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 -

- 9.4 million incident TB cases: Asia (55%) and Africa (30%)
- 1.8 million deaths due to TB
Two overlapping epidemics: HIV and TB

- 2008 -

- Co-infection of TB and HIV common
- Co-infection highest in highest prevalence areas

9.4 million incident TB cases → 13-16% HIV infected
1.8 million deaths due to TB → 28% HIV infected
One third of people living with HIV suffer from TB
Current treatment strategies for HIV

HIV treatment when CD4 count $\leq 350$ cells/mm$^3$

- 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

www.who.int/hiv/en
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

Infectious patient

- Early case finding and treatment
- Quick and sensitive diagnosis

Non-infectious patient

(Re)activation

- Preventive treatment

Healthy non-infected individual

Transmission of *M. tb*

Development of latent TB infection
Transmission cycle of tuberculosis

Infectious patient

Non-infectious patient

(Re)activation

Transmission of *M. tb*

Healthy non-infected individual

Interruption by use of a vaccine

Development of latent TB infection
Options for TB vaccines

- **Pre-exposure vaccine**
  - newborns
  - infants

- **Therapeutic vaccine**
  - TB patients, on treatment

- **Post-exposure vaccine**
  - schoolchildren
  - adolescents
  - adults

Potential Uses of a TB Vaccine

www.aeras.org
• *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 livelong; 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)
- **V** = vaccinated subject
- **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%**

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 -

Baseline scenario
Prevention and treatment efforts extended to maximum coverage by 2013; without a vaccine new HIV infections will persist.

% reduction in new infections between 2016-2050

- LOW: 15%
- MEDIUM: 37%
- HIGH: 59%

100 (thousands of new adult infections)
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

Young and Dye, Cell 2006
# Vaccine development phases

<table>
<thead>
<tr>
<th>Basic science (discovery)</th>
<th>Pre-clinical studies</th>
<th>Clinical trials Phase I, II, III</th>
<th>Vaccine product &amp; Phase IV trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection of antigen</td>
<td>Safety</td>
<td>First in human</td>
<td>Monitoring rare AEs</td>
</tr>
<tr>
<td>Type of vaccine</td>
<td>Immunogenicity</td>
<td>Safety</td>
<td>Effectiveness</td>
</tr>
<tr>
<td>(vector, live/killed, adjuvant)</td>
<td>Proof of concept (protection)</td>
<td>Immunogenicity</td>
<td></td>
</tr>
<tr>
<td>Delivery method</td>
<td>Study a useful animal model</td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>(i.m, i.d, i.n)</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>
Examples of HIV vaccine trials...
# History of potential HIV vaccines

## 25 years since discovery of HIV......

<table>
<thead>
<tr>
<th>Company</th>
<th>Vaccine Type</th>
<th>Components</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Merck</td>
<td>Ad5</td>
<td>gag pol nef</td>
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...only 3 vaccines reached phase 3 efficacy trials
# History of potential HIV vaccines

25 years since discovery of HIV.......  

<table>
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<th>Company</th>
<th>Vaccine Type</th>
<th>Antigens</th>
<th>Phase</th>
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...only 3 vaccines reached phase 3 efficacy trials
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

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?

MITT Cases up till Oct 2007

1-tailed p-value = 0.322 (for \( V_{E_{\text{INF}}} \neq 0 \))
2-tailed p-value = 0.581 (for \( V_{E_{\text{INF}}} \neq 0 \))

1-tailed p-value = 0.020 (for \( V_{E_{\text{INF}}} \neq 0 \))
2-tailed p-value = 0.029 (for \( V_{E_{\text{INF}}} \neq 0 \))
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**
  - Ad5
  - gag pol nef
  - 2005-2007

- **VRC Genvec**
  - DNA - Ad5
  - gag pol Env
  - 2010-ongoing

- **Sanofi pasteur VaxGen**
  - ALVAC –AIDSVAX
  - gag prot env
  - 2009

...only 3 vaccines reached phase 3 efficacy trials

Program discontinued
# History of potential HIV vaccines

**25 years since discovery of HIV…….**

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<th>Company</th>
<th>Vaccine Details</th>
<th>Years</th>
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...only 3 vaccines reached phase 3 efficacy trials
VRC HIV-program: DNA combined with rAd5 studied in phase 1/2

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

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

Dan H. Barouch, Jinyan Liu, Diana M. Lynch, Kara L. O’Brien, Annalena La Porte, Nathaniel L. Simmons, Ambyrige M. Riggs, Sarah Clark, Peter Abbink, David C. Montefiori, Gary Landucci, Donald N. Forthal, Steven G. Self, Angela Curville, Keith Mansfield, and Jaap Goudsmit

0022-538X/09/3980.00+0 doi:10.1128/JVI.00821-09
Copyright © 2009, American Society for Microbiology. All Rights Reserved.
## History of potential HIV vaccines

### 25 years since discovery of HIV......

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...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......

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...only 3 vaccines reached phase 3 efficacy trials
Thai trial: phase III study that combined ALVAC and AIDSVAX

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

Supachai Rerks-Ngarm, M.D., Punnee Pitsutthithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nalorn Premtri, M.D., Chawetsan Narniwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gunanathan, 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., Suparnit Chunsuttiwat, M.D., Chirasak Khambonruang, 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∗

### ALVAC ALVAC

- Wk 0
- Wk 4

### ALVAC AIDSVAX

- Wk 12

### AIDSVAX AIDSVAX

- Wk 24

The vaccine showed modest protection
- No effect on viral load -

Vaccine Efficacy (MITT): 31.2% (95% CI 1.7-51.8%)
**Vaccination induced mainly Env-specific antibodies**

<table>
<thead>
<tr>
<th>Assay and Antigen</th>
<th>Baseline no. positive/total no. (%)</th>
<th>12 Months * Vaccine no. positive/total no. (%)</th>
<th>Placebo no. positive/total no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ELISPOT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gag</td>
<td>7/194 (3.6)</td>
<td>13/156 (8.3)</td>
<td>3/41 (7.3)</td>
</tr>
<tr>
<td>Env</td>
<td>7/198 (3.5)</td>
<td>25/157 (15.9)</td>
<td>3/41 (7.3)</td>
</tr>
<tr>
<td>Gag or Env</td>
<td>8/198 (4.0)</td>
<td>31/157 (19.7)</td>
<td>3/41 (7.3)</td>
</tr>
<tr>
<td><strong>Intracellular cytokine staining</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8 Gag</td>
<td>11/200 (5.5)</td>
<td>11/144 (7.6)</td>
<td>4/56 (7.1)</td>
</tr>
<tr>
<td>CD8 Env</td>
<td>15/200 (7.5)</td>
<td>16/144 (11.1)</td>
<td>8/56 (14.3)</td>
</tr>
<tr>
<td>CD4 Gag</td>
<td>0/200</td>
<td>2/144 (1.4)</td>
<td>0/56 (0.0)</td>
</tr>
<tr>
<td>CD4 Env</td>
<td>4/200 (2.0)</td>
<td>49/144 (34.0)</td>
<td>2/56 (3.6)</td>
</tr>
<tr>
<td><strong>Binding antibody</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gp120 MN</td>
<td>8/200 (4.0)</td>
<td>140/142 (98.6)†</td>
<td>0/58 (0.0)</td>
</tr>
<tr>
<td>gp120 A244</td>
<td>1/200 (0.5)</td>
<td>140/142 (98.6)†</td>
<td>0/58 (0.6)</td>
</tr>
<tr>
<td>p24</td>
<td>2/200 (1.0)</td>
<td>74/142 (52.1)†</td>
<td>0/58 (0.0)</td>
</tr>
<tr>
<td><strong>Lymphoproliferation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gp120 MN</td>
<td>23/96 (24.0)</td>
<td>62/71 (87.3)†</td>
<td>5/25 (20.0)</td>
</tr>
<tr>
<td>gp120 A244</td>
<td>12/96 (12.5)</td>
<td>64/71 (90.1)†</td>
<td>4/25 (16.0)</td>
</tr>
<tr>
<td>p24</td>
<td>19/96 (19.8)</td>
<td>35/71 (49.3) ‡</td>
<td>4/25 (16.0)</td>
</tr>
</tbody>
</table>

* 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**
  - Ad5
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  - 2005-2007

- **VRC Genvec**
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  - ALVAC –AIDSVAX
  - gag prot env
  - 2009

...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
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 Zhang³, Mark Muldoon³, Sydeaka Watson⁴,⁵, Will Fischer⁴, James Thelcer⁴, James Szinger⁵, Harikrishnan Balachandran⁶, Adam Buzby⁷, David Quinn⁸, Robert J Parks², Chun-Yen Tsao², Angela Carville⁹, Keith G Mansfield⁶, George N Pavlakis¹⁰, Barbara K Felber¹¹, Barton F Haynes⁸, Bette T Korber⁴,⁵ & Norman L Letvin¹²

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

Dan H Barouch¹³,², Kara L O’Brien¹, Nathanial L Simmons¹, Sharon L King¹, Peter Abbink¹, Lori F Maxfield¹, Ying-Hua Sun¹, Annalena La Porte¹, Ambryrice M Riggs¹, Diana M Lynch¹, Sarah L Clark¹, Katherine Backus¹, James R Perry¹, Michael S Seaman¹, Angela Carville⁹, Keith G Mansfield⁶, James J Szinger⁵, Will Fischer⁴, Mark Muldoon³,¹⁰ & Bette Korber⁴,⁵

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.

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

Nature (2009); 457 (7225): 87-91
Improved immunogenicity after heterologous prime-boost

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

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

Polyfuctional 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)

Phase I study in infants (C-018-402)

Healthy infants aged 6-9 months were vaccinated at day 0 and day 56.

Vaccine is immunogenic at highest dose

CD8 response to Ag85B
(any of 3 cytokines IFN-γ, TNF-α, IL-2)

Healthy infants aged 6-9 months were vaccinated at day 0 and 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