Acute HIV infection and HIV elite control: pathways to a vaccine and cure?

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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

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for prevention</td>
<td>96% (73; 99)</td>
</tr>
<tr>
<td>(Africa, Asia, America’s)</td>
<td></td>
</tr>
<tr>
<td>PrEP for discordant couples</td>
<td>73% (49; 85)</td>
</tr>
<tr>
<td>(Partners PrEP)</td>
<td></td>
</tr>
<tr>
<td>PrEP for heterosexuals</td>
<td>63% (21; 48)</td>
</tr>
<tr>
<td>(Botswana TDF2)</td>
<td></td>
</tr>
<tr>
<td>Medical male circumcision</td>
<td>54% (38; 66)</td>
</tr>
<tr>
<td>(Orange Farm, Rakai, Kisumu)</td>
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</tr>
<tr>
<td>PrEP for MSMs</td>
<td>44% (15; 63)</td>
</tr>
<tr>
<td>(America’s, Thailand, South Africa)</td>
<td></td>
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<tr>
<td>STD treatment</td>
<td>42% (21; 58)</td>
</tr>
<tr>
<td>(Mwanza)</td>
<td></td>
</tr>
<tr>
<td>Microbicide</td>
<td>39% (6; 60)</td>
</tr>
<tr>
<td>(CAPRISA 004 tenofovir gel)</td>
<td></td>
</tr>
<tr>
<td>HIV Vaccine</td>
<td>31% (1; 51)</td>
</tr>
<tr>
<td>(Thai RV144)</td>
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</tbody>
</table>

Abdool Karim 2013
Full life expectancy not restored by HAART

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

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

Total projected annual AIDS resource requirements

Billions of US dollars

2007 2010 2015 2020 2025 2030

- Rapid scale-up (80% HAART coverage)
- Current trends (40% HAART coverage)

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

Hecht et al., *Health Affairs* 2009; 28: 1591; Bongaarts et al., *Science* 2010; 328: 1359
<table>
<thead>
<tr>
<th>Disease</th>
<th>Total Cases</th>
<th>Year</th>
<th>Cases in 1994</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diptheria</td>
<td>206,939</td>
<td>1921</td>
<td>2</td>
<td>-99.9%</td>
</tr>
<tr>
<td>Measles</td>
<td>894,134</td>
<td>1941</td>
<td>963</td>
<td>-99.9%</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209</td>
<td>1968</td>
<td>1537</td>
<td>-99.9%</td>
</tr>
<tr>
<td>Pertusis</td>
<td>265,269</td>
<td>1934</td>
<td>4617</td>
<td>-99.9%</td>
</tr>
<tr>
<td>Polio</td>
<td>12,269</td>
<td>1952</td>
<td>0*</td>
<td>100%</td>
</tr>
<tr>
<td>Rubella</td>
<td>57,686</td>
<td>1969</td>
<td>227</td>
<td>-99.9%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1,560</td>
<td>1923</td>
<td>51</td>
<td>-99.9%</td>
</tr>
</tbody>
</table>
## Duration between discovery of microbiologic cause of selected infectious diseases and development of a vaccine

<table>
<thead>
<tr>
<th>Disease</th>
<th>Years to develop vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid</td>
<td>105</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>92</td>
</tr>
<tr>
<td>Pertussis</td>
<td>89</td>
</tr>
<tr>
<td>Polio*</td>
<td>47</td>
</tr>
<tr>
<td>Measles</td>
<td>42</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>15</td>
</tr>
<tr>
<td>HIV</td>
<td>30...</td>
</tr>
</tbody>
</table>

*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.

2003: AIDSVAX STUDIES
VaxGen Env gp120
Humoral Immunity
• Phase III studies in high-risk subjects in the US/Thailand
• Elicited type-specific Abs but not broadly reactive NAbs
• No efficacy

2007: STEP-PHAMBILI STUDIES
Merck Ad5-Gag/Pol/Nef
Cellular Immunity
• Phase IIb study in high-risk subjects in North/South America and South Africa
• Elicited cellular immunity by IFN-γ ELISPOT assays
• No efficacy, possible increased HIV-1 acquisition

2009: RV144
Sanofi ALVAC prime, AIDSVAX gp120 boost
Humoral and Cellular Immunity
• Phase III study in low-risk subjects in Thailand
• 31% reduction in HIV-1 acquisition with no viral load effect

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
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

**Old Paradigm:**
Vaccine-elicited immunity controls infection below threshold for transmission.

**New Paradigm:**
Vaccine-elicited immunity prevents or aborts infection, or provides early complete control.

**Goal of CTL-based vaccine:**
- Virus load (viral RNA copies/ml)
- Time after infection
- AIDS: 30,000
- Control: <1,500

**Graph:**
- Viral Load (viral RNA copies/ml)
- Time after infection
- AIDS
- No Infection or Abortive Infection
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

HIV Viral load

HAART
Residual viral replication

HIV Viral load

HAART

HAART
Anatomical reservoirs
Sterilising cure: lessons learned

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.

Sterilising cure: lessons learned

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

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

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

Time after HIV-1 infection

Viral load at set point (Viral Set Point)

Viral load at peak

Time of infection

Viral antibodies

Threshold of detection in the test

Acute HIV-1 infection (pre-seroconversion)

Early HIV-1 infection (seroconversion)

Early chronic HIV-1 infection

Viral load at set point (Viral Set Point)

14 days 21 days 35 days 88 days Time after HIV-1 infection 1 year

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?
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