HIV/AIDS vaccine development

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Lecture 10
BIOE 301-Bioengineering and World Health

Review of lecture 9

How do vaccines work?

Types ofVaccines:

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:

____ , _____ , _____

Review of lecture 9

How do vaccines work?

Types ofVaccines:

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

Vaccine effectiveness

-From Edward Jenner to Smallpox erradication

Vaccine Safety:

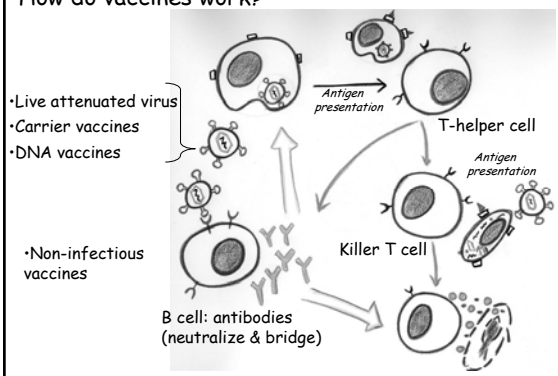
-Clinical trials/VAERS

Challenges of vaccine development

-Developed vs. developing world

-The big three: TB, Malaria, HIV

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

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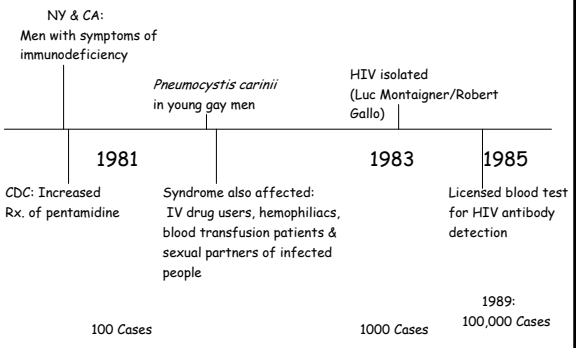
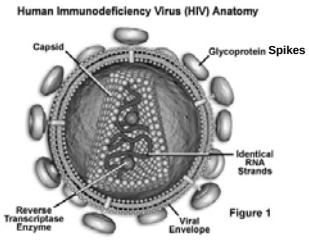
History of HIV/AIDS



The Human Immunodeficiency virus (HIV)

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



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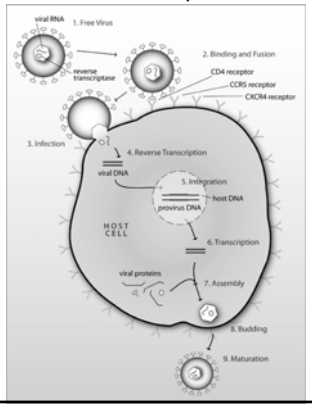


Clinical course of HIV/AIDS

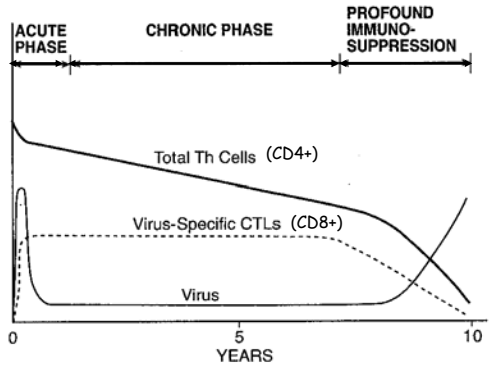
Acute: Infection of CD4+ cells (T-helper cells),
50% of memory cells lost! Loss of defense repertoire!
High viral load
Symptoms 2-8wks: fever, pharyngitis malaise, weight loss

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

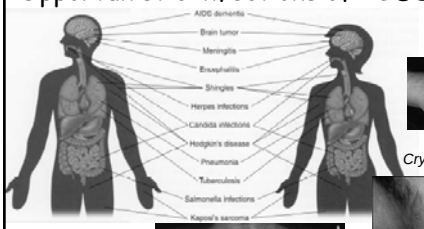
Mostly asymptomatic: fatigue & lymphoadenopathy

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



Opportunistic infections of AIDS



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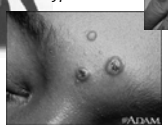
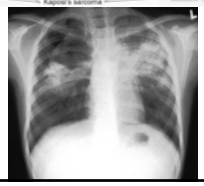
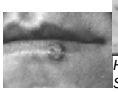
Candida albicans

Cryptococcus



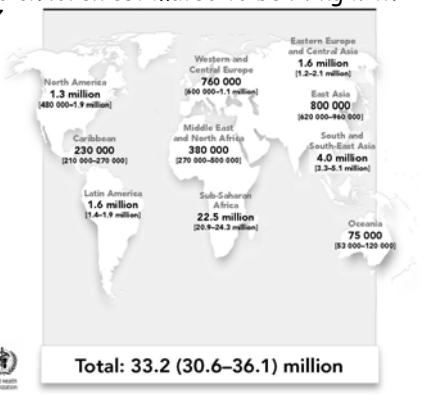


Mycobacterium tuberculosis

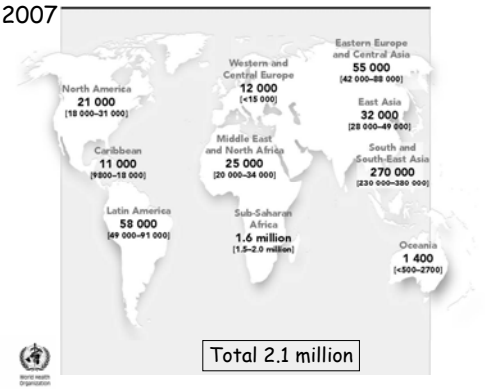


Herpes Zoster/ Simplex

Adults and children estimated to be living with HIV 2007



Estimated adults and child deaths from AIDS during 2007



The social impact of HIV

http://www.pbs.org/wgbh/rxforsurvival/series/diseases/hiv_aids.html

http://images.google.com/imgres?imgurl=http://news.bbc.co.uk/nol/shared/spl/hi/picture_gallery/06/africa_zimbabwe/0c_aids_orphans/img/1.jpg&imgrefurl=http://news.bbc.co.uk/2/shared/spl/hi/picture_gallery/06/africa_zimbabwe/0c_aids_orphans/html/1.stm&h=300&w=416&sz=34&hl=en&start=1&um=1&tbnid=-ACSdzqWD7ReVM:&tbnh=90&tbnw=125&prev=/images%3Fq%3Daids%2Borphans%26svnum%3D10%26um%3D1%26hl%3Den%26rls%3DRNWE,RNWE:2006-04,RNWE:en%26sa%3DN

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: <u>prime/boost strategy</u>**
  - **Merk Ad5**

Discussion:
- Specter 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 1 Methods used for the development of currently licensed vaccines and their failure to yield an HIV/AIDS vaccine

Type of vaccine	Examples	Correlate for protection	Problem for HIV vaccine development
Live attenuated[a]	Oral polio Measles Mumps Rubella Varicella	Antibody	Too risky—live attenuated viruses that have retained sufficient replication potential to effectively vaccinate slowly revert to virulence as well as cause disease in immunocompromised individuals.[6]
Whole inactivated	Inactivated polio Influenza Hepatitis A	Antibody	Inactivated and protein subunit vaccines protect primarily by eliciting antibodies. Both these approaches have failed to elicit protective antibodies for HIV/AIDS.[7,8]
Recombinant protein	Hepatitis B Papilloma	Antibody	? VaxGen subunit vaccine

[a]A live attenuated vaccine that is no longer routinely given is the smallpox vaccine.

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(From Robinson H.L., Clin. Pharmacol. Ther. 2007, 82: 686-693)

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)

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/II: 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 immunogenecity: 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

Phase	Candidate vaccine	Start	Volunteers	
I	Synthetic peptide V3 (B) (United Biomedical)	1994	30	Healthy
I/II	gp120 (B) (VaxGen)	1995	33	IDU
I	gp120 (B) (Chiron)	1995	54	Healthy
I	HIV-1 immunogen (Remune)	1996	30	HIV+ve
II	HIV-1 immunogen (Remune)	1997	297	HIV+ve
I/II	gp120 (B/E) (Chiron)	1997	380	Healthy
I/II	gp120 (B/E) (VaxGen)	1998	92	Recovering IDU
I/II	ALVAC-HIVivCP1521) + gp120 B/E (Aventis Pasteur and Chiron) and ALVAC-HIVivCP1521) + gp160 B/E (Aventis Pasteur)	2000	65	Healthy
			65	Healthy
I/II	ALVAC-HIVivCP1521) + gp120 B/E (Aventis Pasteur and VaxGen)	2000	125	Healthy
III	gp120 B/E (VaxGen)	1999	2500	IDU

IDU, Intravenous drug user.

(From Rerks-Ngarm et al. ;AIDS, 2006, 20: 1471-1479)

HIV trials in progress: 2007

Table 4 HIV vaccines advancing in human trials

Trial phase	Vaccine type	HIV insert	HIV-1 sequences in vaccine	Trial sites	Volunteers	Associated company
Phase III	ALVAC/gp120[37]	1 canary pox expressing Gag, Pol, gp120 followed by boosting with 2 gp120 proteins	B and E	Thailand	Fully enrolled 16,000 volunteers efficacy trial	Sanofi Pasteur, VaxGen
Phase II proof of concept	Ad5[38]	3 Ad5 vectors expressing Gag, Pol, and Nef	B	Americas, Caribbean, South Africa	4,500 volunteers are testing same and cross-clade protection in the presence of low and high levels of pre-existing immunity	Merck
	DNA/Ad5[39]	6 DNAs expressing Gag, Pol, Nef, and clades A-C Envs followed by boosting with 4 Ad5 vectors expressing Gag-Pol and clades A-C Envs	A-C	USA, Caribbean, Central and South Africa	720 volunteers will test for cross-clade protection	Developed by the NIH vaccine research center
Preparing to enter phase II	DNA/MVA[40]	1 DNA expressing Gag, Pol, and Env boosted by 1 MVA expressing Gag, Pol, and Env	B	Americas		GeoVax, developed at the Emory Vaccine Center and NIH
	DNA/MVA[41]	7 DNAs expressing sequences from clade A and B Gag, clade B Pol, clade B Rev, clade B Env, chimeras of clade A and C Envs and 1 MVA expressing a clade A/E recombinant from Thailand	A-C and E	Europe, Africa		Developed by Karolinska Institute, Walter Reed Army Institute for Research, and NIH
	DNA/NYVAC[42]	2 DNAs expressing gp120 and a Gag-Pol-Nef fusion protein boosted by a single MVA expressing the same proteins	Chinese B/C recombinant	China		Developed by EuroVac

NIH, National Institutes of Health.

(From Robinson H.L., Clin. Pharmacol. Ther. 2007, 82: 686-693)

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

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 / boos 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
- Pontiano Kaleebu, virologist in Uganda
- Seth Berkley, IAVI
- Larry Conroy, coordinates NIH vaccine trials
- Ugandan Medical Student
- Ezekial Emanual, 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 dosen't protect enough people, will you simply loose 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 though 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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The end