HIV/AIDS vaccine development

Lecture 10

Review of lecture 9

How do vaccines work?

Types of Vaccines:

- Non-infectious: Inactivated, subunit & toxoid
- Live-attenuated
- Carrier
- DNA

Vaccine effectiveness
- From Edward Jenner to Smallpox eradication

Vaccine Safety:
- Clinical trials/VAERS

Challenges of vaccine development
- Developed vs. developing world
- The big three: TB, Malaria, HIV

Review of lecture 9

Are vaccines effective?
- Edward Jenner's experiment
- Name big success example: _______

How are vaccines tested?

Review of lecture 9

What are some challenges of vaccine development?
- Developed countries
- Developing countries

The big three: _______ , _______ , _______ 

How do vaccines work?

...By inducing adaptive immunity & memory!
Lecture map

HIV-1 / AIDS
- History of epidemic
- The HIV-1 virus
- Clinical course of infection

The HIV vaccine
- History of HIV vaccines
- Challenges for vaccine development
- Types of vaccines
  - VaxGen’s gp120
  - Sanofi Pasteur ALVAC: prime/boost strategy
  - Merk Ad5

Discussion:
- Specter article

History of HIV/AIDS

NY & CA: Men with symptoms of immunodeficiency

- Pneumocystis carinii in young gay men
- HIV isolated (Luc Montagnier/Robert Gallo)

1981 1983 1985

CDC: Increased Rx. of pentamidine
Syndrome also affected: IV drug users, hemophiliacs, blood transfusion patients & sexual partners of infected people

100 Cases 1000 Cases 100,000 Cases

Today = 1.3 million!

The Human Immunodeficiency virus (HIV)

Viral components:
- nucleic acid core (RNA)
- protein capsid
- envelope
- Glycoproteins

Clinical course of HIV/AIDS

Acute: Infection of CD4+ cells (T-helper cells), 50% of memory cells lost! Loss of defense repertoire!
High viral load
Symptoms 2-8wks: fever, pharyngitis, malaise, weight loss

Chronic: Decreased CD4+ cells cannot support rate of replication
Innate and adaptive immune responses control expansion
Integrated provirus acts as latent virus reservoir:
- no viral synthesis
- reservoir protected from antivirals and immune attack
Mostly asymptomatic: fatigue & lymphadenopathy

AIDS: Progressive loss of CD4+ (T helper) cells
= profound defect on cellular immunity
Increased viral load & opportunistic infections and cancer
Clinical course of HIV/AIDS

**ACUTE PHASE**
- Total CD4+ T cells decrease

**CHRONIC PHASE**
- CD8+ T cells decrease
- Virus-specific CTLs decrease

**PROFOUND IMMUNOSUPPRESSION**
- Total Th cells (CD4+)

Opportunistic infections of AIDS
- KS
- Candida albicans
- Cryptococcus
- Mycobacterium tuberculosis
- Herpes Zoster/Simpex

Adults and children estimated to be living with HIV 2007

**Total: 33.2 (30.6–36.1) million**

Estimated adults and child deaths from AIDS during 2007

**Total 2.1 million**

The social impact of HIV

Lecture map

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Discussion:
- Speret article
History of HIV vaccines

• 1984:
  - Robert Gallo discovers virus that causes HIV
  - Margaret Heckler, Secretary of HEW, predicts we will have vaccine within 2 years

• 1997:
  - President Clinton declares, "an HIV vaccine will be developed in a decade's time."

• 2003:
  - President Bush asks congress to appropriate $15B to combat the spread of HIV in Africa and the Caribbean

• Today: Where is the vaccine?

Challenges of HIV vaccine

1. Many forms of HIV
   - HIV-1: Many subtypes: 9 clades
   - HIV-2: Western Africa

2. Each sub-type may require different vaccine

3. HIV mutates rapidly: error-prone reverse transcriptase

4. Surface glycoproteins not readily available for antibodies:
   - Coated in sugary molecules: N-linked glycans
   - Change shape after attachment step

5. HIV infects, suppresses and destroys key cells of the immune system

Design Goals for HIV Vaccine

• Must produce both:
  - Antibody mediated immunity (B cells)
    - Immune system must see virus or viral debris
  - Cell mediated immunity (killer T cells)
    - HIV viral proteins must be presented to immune system on MHC receptors

Types of Vaccine

• Non-infectious vaccines
  - Stimulate B-cells
    - Killed virus
    - Subunit
    - Toxoid
  - Live attenuated vaccines
    - Stimulate both B-cells and killer T-cells
  - Carrier vaccines
    - Stimulate both B-cells and killer T-cells
  - DNA vaccines:
    - Stimulate both B-cells and T-cells

Methods tried for HIV vaccine development

<table>
<thead>
<tr>
<th>Type of vaccine</th>
<th>Example</th>
<th>Criteria for selection</th>
<th>Problems for HIV vaccine development</th>
</tr>
</thead>
</table>
| Live attenuated | Killed virus | Recombinant | "Live, low attenuated strains that have retained sufficient virulence."
|                 | Subunit  | Neutral                | "Live, non attenuated strains that are non-pathogenic."
|                 | Toxoid   | Neutral                | "Live, non attenuated strains that are non-pathogenic."

Vaccines used were:
- VaxGen subunit vaccine
- Live attenuated viral vaccine
- Most likely to stimulate necessary immune response
- Too dangerous!
  - Virus mutates constantly
  - If it undergoes mutation that restores its strength, would be devastating
- Monkey experiments:
  - All vaccinated animals developed AIDS and died (although more slowly than those infected with unaltered virus)

Live attenuated viral vaccine

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- Monkey experiments:
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Non infectious vaccines
- Whole virus: May not inactivate all virus
  Animal studies:
  - Stimulates Ab which block a small # of HIV viruses
  - Does not stimulate cell mediated immunity
- Viral subunit: envelope glycoprotein: VaxGen
  - Animal studies:
    - Not successful: protection only vs. virus with exact same envelope proteins
    - Phase I/III: Are memory B cells enough to protect vs. HIV?
      - Modest Ab response vs. limited spectrum of HIV strains
      - No cell-mediated immune response
    - Phase III: placebo, 2ble blind trials: Antibodies in 90% of vaccinated people, yet no protection (2005-2006; volunteer 2500 IV drug users Thailand, 5000 American gay men at risk for HIV-1)

Carrier vaccines
Use harmless viral vectors to transport HIV-1 genes into human cells. If booster is needed, different carrier must be used

ALVAC: Canarypox virus expressing 3 HIV proteins
Prime/boost strategy:
- Combination ALVAC/ VaxGen
  - Phase I/II: Safe and immunogenic: Ab, CD4+ & few CD8+ cells
  - Phase III: Thailand study: 16,000 patients, $120 million

Merk Ad5: Adenovirus5 expressing 3 HIV proteins
  - Phase I: Safety and immunogenicity: elicits CD8+ responses
  - Phase II: currently ~3000 volunteers in US and Caribbean
Problem: In developing countries ~80% pre-existing immunity to Ad5!

DNA vaccines
- Strategy:
  - Inject large amounts of DNA which codes for viral protein
  - Elicits immune response against that protein
  - Successful in animal trials
  - Generate killer T cell response
  - Can we find a single protein that will elicit immune response against many HIV strains?
  - Currently in Phase I: Oxford-Nairobi Prostitute Vaccine
    (Prime/boost: naked DNA - modified vaccinia Ankara virus as HIV gene carrier)

HIV trials in progress: 2006

HIV trials in progress: 2007

Dangers of Vaccine Trials
- Most researchers feel first HIV vaccines will not be more than 40-50% effective
  - Will vaccinated individuals engage in higher risk behaviors?
  - Vaccine could cause as much harm as it prevents
- Future vaccines cannot be tested against placebo, would be unethical

(From Rerks-Ngarm et al. AIDS, 2006, 20: 1471-1479)
Summary of lecture 10

The HIV-1 virus
- Life cycle
- Clinical course of disease: acute, chronic, AIDS

The HIV vaccine
- 5 challenges for vaccine development
- Possible vaccine alternatives
- Current HIV vaccines in advanced clinical trials: VaxGen, ALVAC, AD5
- Dangers of vaccine trials

Assignments for 2/19/2008
Homework 6

Discussion: The Uganda trials

Uganda Health Data
- Stable political situation
- African country most willing to openly confront HIV
- Adult HIV infection rate:
  - Ten years ago: 20% today: 6%
  - Each of the past 10 yrs: Fewer infections than yr before
- Life Expectancy:
  - Before HIV: 64 years today: 42 years
- Annual Income:
  - $300 per person
- Annual Health Expenditures:
  - $6 per person
- Vaccination rate
  - 1995: 47%
  - 2002: 37%

The Oxford Vaccine
- Combination of vaccines in prime / boost strategy
  - Naked DNA which codes for 3 HIV proteins
  - Carrier based vaccine (Modified vaccinia Ankara virus carrying same DNA)
- Early evidence:
  - Combination prime / boost generates bigger immune response than either component alone
  - Booster shots may be needed

The VaxGen Vaccine
- Subunit vaccine: good antibody response, but:
- Not very effective in 2 previous phase III trials (Thailand & US)

Cast of Characters
- Don Francis, President of VaxGen
- Andrew McMichael & Sarah Rowland-Jones
  - Developers of Nairobi prostitute vaccine
- Marcia Angel, former editor of NEJM
- Peter Lurie, Public Citizen's Health Group
- Pontiana Kaleebu, virologist in Uganda
- Seth Berkley, IAVI
- Larry Conroy, coordinates NIH vaccine trials
- Ugandan Medical Student
- Ezekial Emanuel, Chief of Bioethics, NIH
- Edward Mbidde, Uganda Cancer Inst.
Goal of Town Meeting
YOU ARE THE RESIDENTS OF MASAKA AND YOU HAVE TO DISCUSS & DECIDE:

Should your community:
  a) Participate in VaxGen Trial
     - No treatment for those who develop AIDS
  b) Wait for Oxford Vaccine
     - No treatment for those who develop AIDS
  c) Not participate in any trial unless treatment is provided for those who develop AIDS

Ezekial Emanual, Chief of Bioethics
NIH

• Simple idea: justice requires treating everyone, everywhere in exactly the same way
• Justice requires no such thing. It simply requires us to treat people fairly.
• If rules of clinical trials require participants to receive the best care on earth, there would be no clinical trials.

Marcia Angel
• Medical ethics has no borders
• What is morally right in America is morally right in Africa, too
• International rules of medical expt. require:
  – Volunteers in vaccine trial receive best treatment available, NOT level of care in poor country
• People are not guinea pigs. Research must hold human welfare above interest of society and science. If you don’t, you’re on a slippery slope where first humans are exploited for worthwhile purposes, then for not so worthwhile purposes.

Peter Lurie
• Fears scientists will use poor quality of care available in Africa to do what they want
• You are not permitted to use subjects to collect data just because it is useful to you
  – That is exploitation and abuse
  – That is what Tuskegee was
• Scientists will withhold treatments they know will work in the name of science
  – Will be greatest injustice in hx of medicine
• Tests of AZT proved there was a two-tiered standard for health care in the world
  – One set of rules for rich people, and another for those who are poor

Andrew McMichael
• Abhors hype
• Rarely discusses his vaccine work without saying it all might come to nothing
• First vaccine to target specific viral subtype most prevalent in East Africa
• Might require frequent booster shots

Sarah Rowland-Jones
• Infectious disease specialist
• First vaccine to target specific viral subtype most prevalent in East Africa
• Might require frequent booster shots
• Publicly wonders: If the vaccine doesn’t protect enough people, will you simply lose volunteer support when a better candidate comes along.
Pontiano Kaleebu

- We have asked Ugandans to be guinea pigs before. We have not come back to say, “Here is your reward.”
- Worried that question of whether trials can be done fairly and ethically, will overshadow science
  - We will give people the best care we can afford. That is fair.
  - If I could distribute anti-retroviral drugs, I would be thrilled. But, I don’t see how and I don’t see when. And the debate is a bit patronizing.
- This is not an issue of individual rights. It is a public health emergency.
- I never thought AIDS would be in my children’s futures. I have come to realize that now. And it frightens me.

Edward Mbidde, Uganda Cancer Inst.

- Last 15 years have best Uganda has seen
  - We have leadership, support, we are united
- If we need to go to work and we cannot afford a Mercedes Benz, should we refuse to ride a motorcycle? Or should we get there by the best route we have?
- Principles matter to us as much to us as they do to Americans. But we have been dying for a long time, and you cannot respond to death with principles.

Seth Berkley

- You have to ask yourself what on earth the people on this planet are doing
- In the end only a vaccine will matter
- There is no incentive for companies to make vaccines
- Society can’t get it together. These trials cost hundreds of millions of dollars. How do we pay for it?

Don Francis

- Would be pleased if vaccine worked 1/3 of the time
- If his vaccine is introduced and proven effective, no other vaccines can be tested against placebo

Ugandan Medical Student

- Would it be fair for village people to enter trial if those who became infected did not get anti-retroviral drugs?
  - Indicated missing medical supplies – aspirin, basic antibiotics
- We do not get the care you get. We never will. But I would line up tomorrow to test anything that might help us in any way. And I am sure the rest of the village would too.

Larry Corey

- Let’s be realistic for 5 minutes
- To create a vaccine that works 40% of the time, costs $1,000, and requires that you go to the lab to get a blood test every 6 weeks is crap
- We need a 90% biologically active product with no side-effects that costs at most $150-$200.
- We are asking the Third World to take risks that we have never taken ourselves
- Every other time that we have gone in with a vaccine, we have been able to say, “It works on our people.”
- Now – I have to say I have no idea if I have schlock or I have gold. But you need it and we need it, so we will have to test it on you.
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