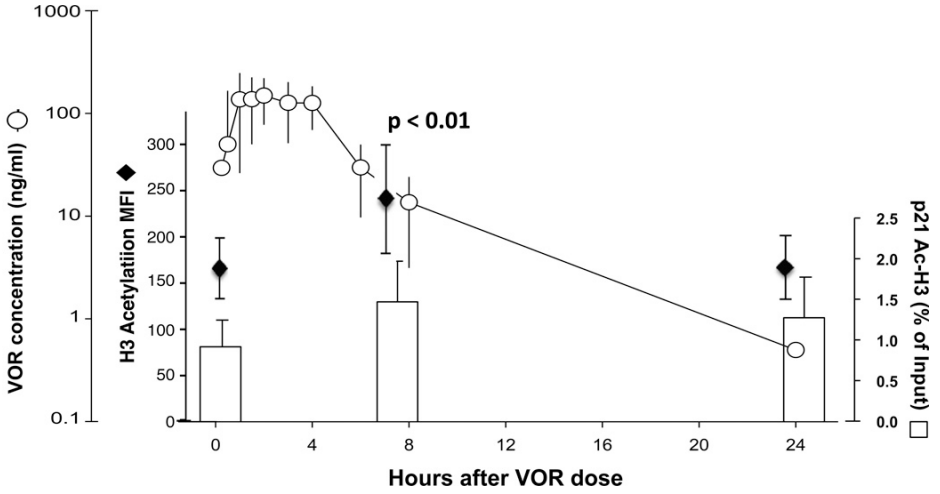
Monotherapy:
Shocking works (a little),
killing not yet

Deeks SG, *Nature.* 2012 Jul 25;487(7408):439-40
Margolis DM *et al.*, *Science.* 2016 Jul 22;353(6297):aaf6517

Challenges / Pitfalls

- Which patients (acute *vs.* chronic)?
- What biomarkers to measure?
- When to measure biomarkers (viral kinetics)?
- Combination strategies?
- Are immune cells up for it?
- Drug distribution?
- What to sample?





Archin NM *et al., Nature.* 2012 Jul 25;487(7408):482-5

Future directions

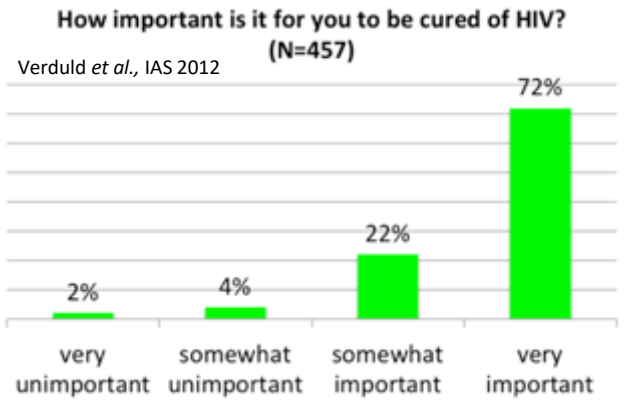
- New LRAs (+ combinations + host immunity boosting)
- Biomarkers for reservoir and cure and penetration of our interventions
- Different interventions in chronic and acute HIV?
- We need a team
  - Ongoing translational research
  - (International) collaboration
  - Young and old. Basic and clinical scientists.

MCQ

- What percentage of HIV-DNA in the reservoir is replication competent?
  - A. ~90%
  - B. ~50%
  - C. ~10%
  - D. ~1%

- Does measuring integrated HIV-DNA underestimate or overestimate the size of the replication competent reservoir?
  - A. Underestimate
  - B. Overestimate
  - C. It does not under, nor overestimate the size

- What percentage of patients do you think finds it very important to be cured of HIV?
  - A. ~25%
  - B. ~50%
  - C. ~75%
  - D. ~99%



Prospects

'I like to refer to my rebirth after being cured as my "cure birthday"'
Timothy Brown – the Berlin patient (AIDS *Res Hum Retrov* 2018)