

New Vaccines against HIV and Tuberculosis

Jaap Goudsmit

Kampala, October 16th, 2010

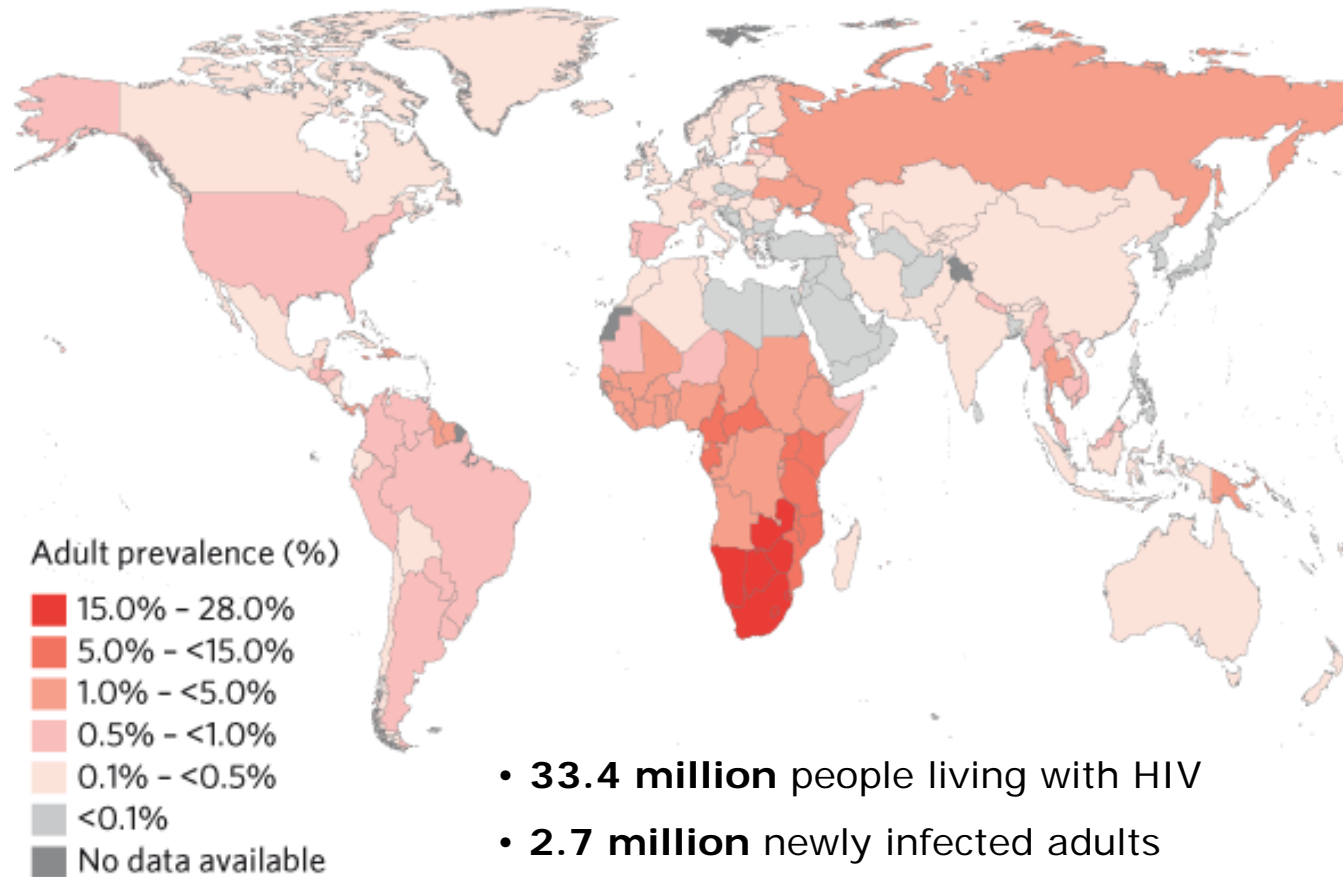
Uganda Symposium 2010 - HEALTH[e]foundation

Topics

- Epidemiology of TB and HIV in Africa
- Therapeutic strategies for TB and HIV
- Prevention of transmission by use of vaccination
 - Options for TB vaccines
 - Options for HIV vaccines
 - Impact of a vaccine (example of an HIV vaccine model for Uganda)
- Examples of HIV vaccines in phase III studies
- Example of TB vaccine

The HIV epidemic

- 2008 -

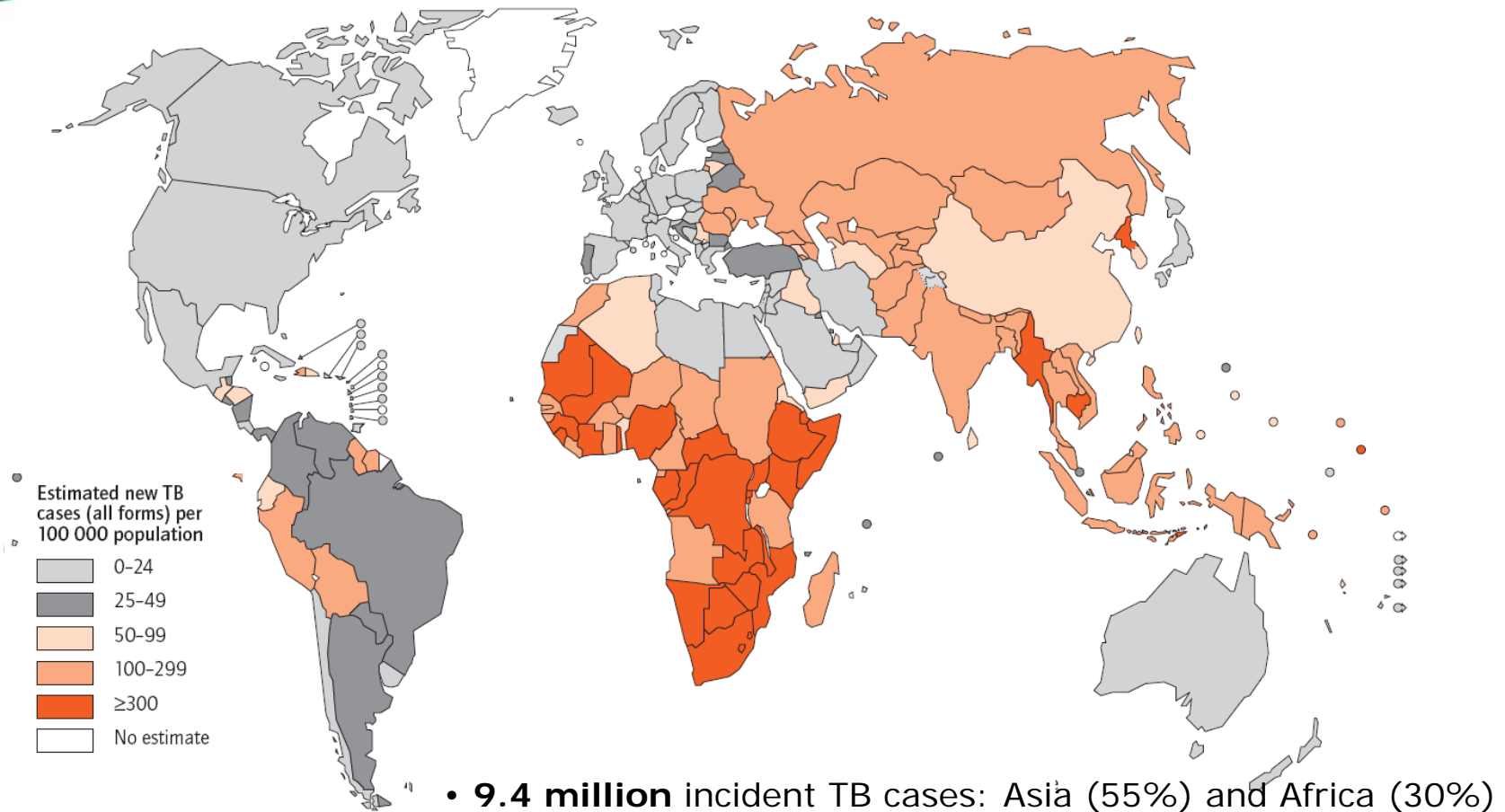


- **33.4 million** people living with HIV
- **2.7 million** newly infected adults
- **430 000** newly infected children under 15 years

The TB epidemic

- 2008 -

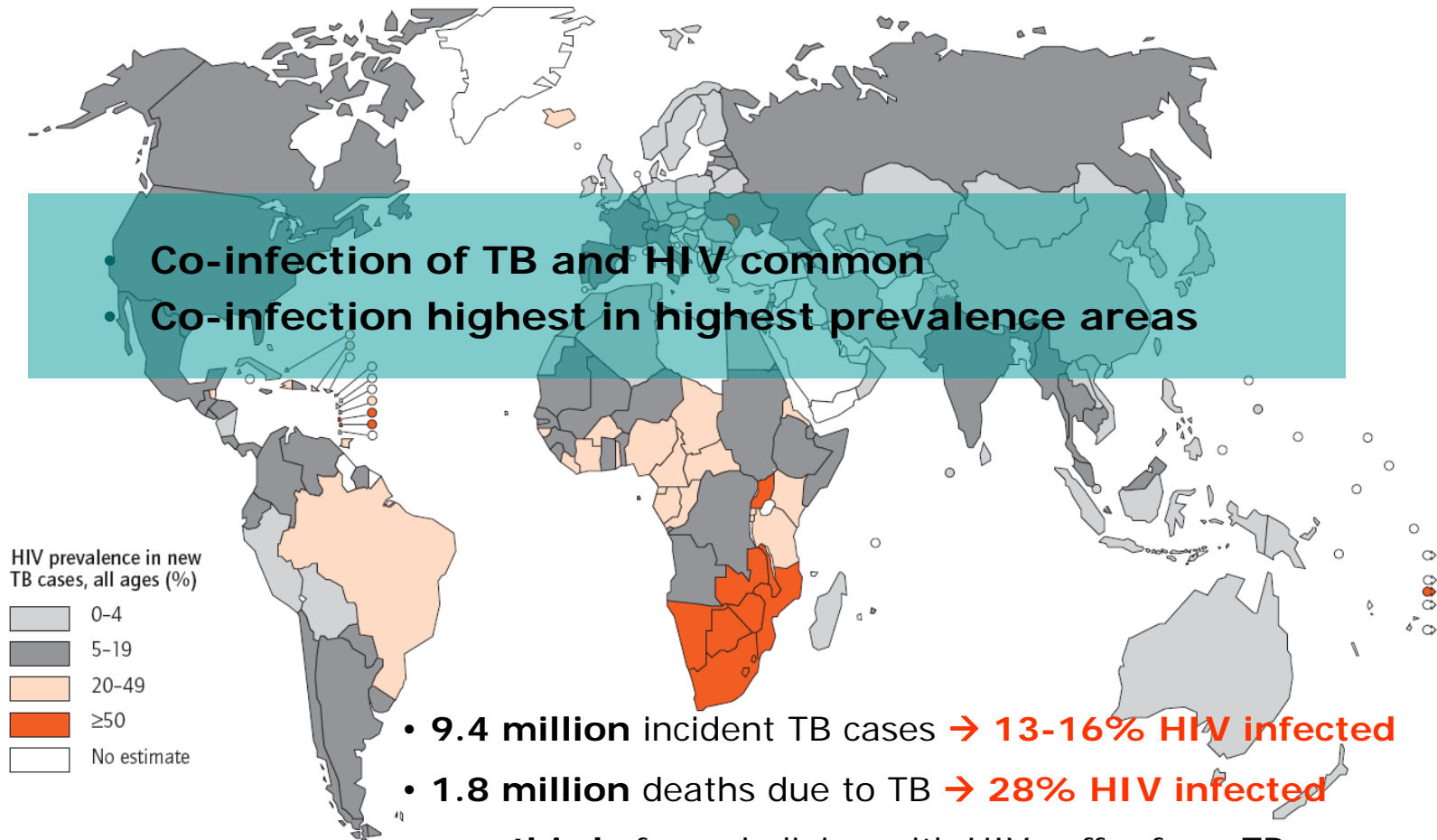
Estimated TB incidence of new TB cases



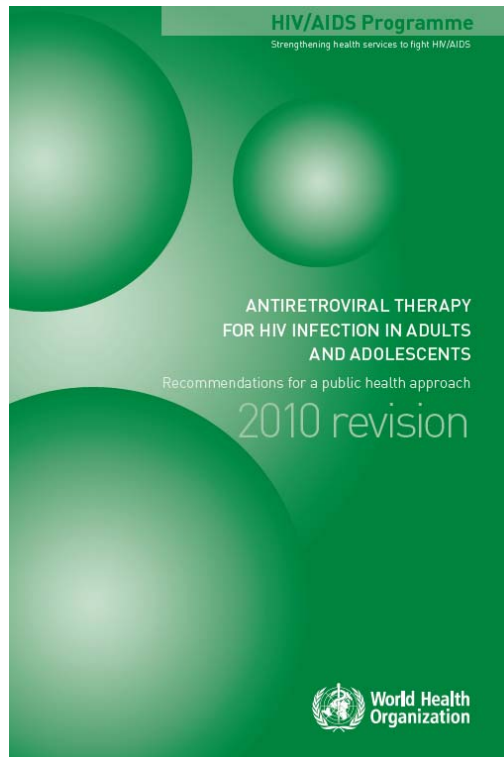
Two overlapping epidemics: HIV and TB

- 2008 -

Estimated HIV prevalence in new TB cases



Current treatment strategies for HIV



www.who.int/hiv/en

HIV treatment when CD4 count \leq 350 cells/mm³

- First line: ART
 - One NNRTI (either NVP or EFV) plus two NRTIs: 3TC or FTC **and** AZT or TDF
- Second line regimen – countries are advised to have at least 1 second line regimen for individuals with first line failure

Challenges

- Access to and willingness of HIV testing
- Accessibility of drugs – lifelong access needed
- Limited availability of second line regimens in resource limited settings

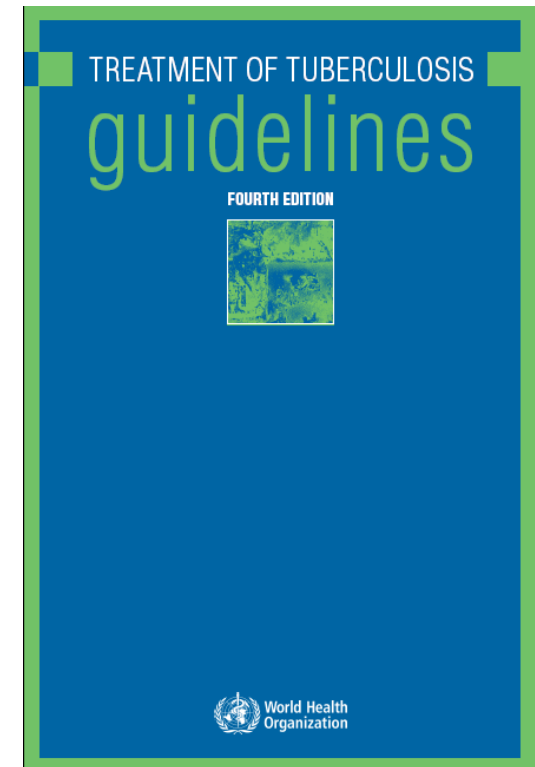
Current treatment strategies for TB

Standard TB treatment:

- 2HRZE/4HR or 2HRZE/4HRE (in areas with high INH resistance)

Challenges

- More difficult regimens in case of drug resistance
- Limited testing for drug resistance (MDR, XDR)
- Case finding (not all cases are easy to find)
- Long duration of treatment - adherence not optimal
- Prevention of active TB by diagnosing and treating LTBI - not often done in resource limited, high-prevalence areas



www.who.int/tb/en/

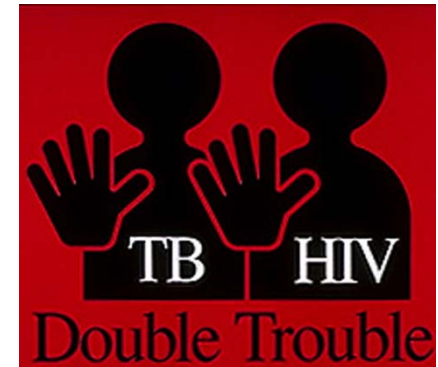
Treatment strategies TB–HIV co infection

TB treatment in HIV infected patients:

- Start with standard TB treatment
- Initiate co-trimoxazole preventive therapy
- Initiate ART shortly after start TB treatment (within 8 weeks after start of TB treatment)

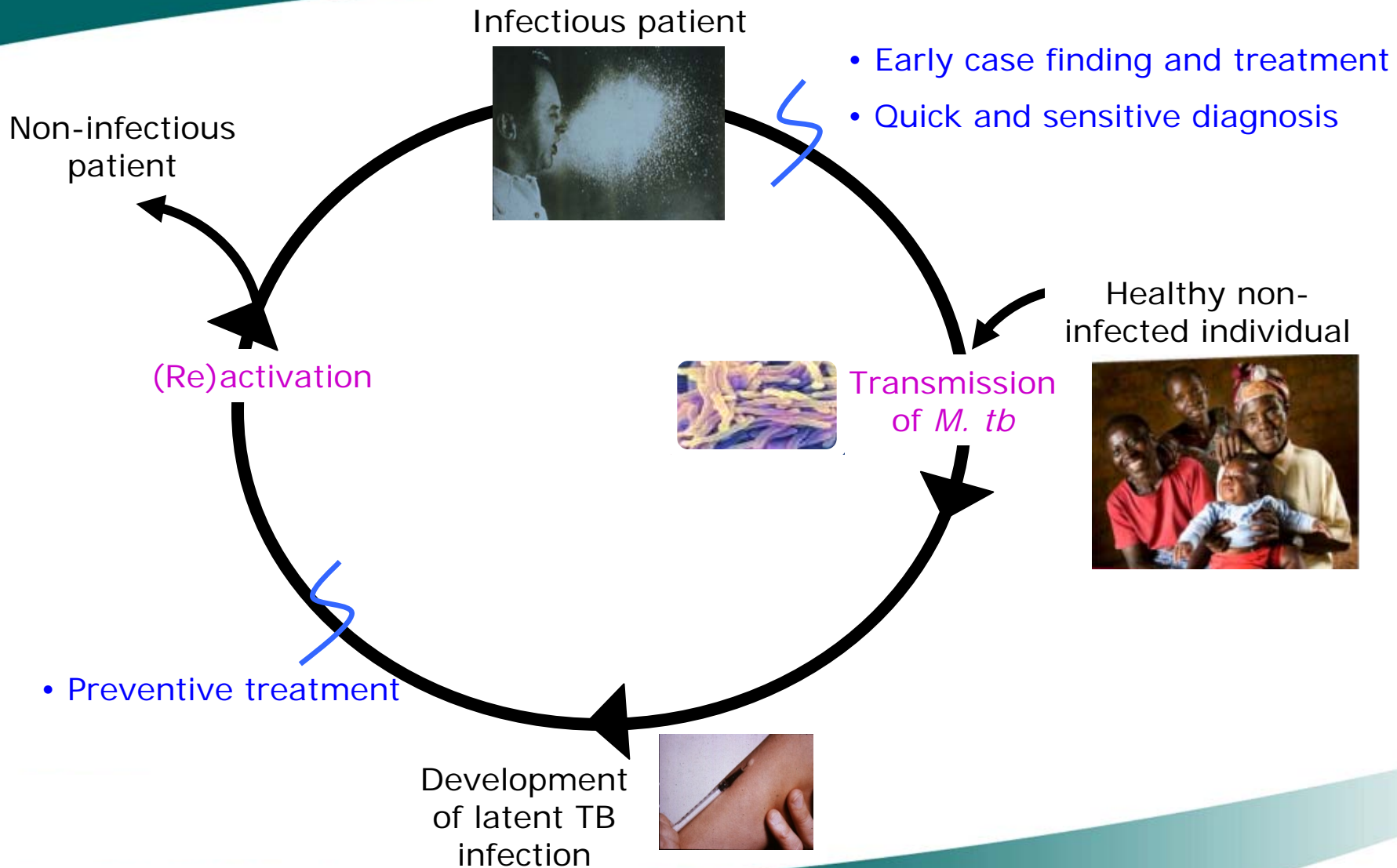
Challenges

- HIV testing – HIV testing among TB patients not everywhere routinely implemented
- IRIS

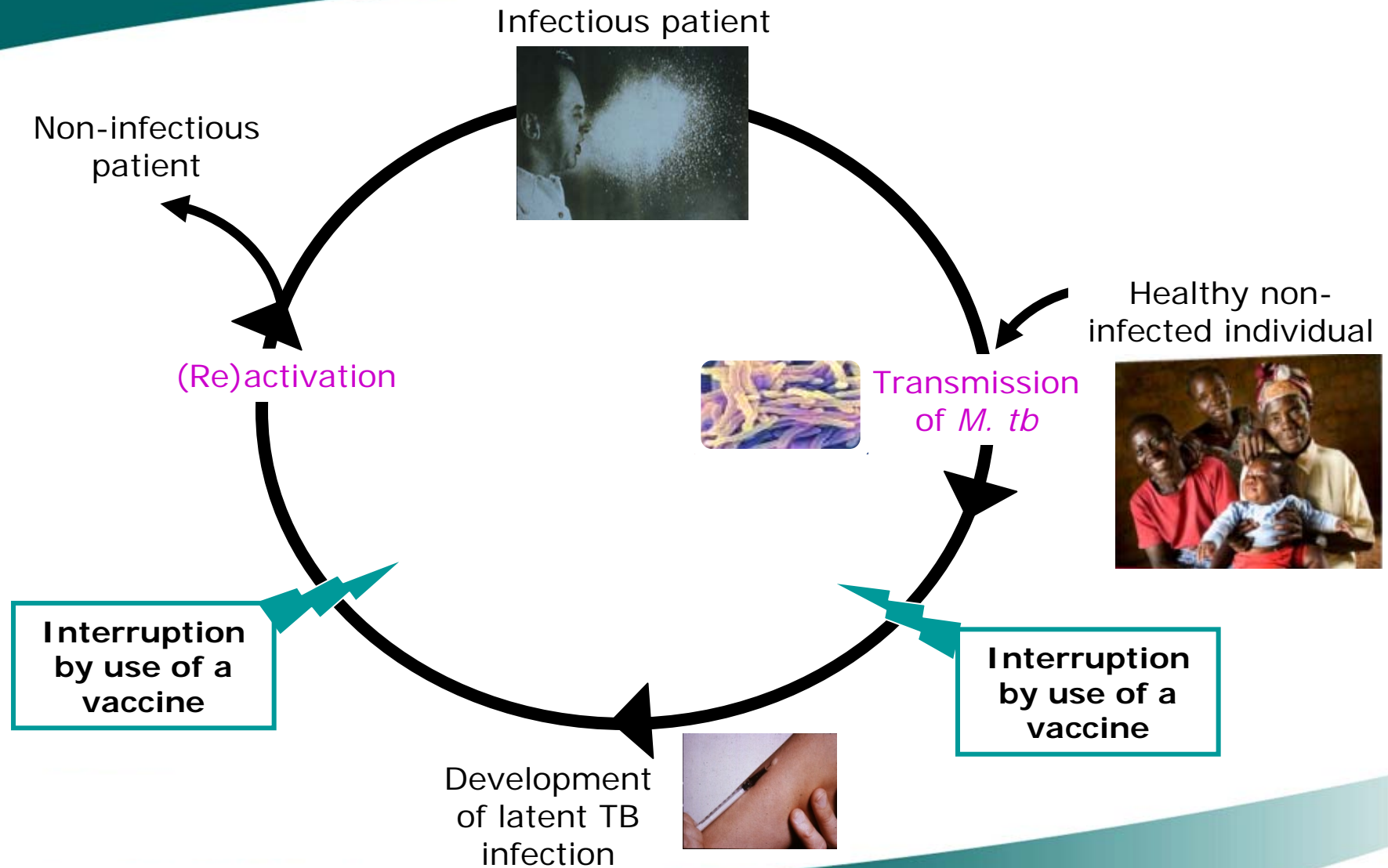


Prevention is better than cure....

Transmission cycle of tuberculosis



Transmission cycle of tuberculosis

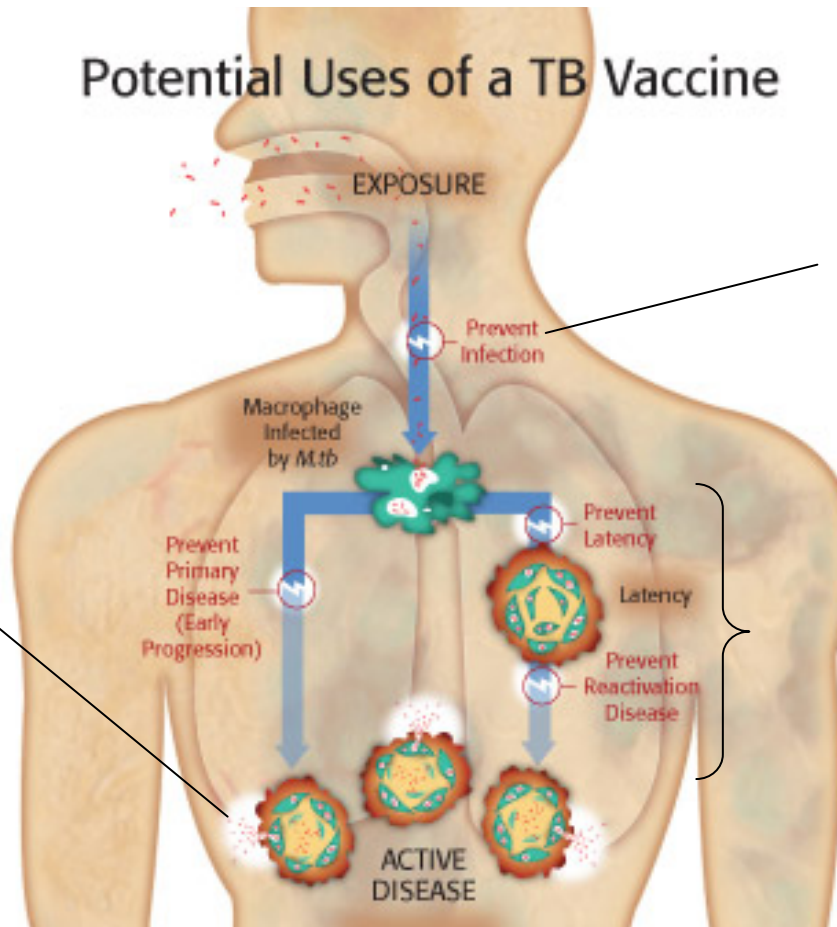


Options for TB vaccines

Potential Uses of a TB Vaccine

Therapeutic vaccine

- TB patients, on treatment



Pre-exposure vaccine

- newborns
- infants

Post-exposure vaccine

- schoolchildren
- adolescents
- adults

Current TB vaccine: BCG

BCG Needs a Boost



Robert Koch



Albert Calmette



Camille Guerin

- *Mycobacterium tuberculosis* identified by Koch (1882)
- Bacille Calmette-Guerin (BCG) developed (1908-1922) by extensive serial passage
- BCG is most widely used vaccine worldwide
 - Provides significant protection against severe childhood forms of disease
 - ! No protection against pulmonary tuberculosis among adolescents and adults

More efficacious TB vaccine needed!

New tuberculosis vaccines



Principle of new tuberculosis vaccines under development

- Prevent infection
- Prevent primary disease
- Prevent latent infection
- Prevent reactivation of latent infection
- Shorten the course and improve the response to chemotherapy

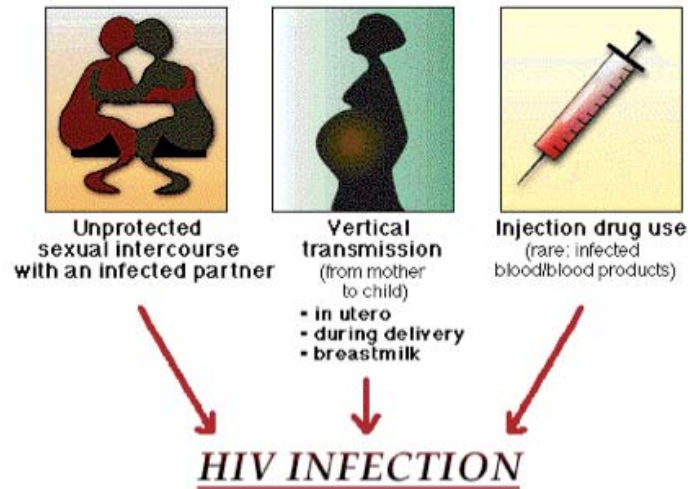
New vaccines can either be a boost to BCG or be used as a prime

See for overview:

www.stoptb.org/wg/new_vaccines

www.aeras.org/portfolio

Transmission of HIV



- Lifelong infection, no cure
- Antiretroviral therapy (ART):
 - reduces viral load
 - reduces risk of progression to AIDS
 - reduces risk of transmission
- Transmission can further be reduced by:
 - Safe sex
 - PEP

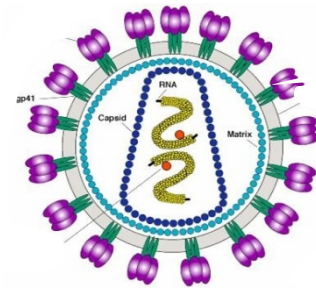
Efficacious HIV vaccine needed!

New HIV vaccines

- **Currently no HIV vaccine available**

Wish list - the ideal HIV vaccine should.....:

- ...Stop viral entry into the cells
- ...Interrupt viral replication
- ...Thwart “broadcasting” of the virus from the initial site of infection
- ...Prevent spread to another person
- ...Induce long lasting immunity
- ...Be effective against all HIV subtypes
- ...Be simple to administer
- ...Be inexpensive



Why is development of TB and HIV vaccines not easy?

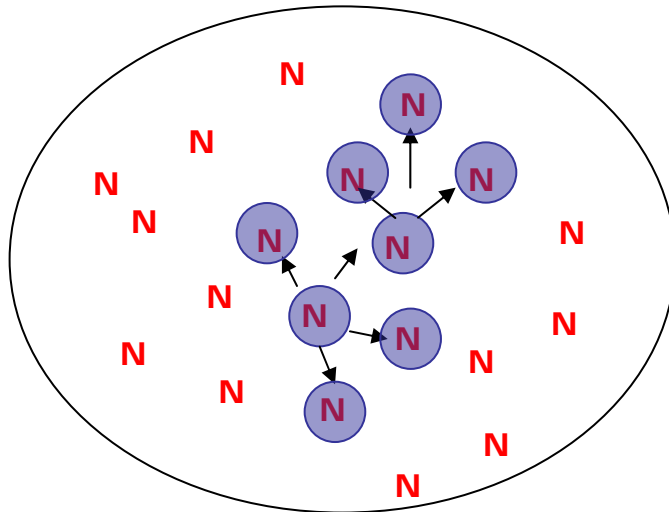
- **Correlate of protection is unknown**
 - Unclear what type of immune response could provide protection
 - Antibodies only seem not to be enough
- **No acquired protection after infection**
 - Previous episodes of TB do not prevent against reinfection and activation of the disease
 - HIV infection is lifelong; no self cure

Impact of vaccines depend on....

- **Efficacy of the vaccine:** the percentage reduction in incidence among vaccinees, which is attributable to the vaccine
- **Coverage:** percentage of the target population that is vaccinated
- **Burden of disease in country:** incidence of the disease
 - For repeated or high-dose exposure (i.e. in highly endemic countries) you might need 'more' protection from a vaccine than for lower exposure gradients
- **Possible herd immunity:** the disease incidence declines not only in the vaccinees, but also in the non-vaccinees due to the introduction of the vaccination

Example of herd immunity

Situation before vaccination

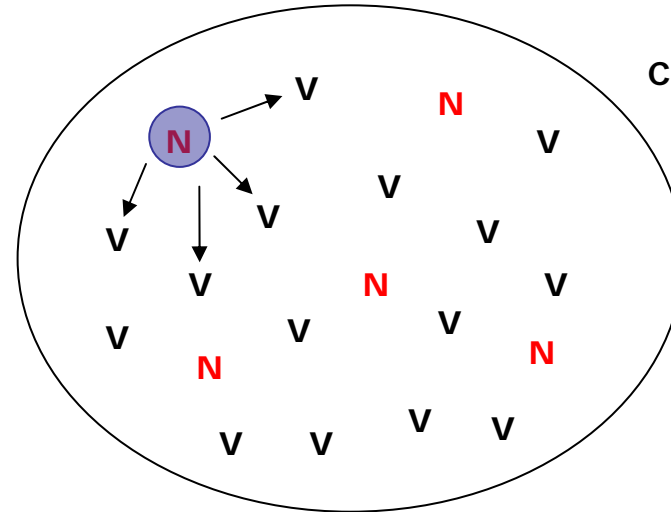


**N= non-vaccinated subject
(susceptible for the disease)**

 **infectious case**

Infectious case is able to spread the disease to other susceptible subjects, all contacts are susceptible

Situation after introduction of vaccination



Coverage =
75%

V=vaccinated subject

**N= non-vaccinated subject
(susceptible for the disease)**

Infectious case is less able to spread the disease to other susceptible subjects, since most contacts are vaccinated

→ reduction of disease incidence also amongst non-vaccinated subjects

Impact of an HIV vaccine

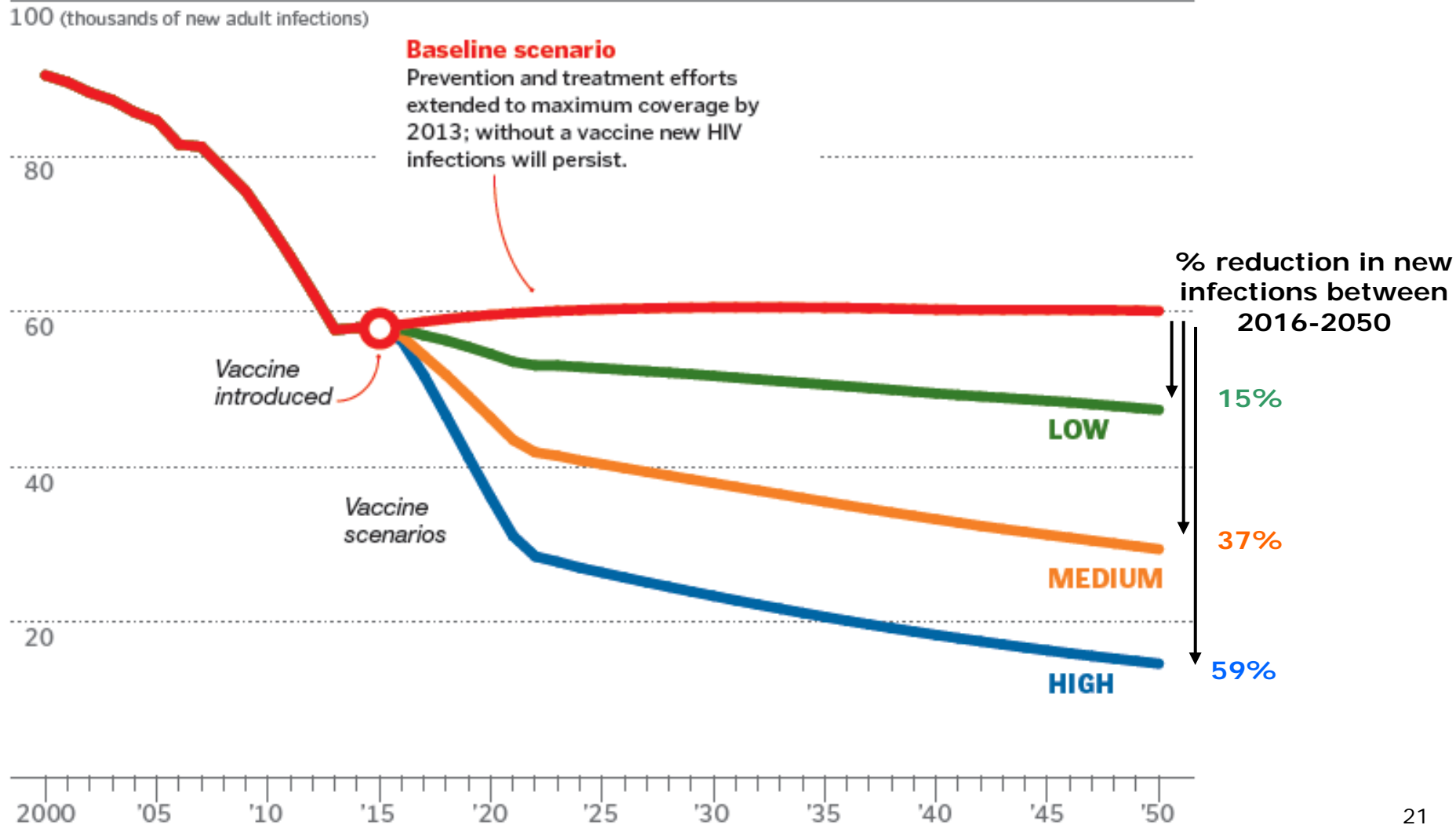
- Modeled for Uganda -

- **Is an HIV vaccine useful when its efficacy is less than 100%?**
 - First generation HIV vaccines are expected to be only partially protective
- **IAVI, the Futures Institute, Uganda AIDS Commission, Makerere University modeled the future of the AIDS epidemic**
 - **Baseline scenario:** extension of prevention and treatment efforts and maximum coverage reached in 2013
 - **LOW:** Vaccine efficacy of **30%**, coverage of **20%** in adult population
 - **MEDIUM:** Vaccine efficacy of **50%**, coverage of **30%** in adult population
 - **HIGH:** Vaccine efficacy of **70%**, coverage of **40%** in adult population

Source: iavi Policy notes, policy brief 22, October 2009

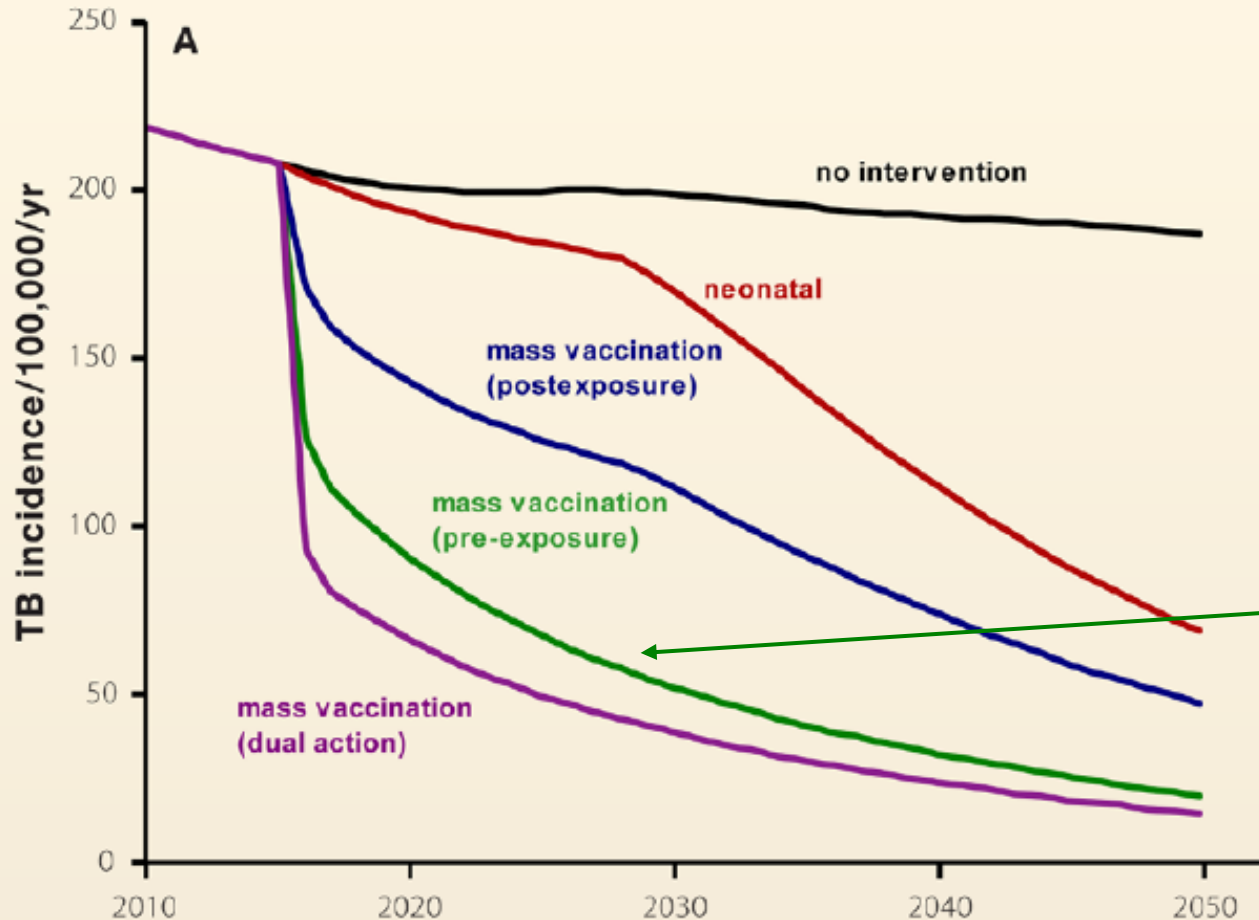
Impact of an HIV vaccine

- Modeled for Uganda -



Impact of a TB vaccine

- Modeled for South Asia -



Assumptions:

- coverage and efficacy protect 70% of target population
- incidence 2010: ~200/100.000
- decline in incidence 1-2% per year

One round of mass vaccination, continuation with neonatal vaccination

Vaccine development phases

Basic science (discovery)

- Selection of antigen
- Type of vaccine (vector, live/killed, adjuvant)
- Delivery method (i.m, i.d, i.n)

Pre-clinical studies

- Safety
- Immunogenicity
- Proof of concept (protection)
- Study a useful animal model

Clinical trials Phase I, II, III

- First in human
- Safety
- Immunogenicity
- Efficacy

Vaccine product & Phase IV trials

- Monitoring rare AEs
- Effectiveness

Examples of HIV vaccine trials...

History of potential HIV vaccines

25 years since discovery of HIV.....

Merck <hr/> Ad5 gag pol nef 2005-2007	VRC Genvec <hr/> DNA - Ad5 gag pol Env 2010-ongoing	Sanofi pasteur VaxGen <hr/> ALVAC –AIDSVAX gag prot env 2009
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...only 3 vaccines reached phase 3 efficacy trials



History of potential HIV vaccines

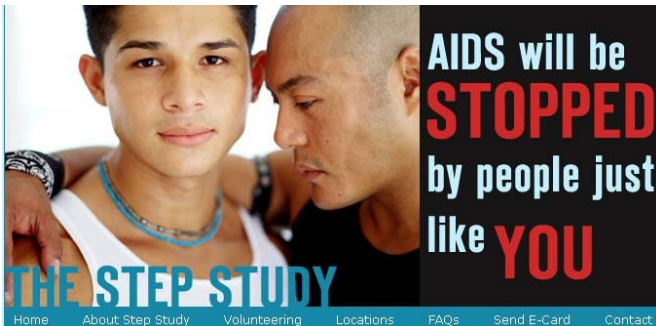
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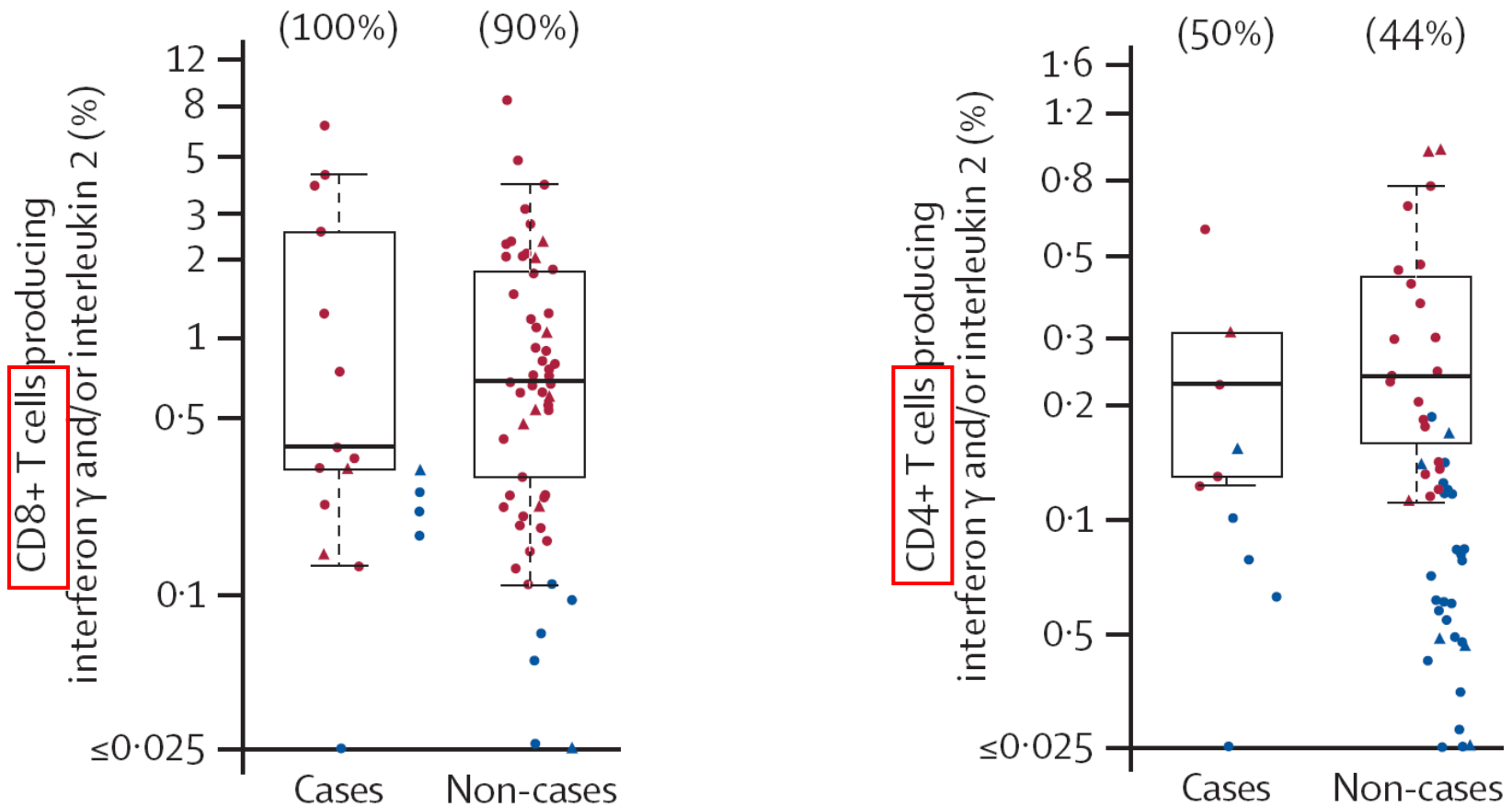


The STEP Study



- Adenovector 5 based HIV vaccine MRKAd5: MRKAd5 HIV-1 gag/pol/nef
- Multi-center double-blind placebo-controlled Phase II test-of-concept clinical trial
- 3,000 uninfected volunteers at high risk for HIV infection
- Start: December 2004; 2-4 years follow-up
- **Interim analysis in 1500 volunteers with low pre-existing immunity to adenovirus 5**

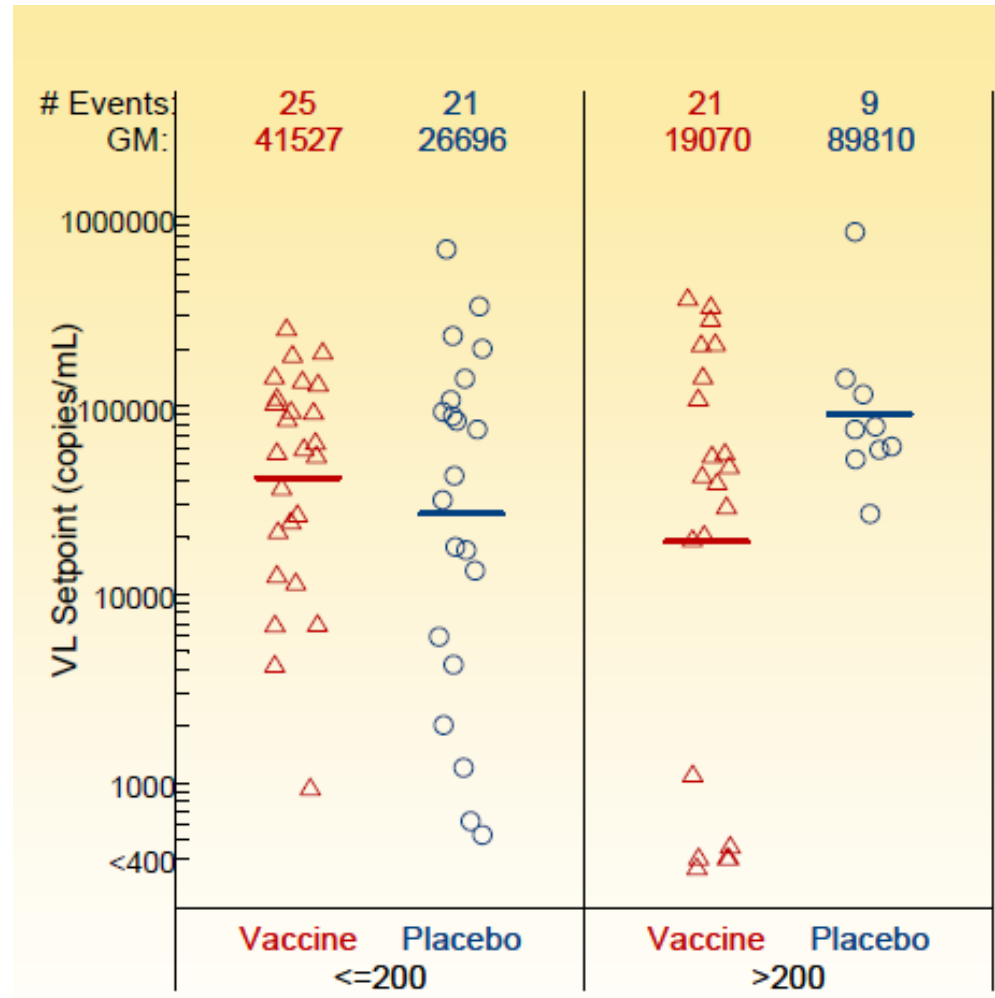
MRKAd5 highly immunogenic for inducing HIV-specific CD8⁺ T cells



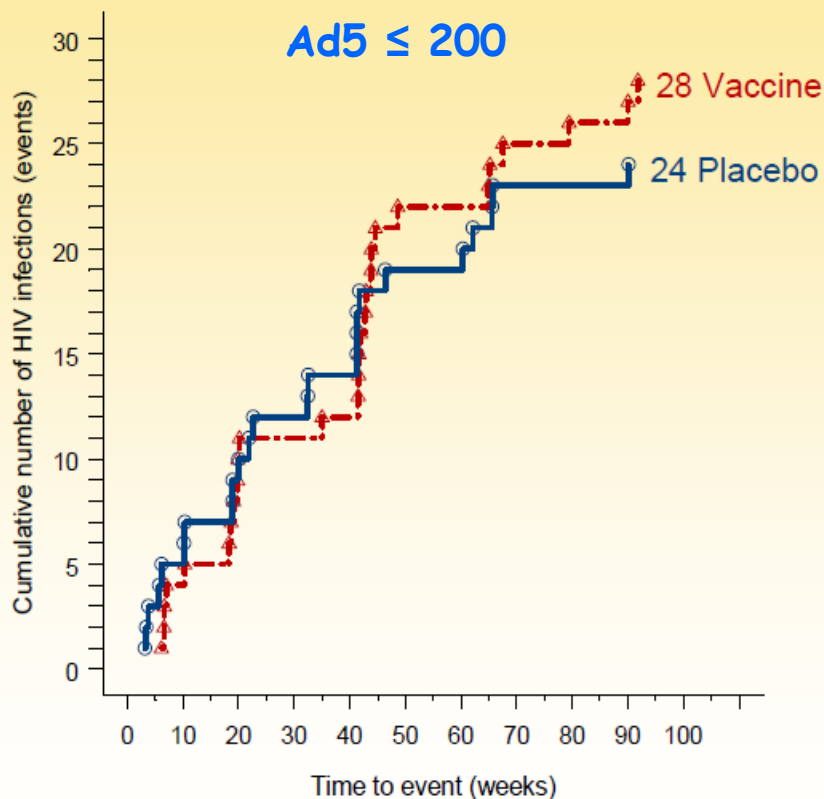
McElrath et al. Lancet 372:1894, 2008.

No reduction in viral setpoint after MRKAd5

- Vaccination did not reduce viral setpoint
- No difference in viral setpoint between baseline Ad5 < 200 and Ad5 > 200 groups

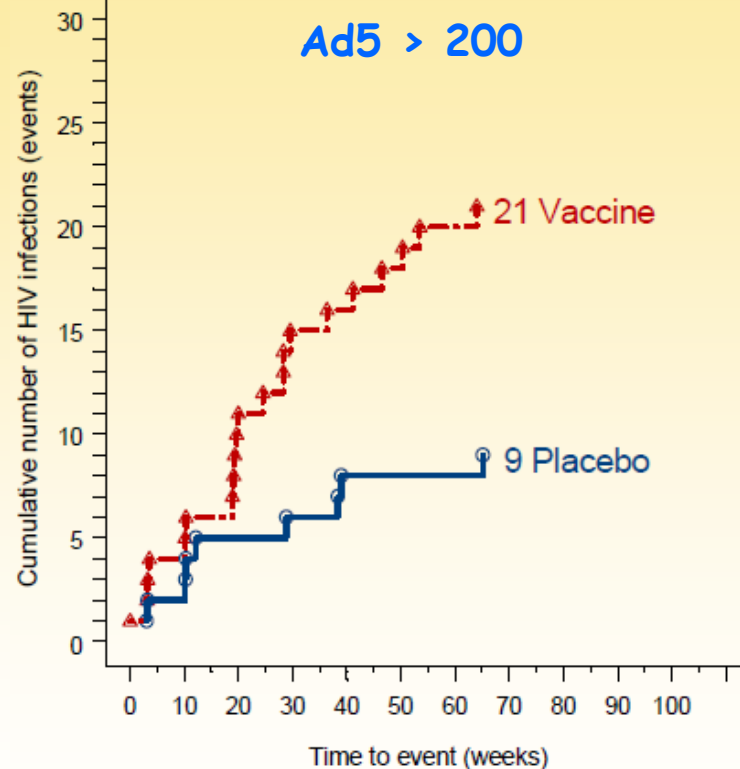


Increased risk of HIV after vaccination in subjects with $Ad5 > 200$?



1-tailed p-value = 0.322 (for $VE_{INF} \neq 0$)

2-tailed p-value = 0.581 (for $VE_{INF} \neq 0$)

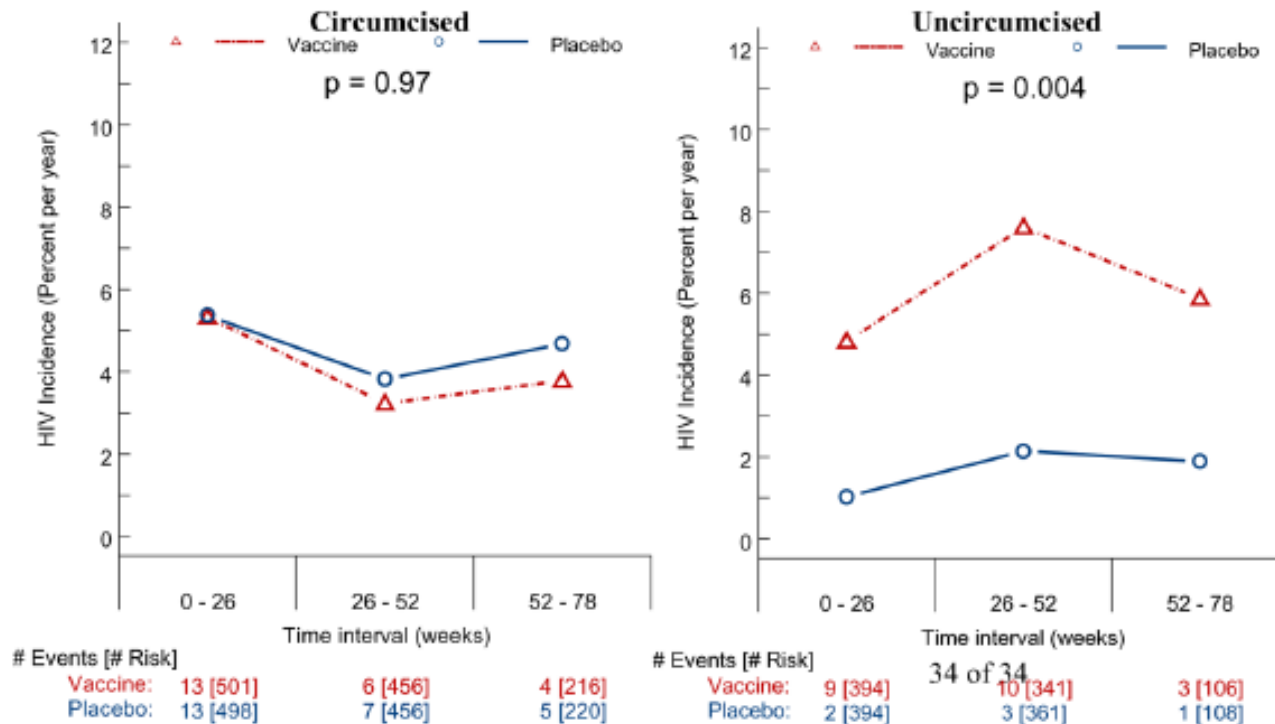


1-tailed p-value = 0.020 (for $VE_{INF} \neq 0$)

2-tailed p-value = 0.029 (for $VE_{INF} \neq 0$)

MITT
Cases up till Oct 2007

Increased risk of HIV after vaccination in Ad5 seropositive uncircumcised men?



Buchbinder et al., Lancet 2008

Lessons learned from the STEP trial

- **MRKAd5 elicited higher CD8+ T-cell response rate and magnitude than did any candidate reported for the last decade, showed no efficacy**
- **Enhancement of HIV acquisition in AD5 seropositive, uncircumcised males was concerning but statistically borderline**
- **Several hypothesis have been tested (in vivo and in vitro), but did not provide any clues for a possible biological mechanism**

History of potential HIV vaccines

25 years since discovery of HIV.....

Merck <hr/> Ad5 gag pol nef 2005-2007	VRC Genvec <hr/> DNA - Ad5 gag pol Env 2010-ongoing	Sanofi pasteur VaxGen <hr/> ALVAC –AIDSVAX gag prot env 2009
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...only 3 vaccines reached phase 3 efficacy trials

Program discontinued



History of potential HIV vaccines

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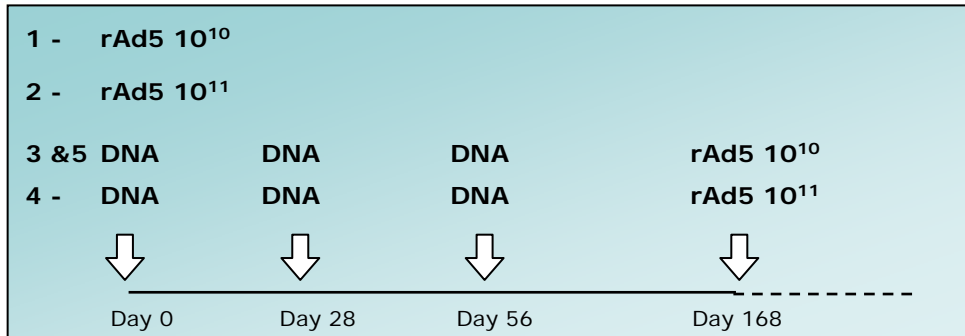
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...only 3 vaccines reached phase 3 efficacy trials

VRC HIV-program: DNA combined with rAd5 studied in phase 1/2

MAJOR ARTICLE



A Phase 1/2 Study of a Multiclade HIV-1 DNA Plasmid Prime and Recombinant Adenovirus Serotype 5 Boost Vaccine in HIV-Uninfected East Africans (RV 172)

Hannah Kibuuka,¹ Robert Kimutai,² Leonard Maboko,³ Fred Sawe,² Mirjam S. Schunk,^{2,4} Arne Kroidl,^{2,4} Douglas Shaffer,² Leigh Anne Eller,^{1,5} Rukia Kibaya,² Michael A. Eller,^{1,5} Karin B. Schindler,^{2,4} Alexandra Schuetz,^{2,4} Monica Millard,¹ Jason Kroll,⁶ Len Dally,⁶ Michael Hoelscher,^{1,4} Robert Bailer,⁷ Josephine H. Cox,⁸ Mary Marovich,⁵ Deborah L. Bix,⁹ Barney S. Graham,⁷ Nelson L. Michael,⁵ Mark S. de Souza,^{5,10} and Merlin L. Robb⁵

¹Makerere University Walter Reed Project, Kampala, Uganda; ²Walter Reed Project, US Army Medical Research Unit—Kenya, Kericho, Kenya; ³Mbeya Medical Research Programme, Mbeya, Tanzania; ⁴Klinikum der Ludwigs Maximilians University, Munich, Germany; ⁵US Military HIV Research Program, ⁶The Emmes Corporation, Rockville, and ⁷Vaccine Research Centre, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; ⁸International AIDS Vaccine Initiative, New York, New York; ⁹Centers for Disease Control and Prevention, Atlanta, Georgia; and ¹⁰Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand.

Kibuuka et al. JID 2010;201:600-607

DNA plasmid mixture (1:1:1:3):

HIV env subtype A

HIV env subtype B

HIV env subtype C

Subtype B *gag*, *pol* and *nef*



rAd5 mixture (1:1:1:3):

rAd5.envA

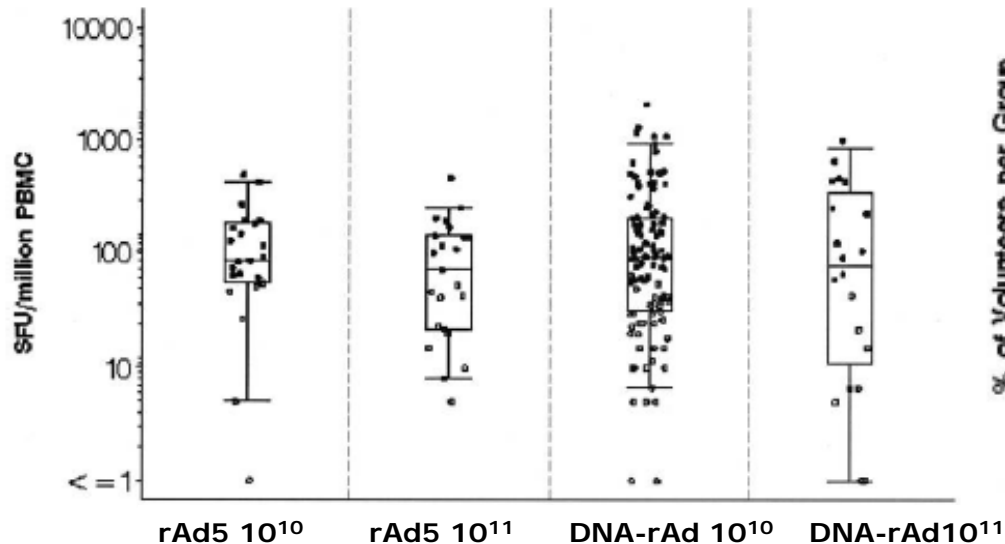
rAd5.envB

rAd5.envC

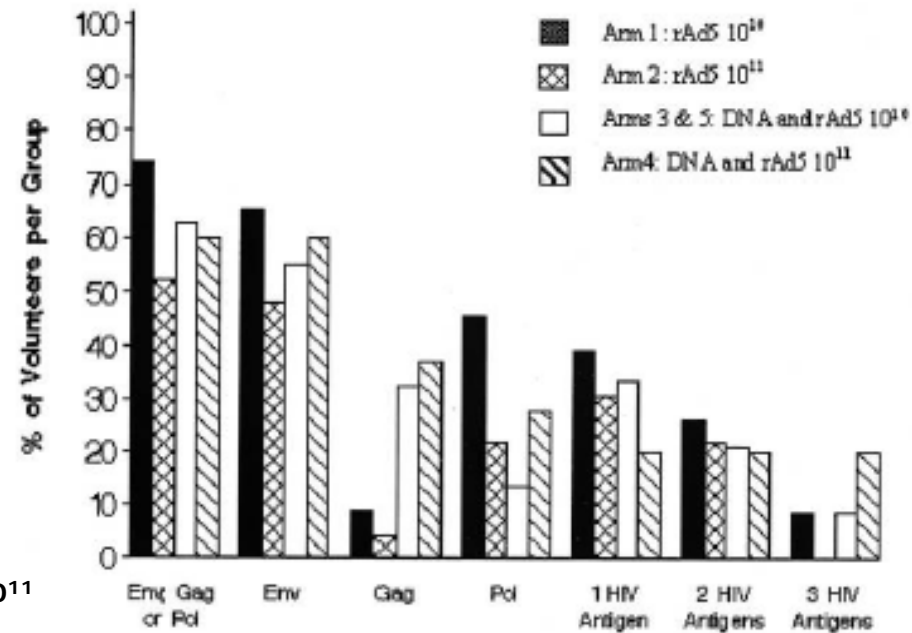
rAd5.HIV-1 *gag/pol* (subtype B)

rAd and DNA-rAd induce similar T-cell responses

Maximum T-cell response
6 weeks after vaccination



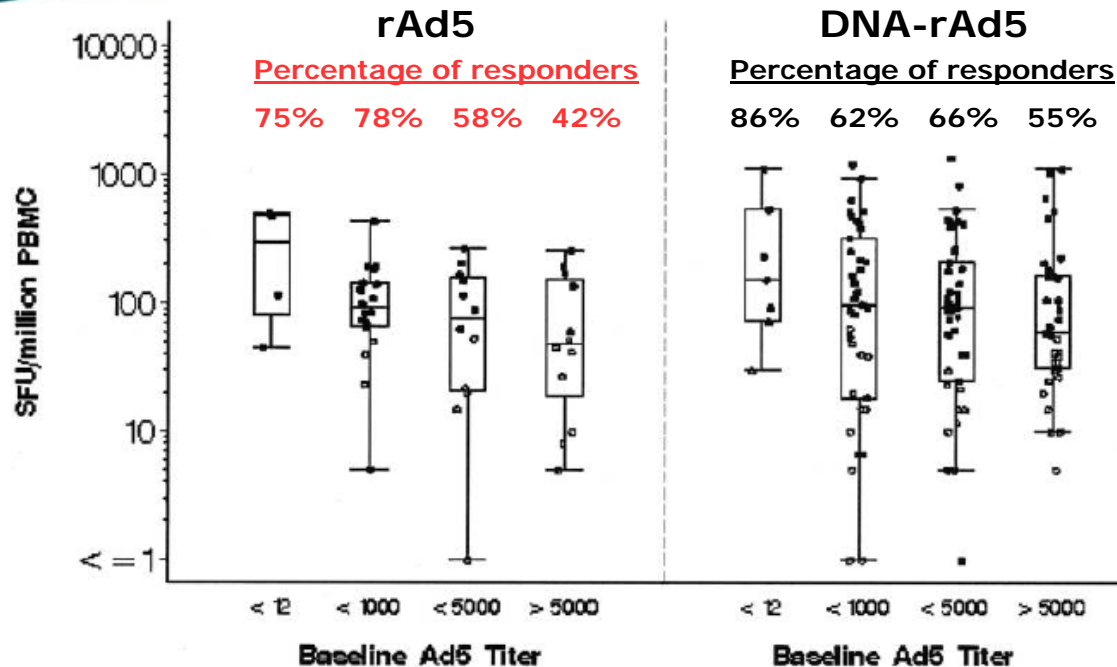
Percentage of T-cell responders
6 weeks after vaccination



rAd compared to DNA-rAd:

- No difference in magnitude of IFN- γ T-cell responses
- No statistical significant difference in percentage of responders to any Env, Gag or Pol peptide pool

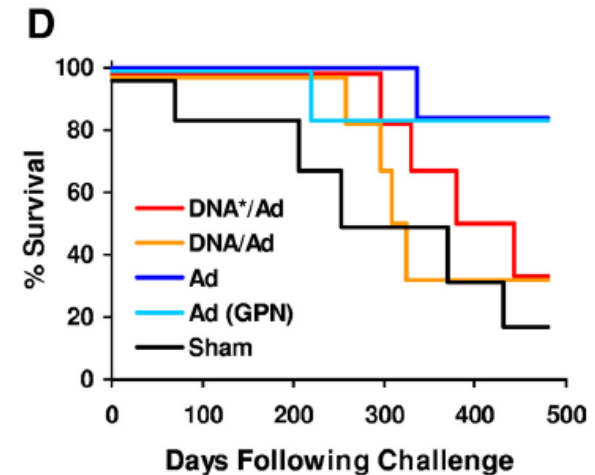
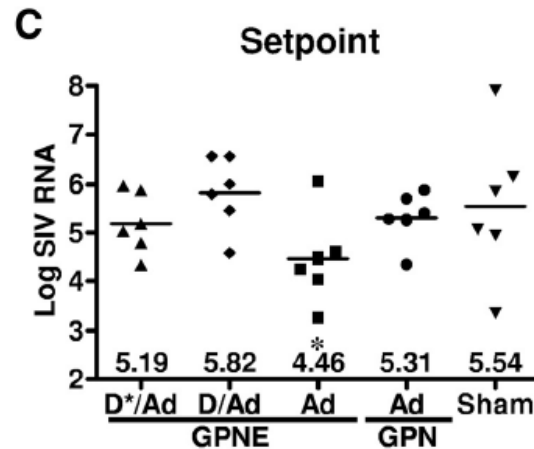
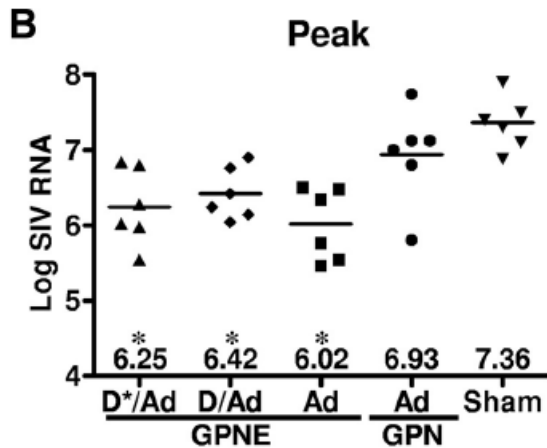
Small decrease in % responders in rAd5 group, with increasing baseline Ad5 titer



Increasing Ad5 titer at baseline :

- No difference in magnitude of T-cell response with increasing baseline Ad5 titer in rAd5 and DNA-rAd5 groups
- **Small decrease in percentage of responders** in subjects with higher baseline Ad5 titer in rAd5 group only (P=0.048)

DNA prime – rAd boost did not improve protection in monkeys



JOURNAL OF VIROLOGY, Sept. 2009, p. 9584–9590
 0022-538X/09/\$08.00+0 doi:10.1128/JVI.00821-09
 Copyright © 2009, American Society for Microbiology. All Rights Reserved.

Vol. 83, No. 18

Protective Efficacy of a Single Immunization of a Chimeric Adenovirus Vector-Based Vaccine against Simian Immunodeficiency Virus Challenge in Rhesus Monkeys[∇]

Dan H. Barouch,^{1,7*} Jinyan Liu,¹ Diana M. Lynch,¹ Kara L. O'Brien,¹ Annalena La Porte,¹
 Nathaniel L. Simmons,¹ Ambryce M. Riggs,¹ Sarah Clark,¹ Peter Abbink,¹
 David C. Montefiori,² Gary Landucci,³ Donald N. Forthal,³ Steven G. Self,⁴
 Angela Carville,⁵ Keith Mansfield,⁵ and Jaap Goudsmit⁶

History of potential HIV vaccines

25 years since discovery of HIV.....

Merck	VRC Genvec	Sanofi pasteur VaxGen
Ad5	DNA - Ad5	ALVAC –AIDSVAX
gag pol nef	gag pol Env	gag prot env
2005-2007	2010-ongoing	2009

...only 3 vaccines reached phase 3 efficacy trials

→ Phase II ongoing to study reduction in viral load.



History of potential HIV vaccines

25 years since discovery of HIV.....

Merck <hr/> Ad5 gag pol nef 2005-2007	VRC Genvec <hr/> DNA - Ad5 gag pol Env 2010-ongoing	Sanofi pasteur VaxGen <hr/> ALVAC –AIDSVAX gag prot env 2009
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...only 3 vaccines reached phase 3 efficacy trials

Thai trial: phase III study that combined ALVAC and AIDSVAX

The NEW ENGLAND JOURNAL of MEDICINE

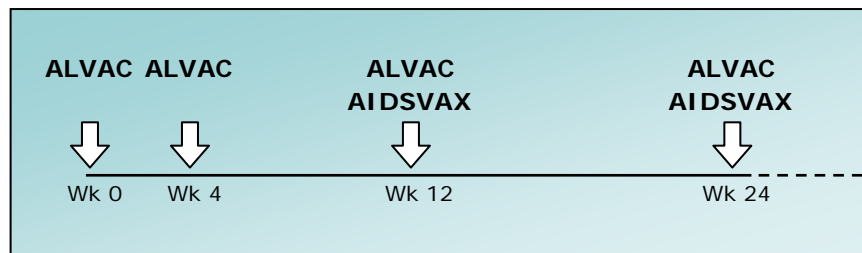
ESTABLISHED IN 1812

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 Prem Sri, 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. Bix, 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*



sanofi pasteur

The vaccines business of sanofi-aventis Group

VaxGen
OVERCOMING INFECTIOUS DISEASE

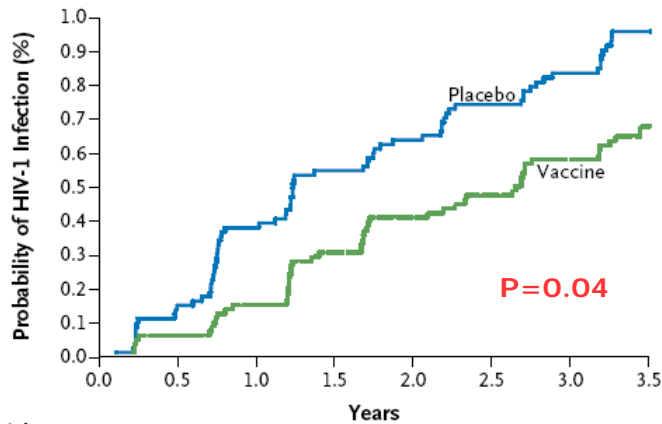
GS
ID GLOBAL SOLUTIONS
FOR INFECTIOUS DISEASES

Rerks-Ngarm et al. N Engl J Med 2009; 361.

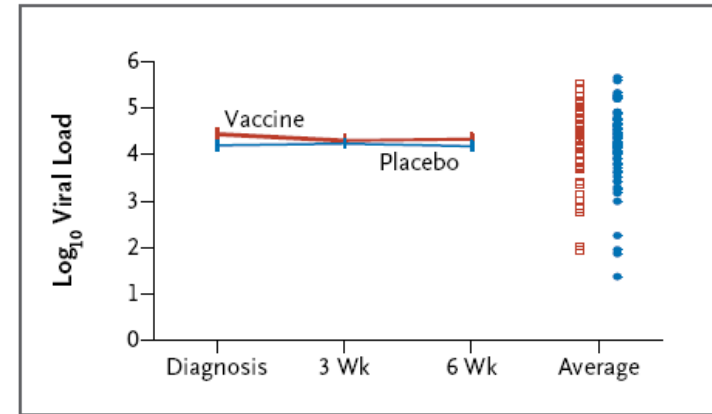
The vaccine showed modest protection

- No effect on viral load -

C Modified Intention-to-Treat Analysis



No. at Risk		Years			
	0.5	1.0	1.5	2.0	2.5
Placebo	8198	7775	7643	7441	7325
Vaccine	8197	7797	7665	7471	7347
Cumulative No. of Infections					
Placebo		30	50	65	74
Vaccine		12	32	45	51



Vaccine Efficacy (MITT):

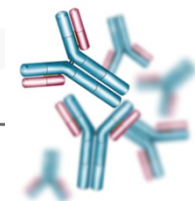
31.2% (95% CI 1.7-51.8%)

Vaccination induced mainly Env-specific antibodies

Table 3. Immunogenicity Analyses at Baseline and 12 Months.*

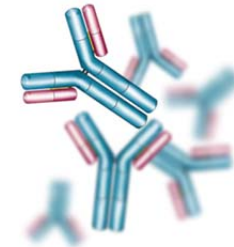
Assay and Antigen	Baseline <i>no. positive/total no. (%)</i>	12 Months *	
		Vaccine <i>no. positive/total no. (%)</i>	Placebo <i>no. positive/total no. (%)</i>
ELISPOT			
Gag	7/194 (3.6)	13/156 (8.3)	3/41 (7.3)
Env	7/198 (3.5)	25/157 (15.9)	3/41 (7.3)
Gag or Env	8/198 (4.0)	31/157 (19.7)	3/41 (7.3)
Intracellular cytokine staining			
CD8 Gag	11/200 (5.5)	11/144 (7.6)	4/56 (7.1)
CD8 Env	15/200 (7.5)	16/144 (11.1)	8/56 (14.3)
CD4 Gag	0/200	2/144 (1.4)	0/56
CD4 Env	4/200 (2.0)	49/144 (34.0)†	2/56 (3.6)
Binding antibody‡			
gp120 MN	8/200 (4.0)	140/142 (98.6)†	0/58
gp120 A244	1/200 (0.5)	140/142 (98.6)†	0/58
p24	2/200 (1.0)	74/142 (52.1)†	0/58
Lymphoproliferation‡§			
gp120 MN	23/96 (24.0)	62/71 (87.3)†	5/25 (20.0)
gp120 A244	12/96 (12.5)	64/71 (90.1)†	4/25 (16.0)
p24	19/96 (19.8)	35/71 (49.3)¶	4/25 (16.0)

* 6 months past final immunization



Lessons learned from the Thai trial

- **31% vaccine efficacy by heterologous prime boost**
 - **But....study was done in a relatively low risk population**
- **Env-specific antibody inducing component needed**
- **Mechanism of protection unclear**



History of potential HIV vaccines

25 years since discovery of HIV.....

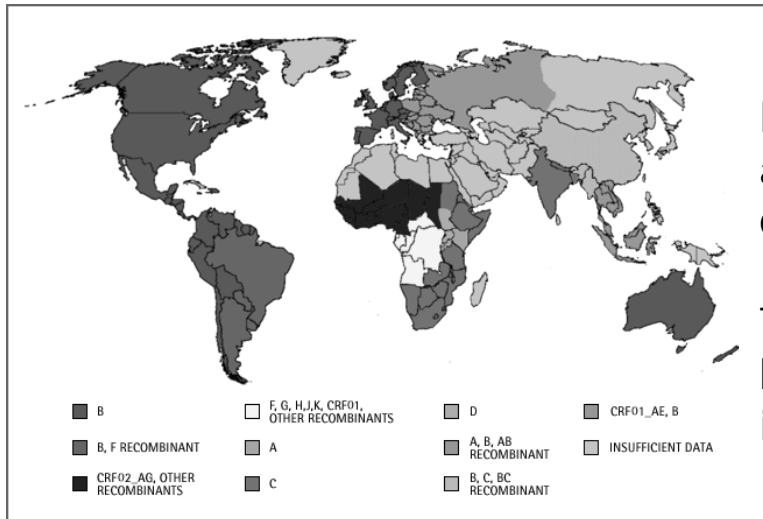
Merck <hr/> Ad5 gag pol nef 2005-2007	VRC Genvec <hr/> DNA - Ad5 gag pol Env 2010-ongoing	Sanofi pasteur VaxGen <hr/> ALVAC –AIDSVAX gag prot env 2009
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...only 3 vaccines reached phase 3 efficacy trials

Further testing in phase 3 ←



Improving the antigens in the vaccine by Mosaic antigens



HIV-1 can be divided into different clades and recombinants between clades based on genetic differences.

The breadth and potency of a vaccine may be increased if it induces cross-clade immunity.

Mosaic Antigen

assembled antigen that contains in one viral protein the immunological T-cell epitopes derived from different HIV-1 clades



Bette Korber

Mosaic vaccine increase the breadth of cellular immune responses in NHP

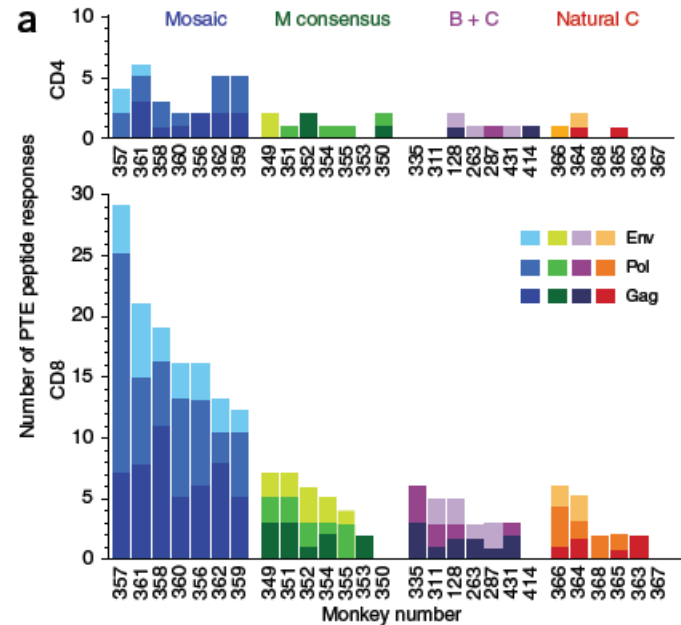


Mosaic vaccines elicit CD8⁺ T lymphocyte responses that confer enhanced immune coverage of diverse HIV strains in monkeys

Sampa Santra¹, Hua-Xin Liao², Ruijin Zhang², Mark Muldoon³, Sydeaka Watson^{4,5}, Will Fischer⁴, James Theiler⁴, James Szinger⁴, Hari Krishnan Balachandran¹, Adam Buzby¹, David Quinn¹, Robert J Parks², Chun-Yen Tsao², Angela Carville⁶, Keith G Mansfield⁶, George N Pavlakis⁷, Barbara K Felber⁷, Barton F Haynes², Bette T Korber^{4,8} & Norman L Letvin¹

Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys

Dan H Barouch^{1,2}, Kara L O'Brien¹, Nathaniel L Simmons¹, Sharon L King¹, Peter Abbink¹, Lori F Maxfield¹, Ying-Hua Sun¹, Annalena La Porte¹, Ambryce M Riggs¹, Diana M Lynch¹, Sarah L Clark¹, Katherine Backus¹, James R Perry¹, Michael S Seaman¹, Angela Carville³, Keith G Mansfield³, James J Szinger⁴, Will Fischer⁴, Mark Muldoon^{5,6} & Bette Korber^{4,6}

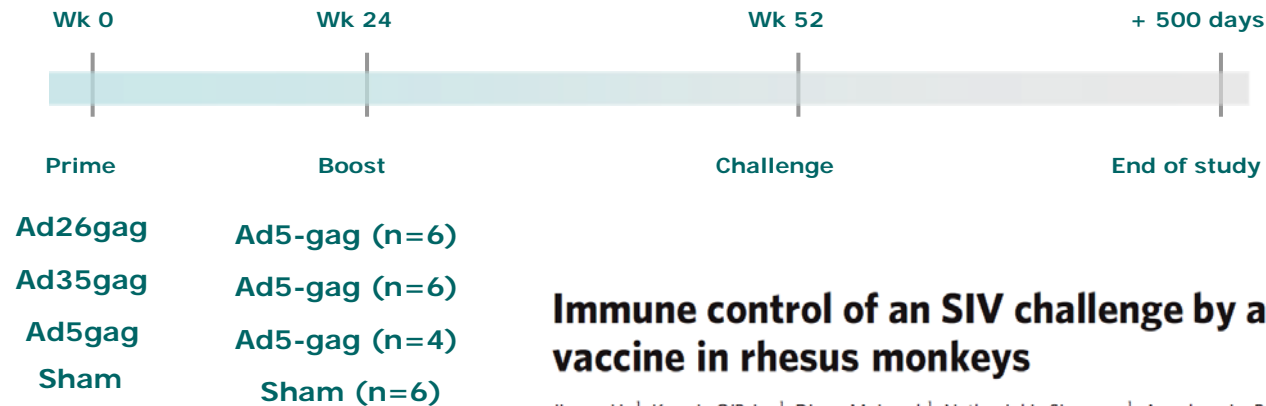


Breadth of vaccine coverage is vastly improved

SIV Protection after heterologous prime - boost in Rhesus



- Rhesus monkeys (*Macaca mulatta*)
- Prime wk0, boost wk 24 with 10^{11} vp
- Challenge at wk 52 with 100 IU SIV_{MAC251}
- One monkey each in the treatment groups Ad26/Ad5, A5/Ad5 and sham control expressed the protective *Mamu-B*08 allele*.

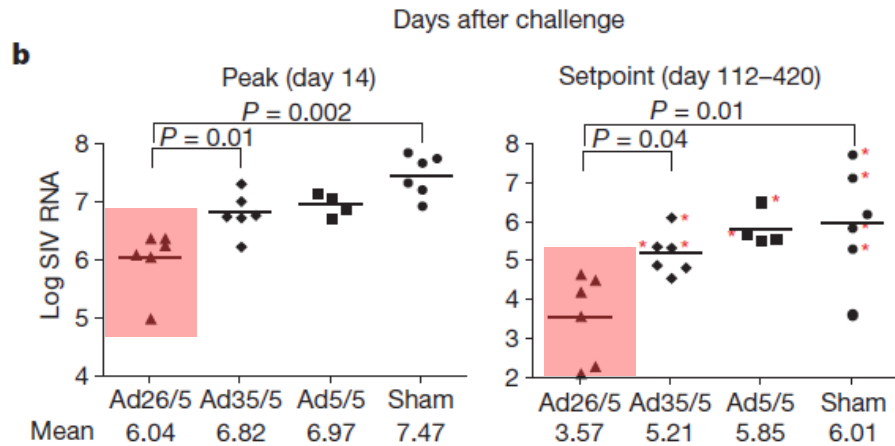
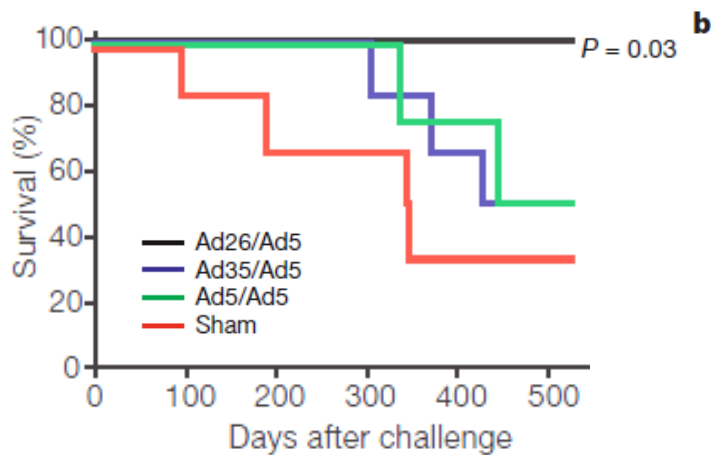


Immune control of an SIV challenge by a T-cell-based vaccine in rhesus monkeys

Jinyan Liu¹, Kara L. O'Brien¹, Diana M. Lynch¹, Nathaniel L. Simmons¹, Annalena La Porte¹, Ambryce M. Riggs¹, Peter Abbink¹, Rory T. Coffey¹, Lauren E. Grandpre¹, Michael S. Seaman¹, Gary Landucci², Donald N. Forthal², David C. Montefiori³, Angela Carville⁴, Keith G. Mansfield⁴, Menzo J. Havenga⁵, Maria G. Pau⁶, Jaap Goudsmit⁶ & Dan H. Barouch¹

Nature (2009); 457 (7225): 87-91

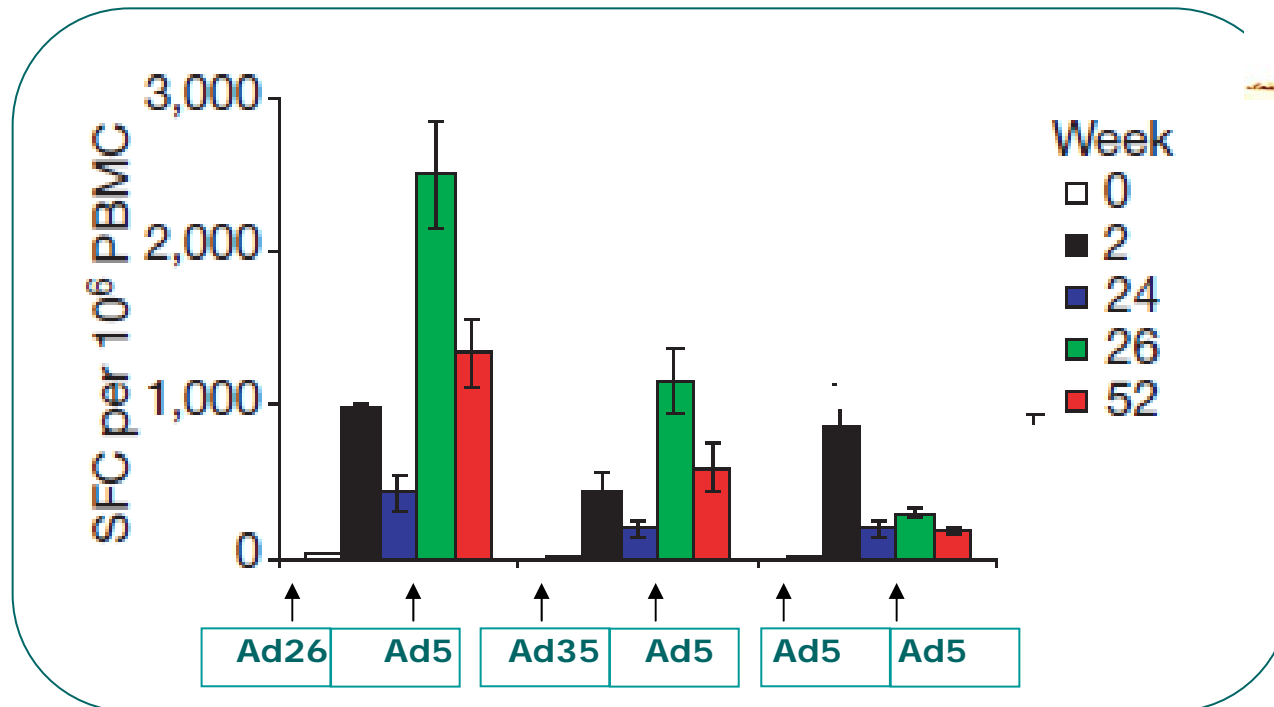
Improved survival after heterologous prime-boost



Ad26-Ad5 compared to placebo:

- 1.4 log reduction of peak (D14)
- 2.4 log reduction of *set point viral loads*

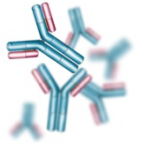
Improved immunogenicity after heterologous prime-boost



- *Heterologous* regimens induce higher T-cell response than homologous regimen

The way forward for an HIV vaccine

- Antibody inducing component thought to be needed (Thai trial)
- Only CD8+ T-cell inducing component seemed not sufficient to provide protection (STEP)
- Vaccine will probably consist of a combination of multiple components i.e. adenovirus / poxvirus / protein
- Several trials ongoing or planned to start in the near future

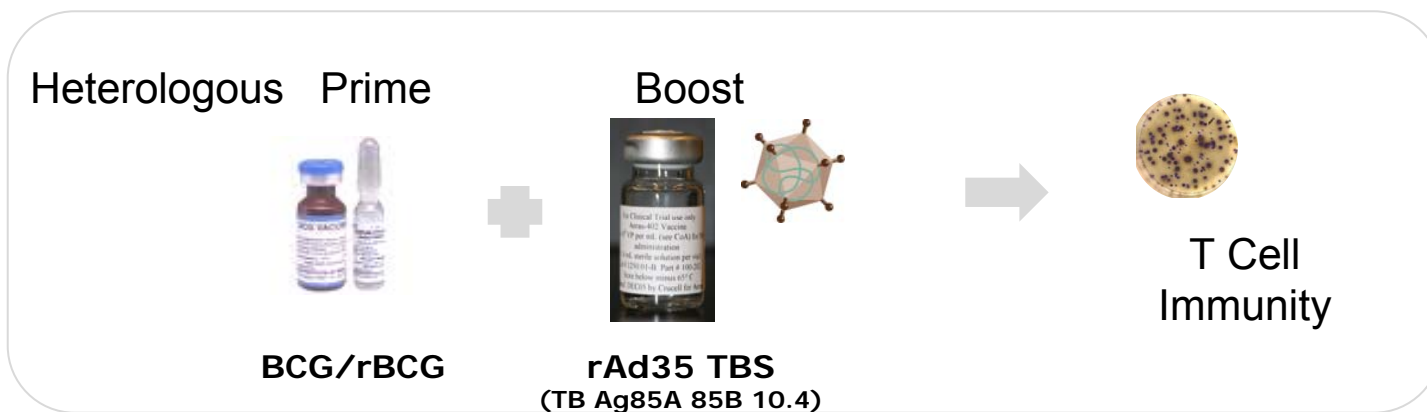


Results from the Thai trial, although low efficacy, give researchers hope!

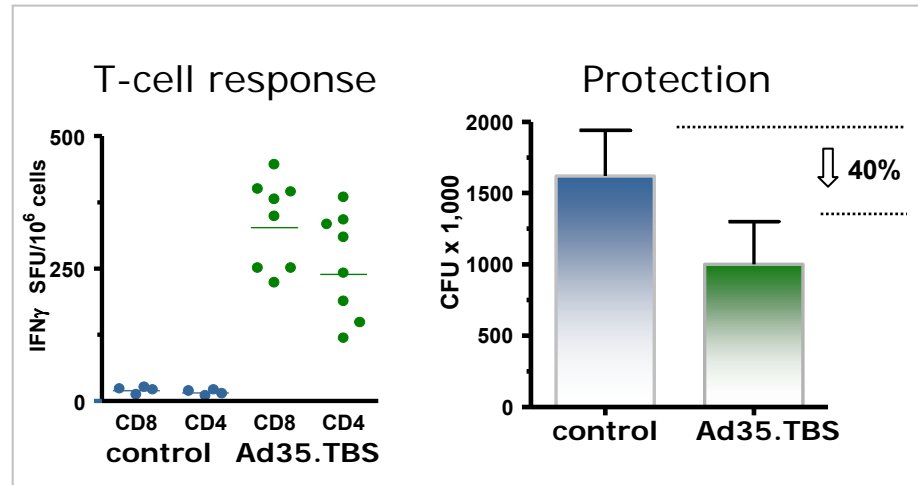
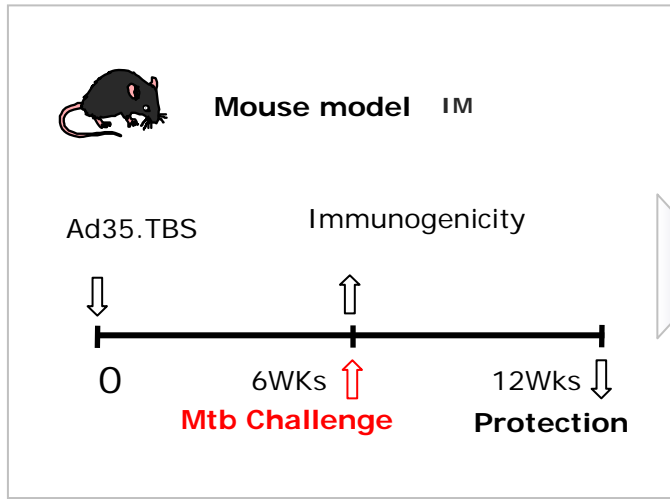
Example of TB vaccine trials...

Aim of Crucell/AERAS TB vaccine program

- Development of an rAd35 AdVac[®] vaccine for prophylaxis against TB, as boost to BCG, widely available and affordable in endemic countries



Ad35.TBS induced both CD4 and CD8 T-cell responses

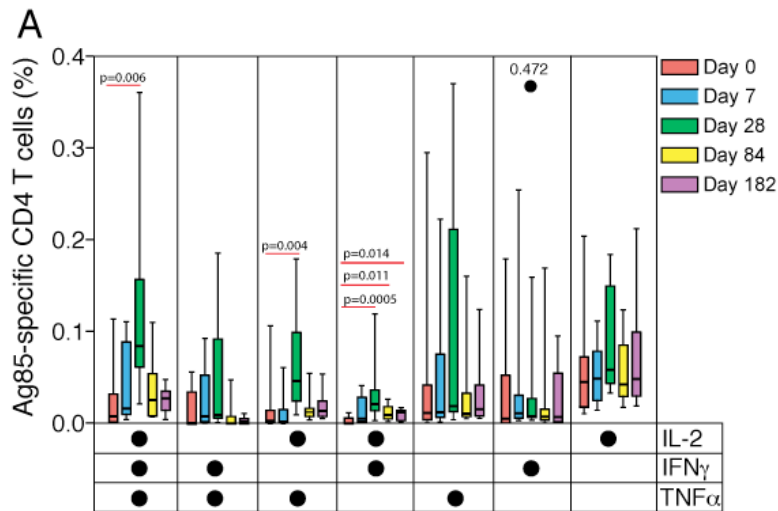


Radošević et al. Infect Immun 75:4105, 2007.



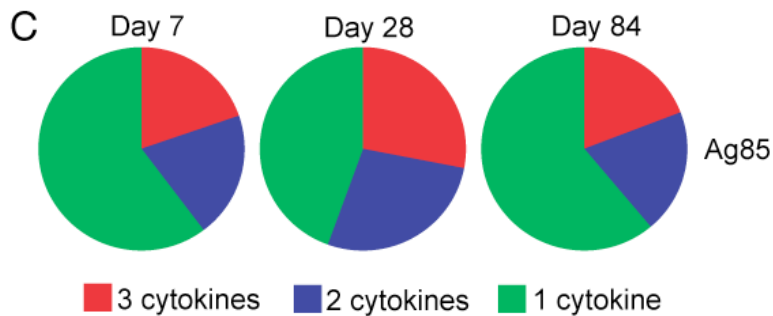
Polyfunctional T-cells after Ad35.TBS

C003: BCG-remote adults in South Africa



South Africa

- Healthy BCG-vaccinated adults
- 2 vaccinations with Ad35.TBS/AERAS-402 (day 0, day 56)



Summary

- TB and HIV: two major public health problems
- Although therapy available, high need for (more) preventive measures
- Vaccines are able to have significant impact on transmission
- Even vaccines with low efficacy or low coverage are able to reduce many infections

- Several potential HIV vaccines reached phase 3 efficacy studies
 - Studies provided more insight for further development
 - Recent Thai trial provided hopeful results for future development

- First new TB vaccines are reaching phase II and III studies