Biomedical Engineering for Global Health

Lecture 10

HIV/AIDS vaccine development

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

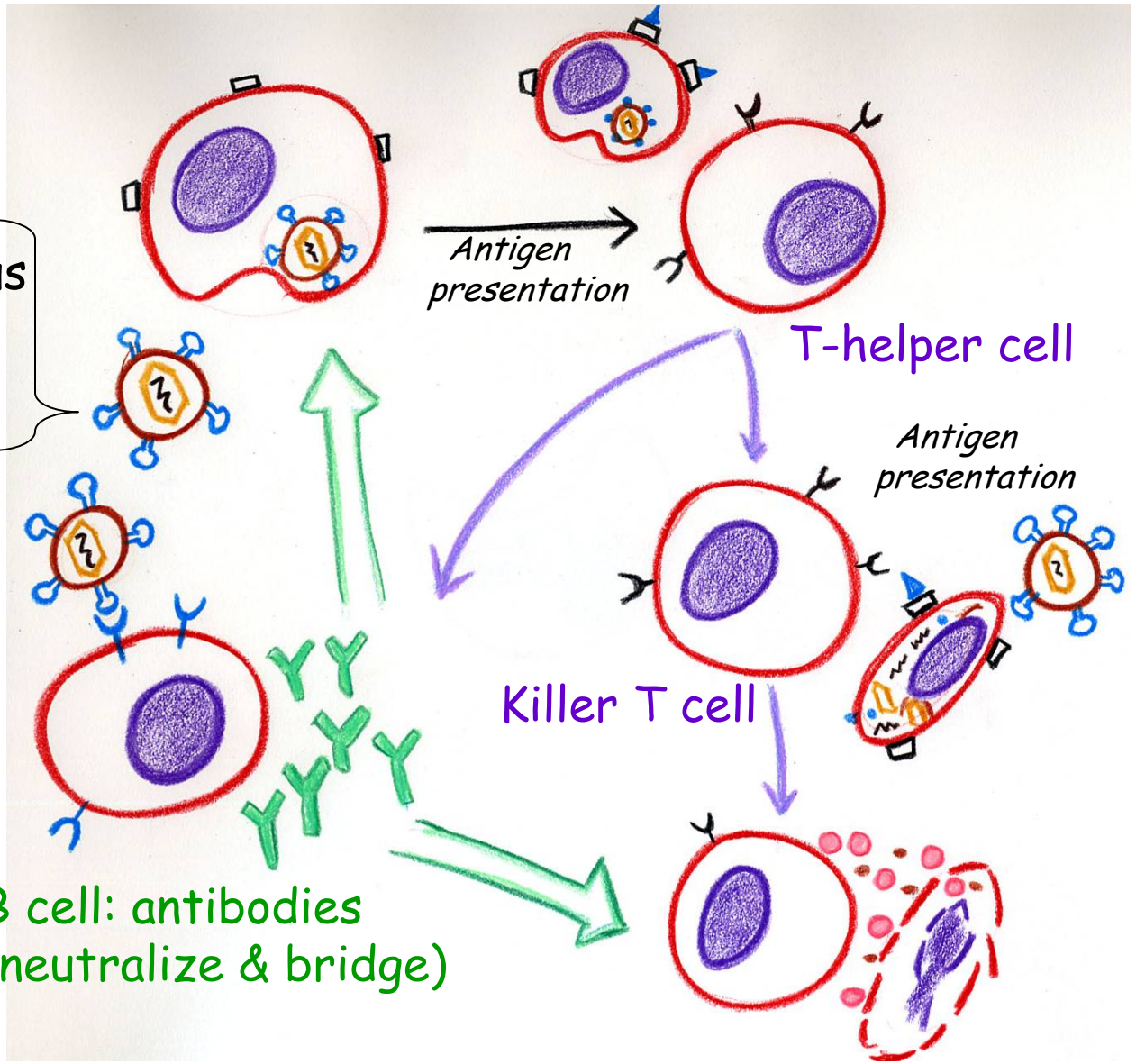
-Developed vs. developing world

-The big three: TB, Malaria, HIV

How do vaccines work?

- Live attenuated virus
- Carrier vaccines
- DNA vaccines

- Non-infectious vaccines



…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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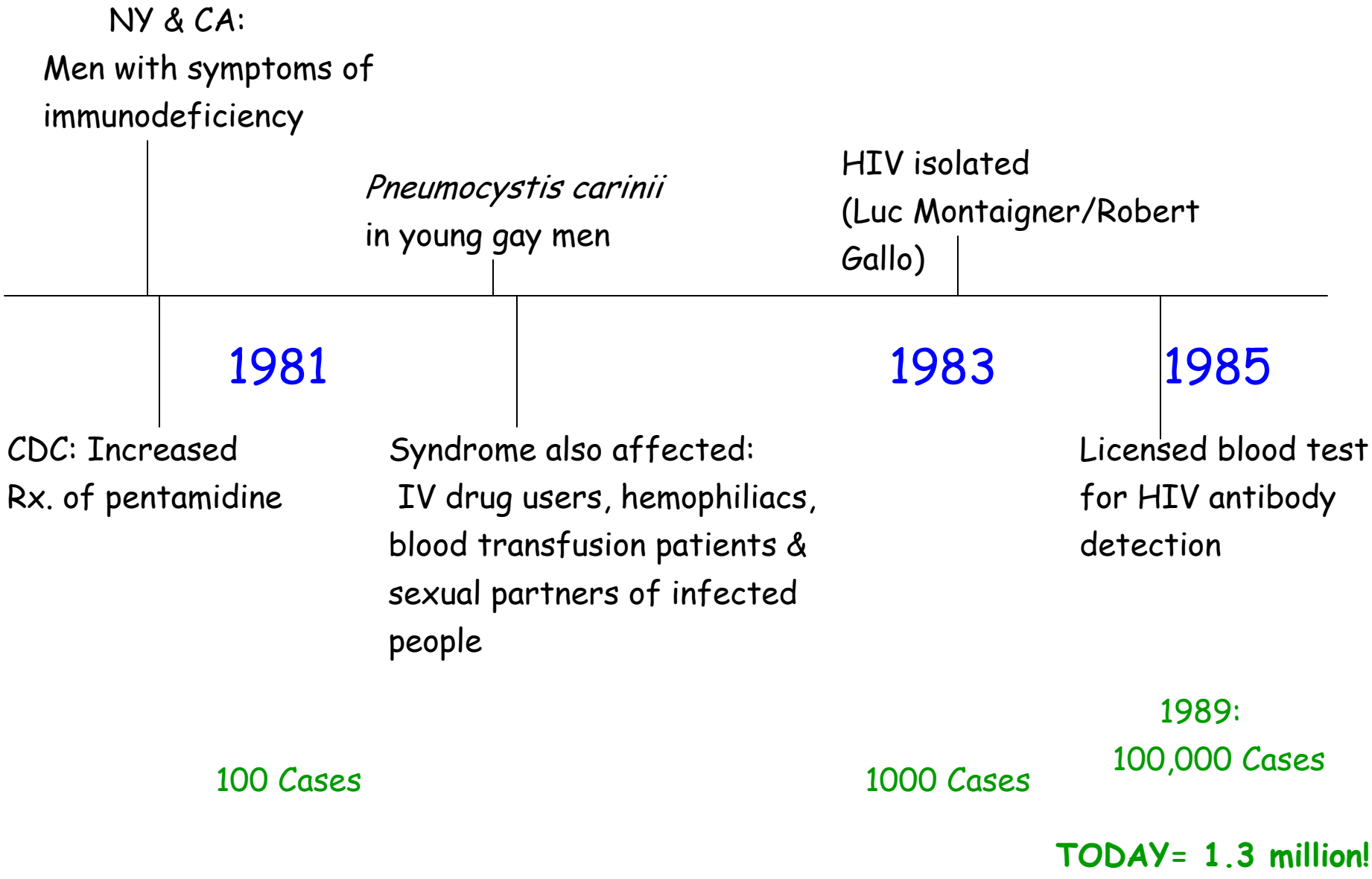
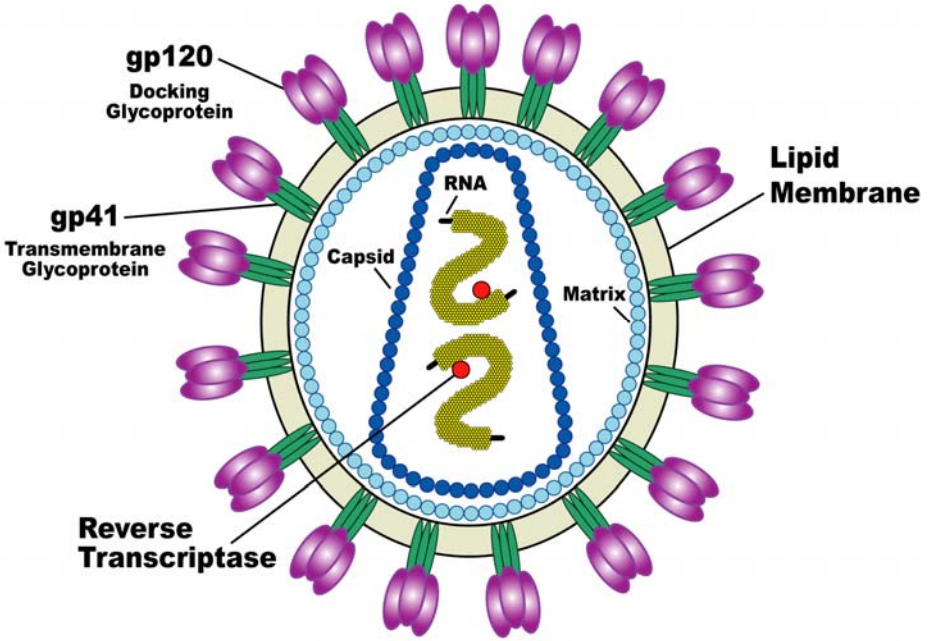
History of HIV/AIDS



The Human Immunodeficiency virus (HIV)

Viral components:

- -nucleic acid core (RNA)
- -protein capsid
- -envelope
- -Glycoproteins



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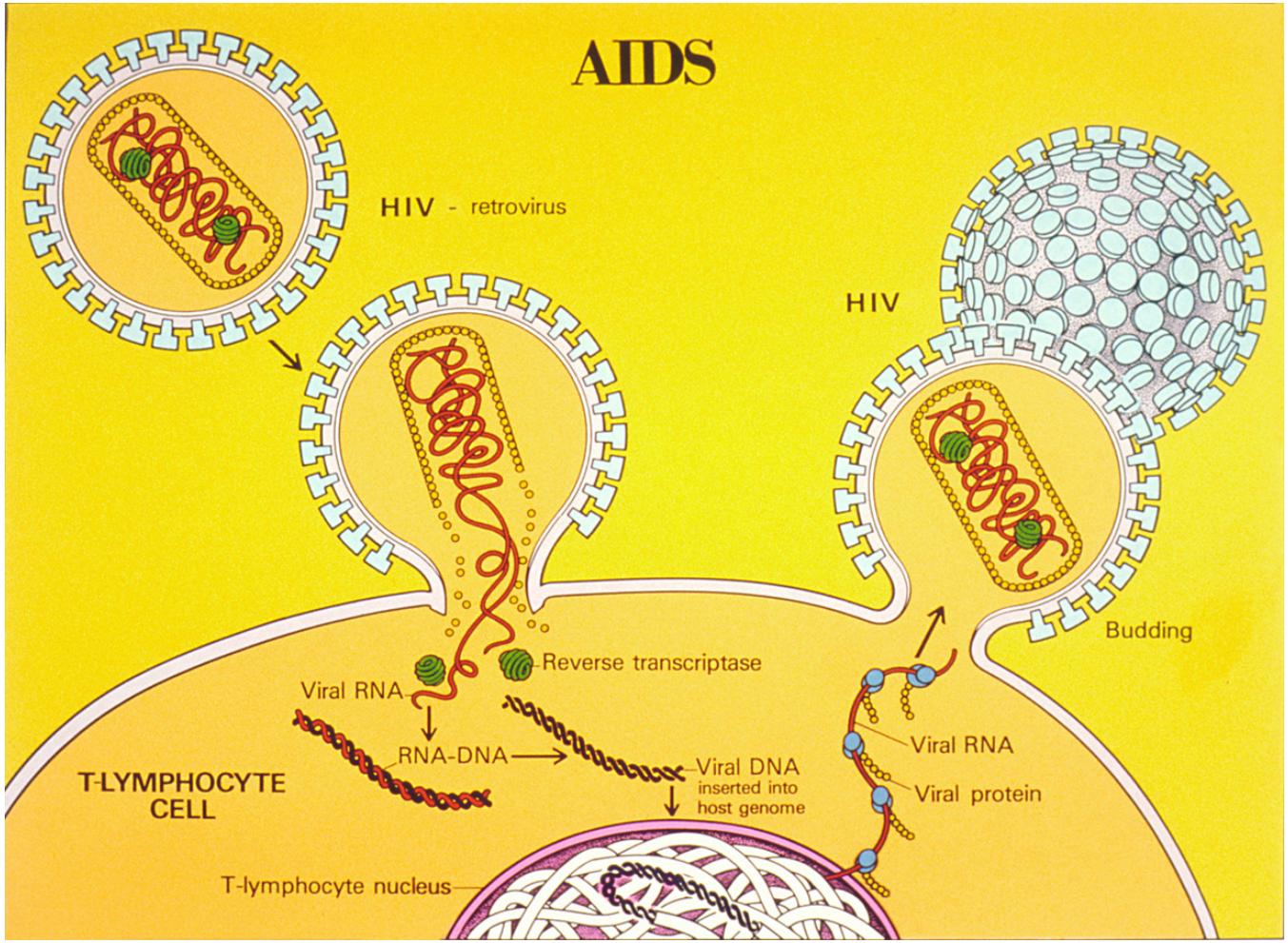


NCI/Trudy Nicholson.

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

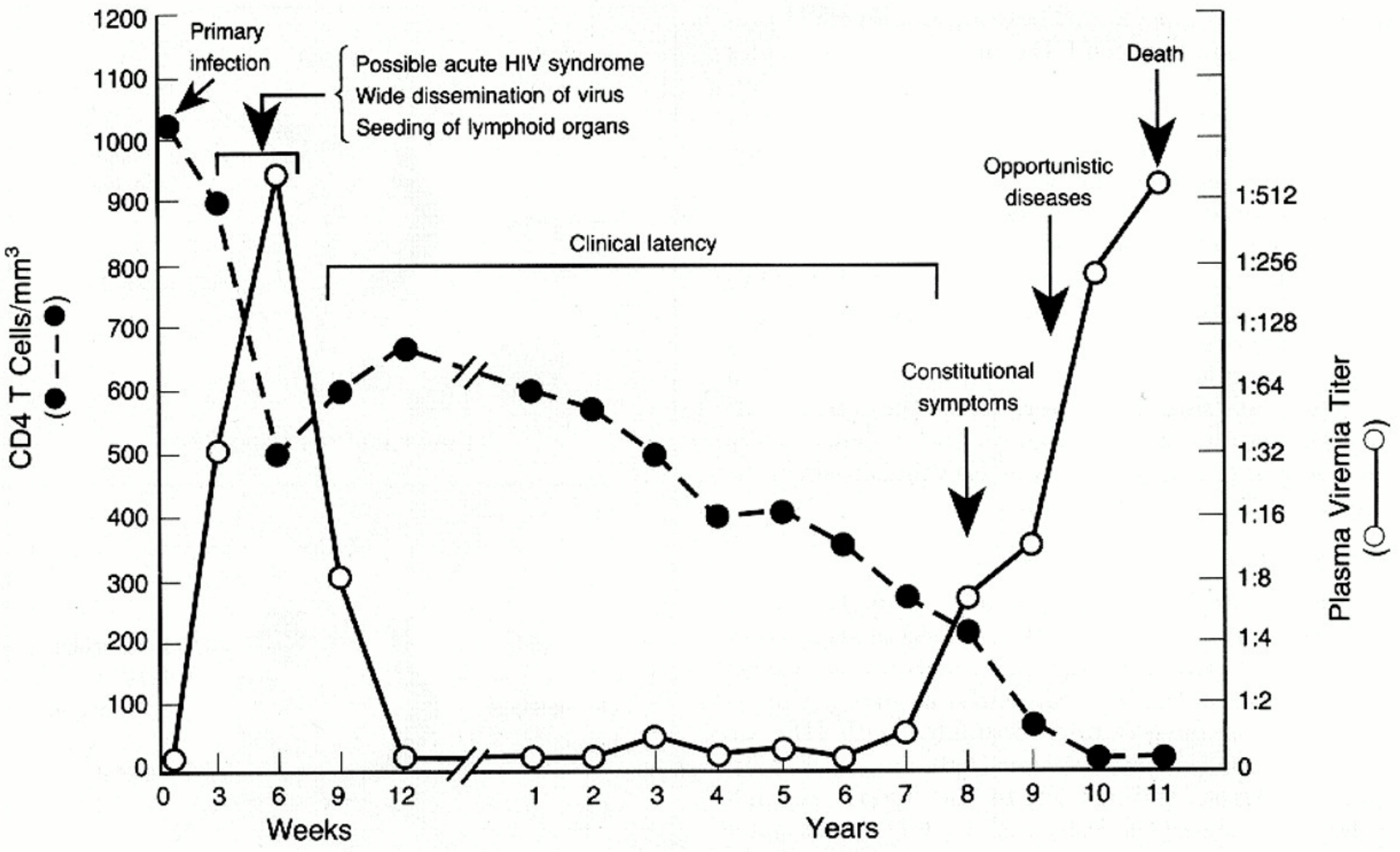
Mostly asymptomatic: fatigue & lymphoadenopathy

AIDS: Progressive loss of CD4+ (T helper) cells

= profound defect on cellular immunity

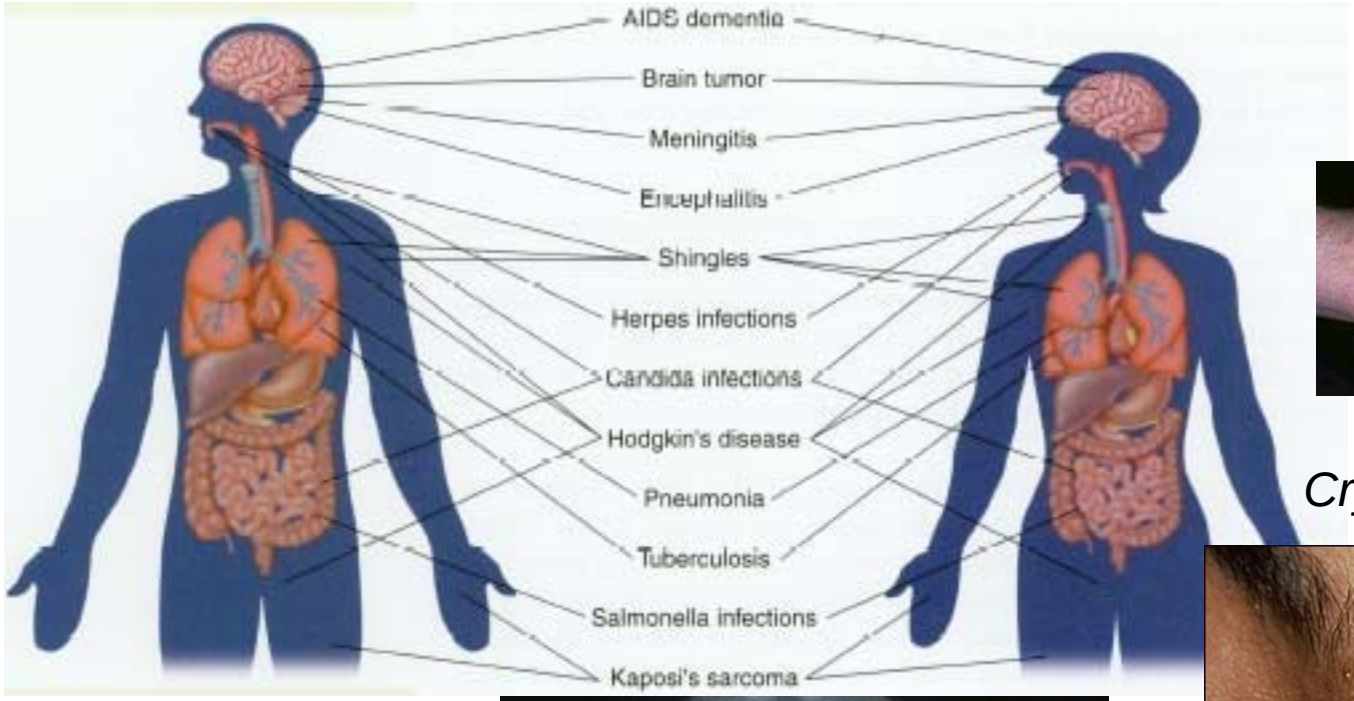
increased viral load & opportunistic infections and cancer

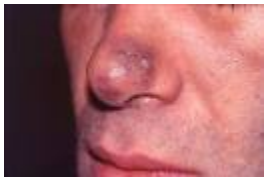
Clinical course of HIV/AIDS



G. Pantaleo et al. Mechanisms of Disease: the Immunopathogenesis of HIV Infection. NEJM. **328** (327–35) © 1993. Massachusetts Medical Society.

Opportunistic infections of AIDS





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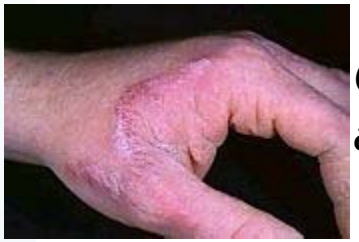
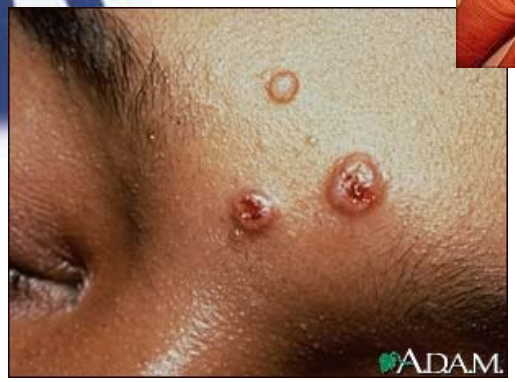
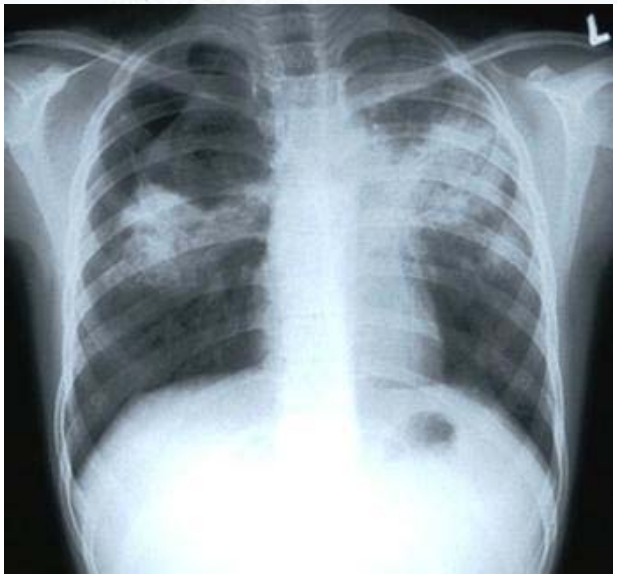


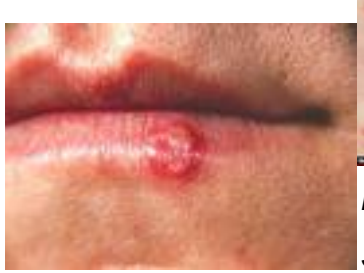
Candida albicans

Cryptococcus



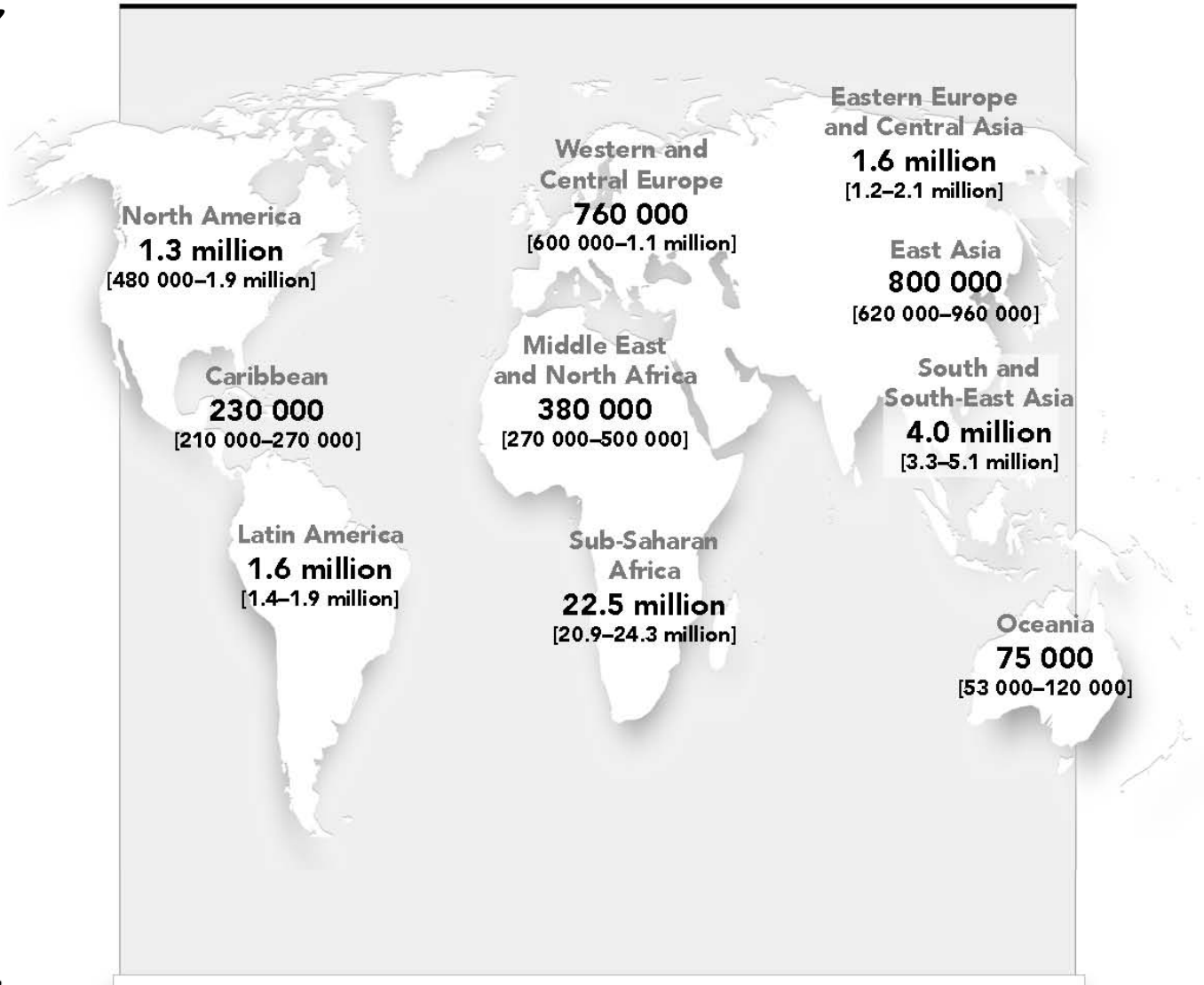
Mycobacterium tuberculosis





Herpes Zoster/ Simplex

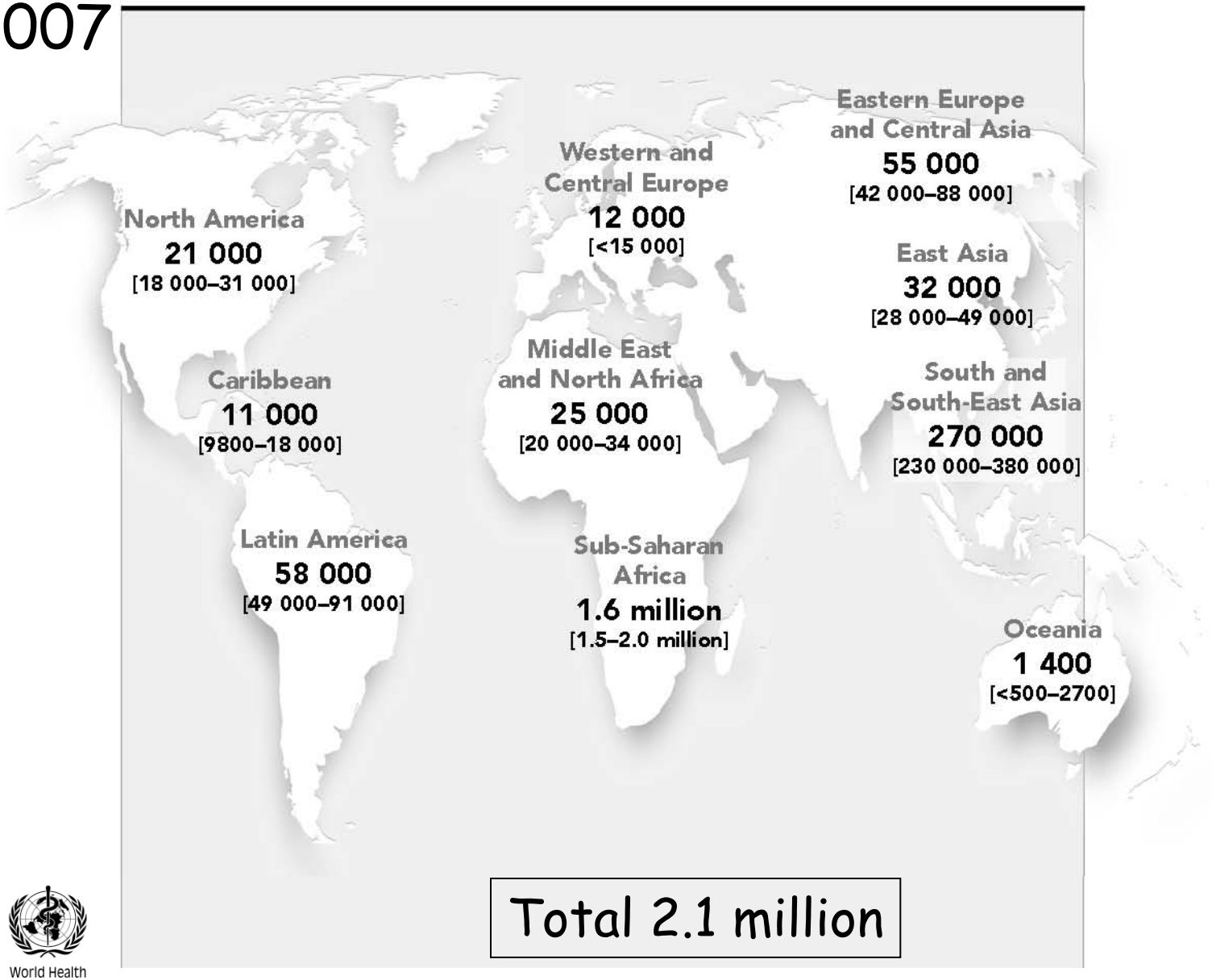
Adults and children estimated to be living with HIV 2007



UNAIDS
Joint United Nations Programme on HIV/AIDS
UNHCR • UNICEF • WFP • UNDP • UNFPA
UNODC • ILO • UNESCO • WHO • WORLD BANK

World Health Organization

Estimated adults and child deaths from AIDS during 2007



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World Health Organization

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_zimbabwe0s_aids_orphans/img/1.jpg&imgrefurl=http://news.bbc.co.uk/2/shared/spl/hi/picture_gallery/06/africa_zimbabwe0s_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
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- 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:

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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.

(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-HIV(vCP1521) + gp120 B/E (Aventis Pasteur and Chiron)	2000	65	Healthy
	and ALVAC-HIV(vCP1521) + gp160 B/E (Aventis Pasteur)		65	Healthy
I/II	ALVAC-HIV(vCP1521) + 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[57]	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[58]	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[59]	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[60]	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[61]	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[62]	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