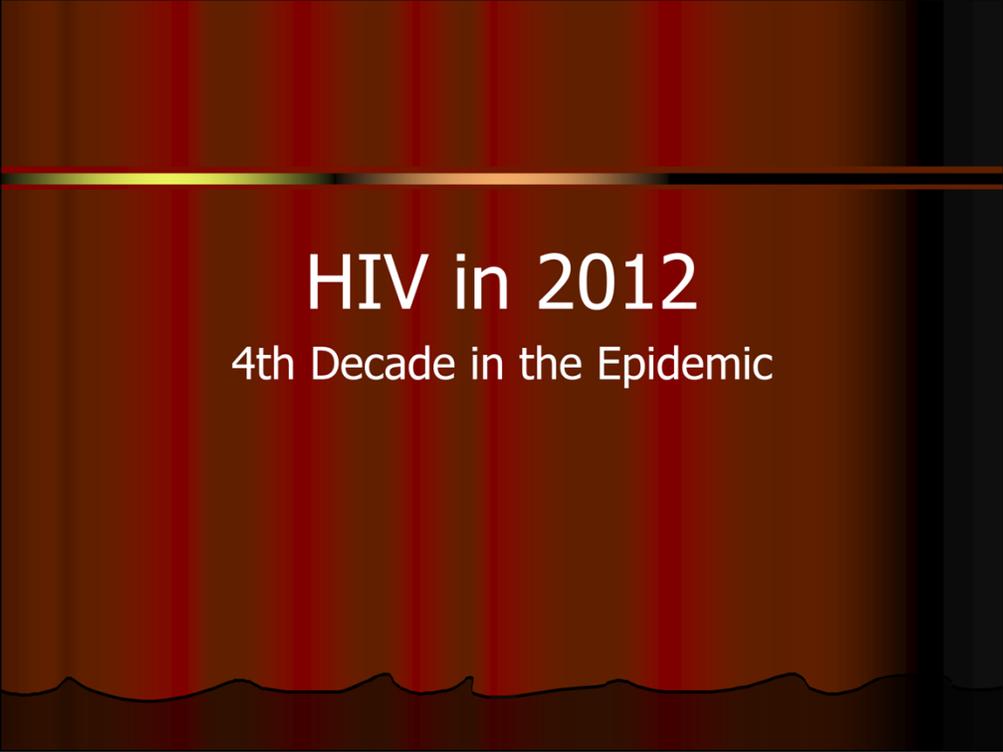


Virology Treatment Center  
AIDS Consultation Service  
Maine Medical Center

## Consultation Team

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This slide show was presented in a webinar session by Sandra Putnam on January 26, 2012 for the Maine Department of Education, HIV Prevention Education Program.



# HIV in 2012

4th Decade in the Epidemic

## World Pandemic

- >38 million people living with HIV or AIDS, 67% in sub-Saharan Africa
- 8000-10000 new infections every day (95% in developing countries)
- Fifty percent of adults living with HIV are women
- HIV is a disease of young people in world, 45 % of new infections in ages 15 to 24

## U.S. Demographics

- 1.2 million people living with HIV
- 54,000 new infections each year (incidence rate stable)
- 73% new infections in men; 27% in women
- 45% of new infections in African Americans;
- 34% in ages < 30 years
- Death rate dropped 70% post 1996

## Maine HIV Epi.

- 59 new cases 2010 (49 male; 10 female)
- 1 new diagnosis under 19 yrs; 8 >49 yrs. In 2010
- 1563 living with HIV
- 1310 males
- 253 females
- 300 approx have undiagnosed HIV
- Approx 800 under care and treatment now: 85% male; 15% female
- MSM – 59 % of cases (may be as high as 79-80% overall)
- IDU – 5.0 %
- Heterosexual – 22 %

## Maine HIV Stats

- 2010: New Diagnoses:
  - 50% already have AIDS diagnosis
  - 82% white; 7% black; 5.4% Spanish; 0.7% Native American

People have been living with HIV for 10-15 years and potentially transmitting the disease before they are diagnosed in Maine. That's why everyone should be tested.

## Maine STD Prevalence: Danger signs

- Gonorrhea
  - 2010: 162
  - 55% in males; 50% of that in 20-29 yo
- Chlamydia
  - 2010: 2586; 70 % in females
  - age 20-24 highest age group
- Syphilis
  - 2010: 39
  - Biggest risks: Internet hook-ups; anonymous sex.

All 3 STDs have seen a significant increase in numbers of people infected.

## Milestones of HIV Treatment

- 1981 – first cases of AIDS reported
- 1985 – HIV antibody test
- 1987 – AZT approved (1<sup>st</sup> antiviral)
- 1987-early 1990's: more antiviral (NRTI) agents (ie., DDI, D4T, 3TC); OI treatments improved
- 1996 – Vancouver Conference – PI's in combo: use of 3 drugs to treat HIV becomes standard of care: virus is controlled

## Milestones continued

- 1996-2008 - Continuing drug research: 6 classes of drugs now approved; 24 individual agents
- Vaccine trials still not successful, some hope with newest trial from Thailand (use of 2 early vaccines together gave 30% immunity over 3 years)

## Prevention Milestones

- Key to Transmission Prevention: Diagnose and Treat Early
- Partner PrEP
- 'Community' PrEP

PrEP stands for:

Pr = Pre, before person is exposed to HIV

E = Exposure, coming into contact with HIV

P = Prophylaxis, —taking medication to prevent becoming HIV infected

## Where and How Did HIV Arise?

- Molecular epidemiology:
  - HIV-1....SIV cpz
  - HIV-2....SIV sm
- Emergence of HIV-1 in humans:
  - Time frame (1914-1941)
  - Where: Central Africa
  - How?? Bush meat trade (likely)

HIV-1 is more virulent and infective.

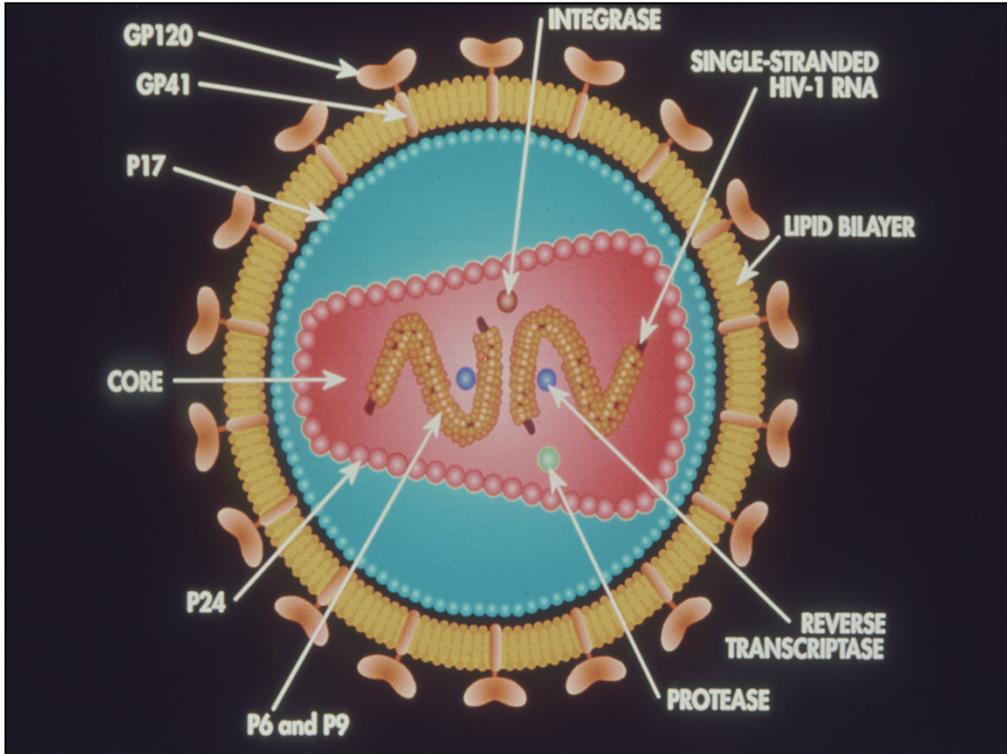
Need perfect adherence to medication because cells can replicate and are drug resistant.

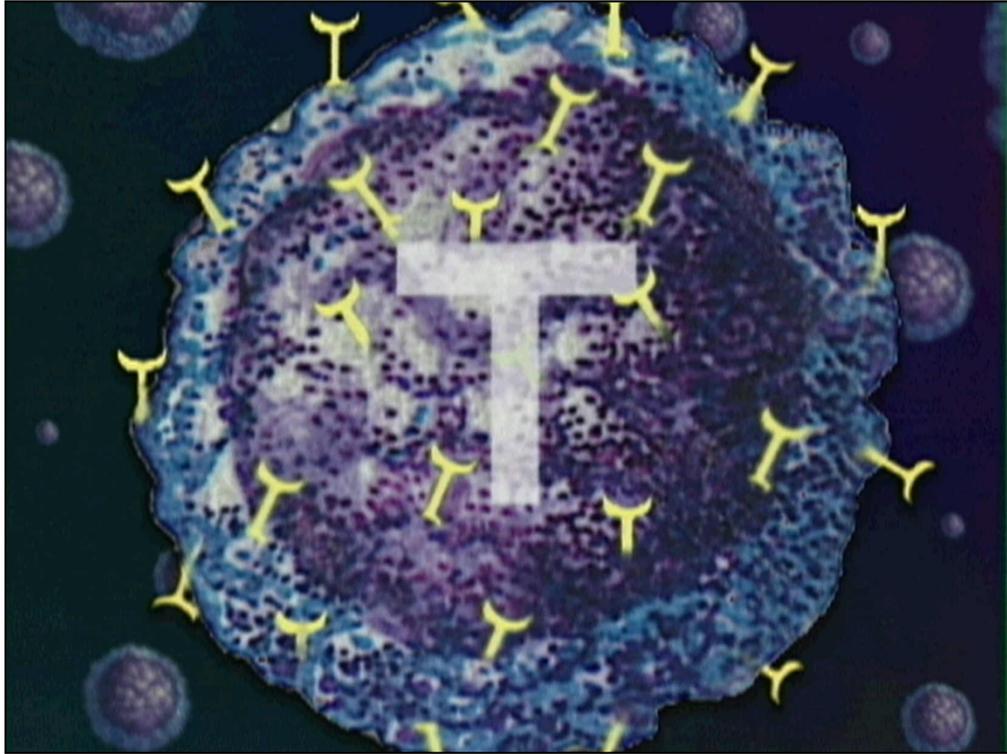
## HIV/AIDS: What is the Difference?

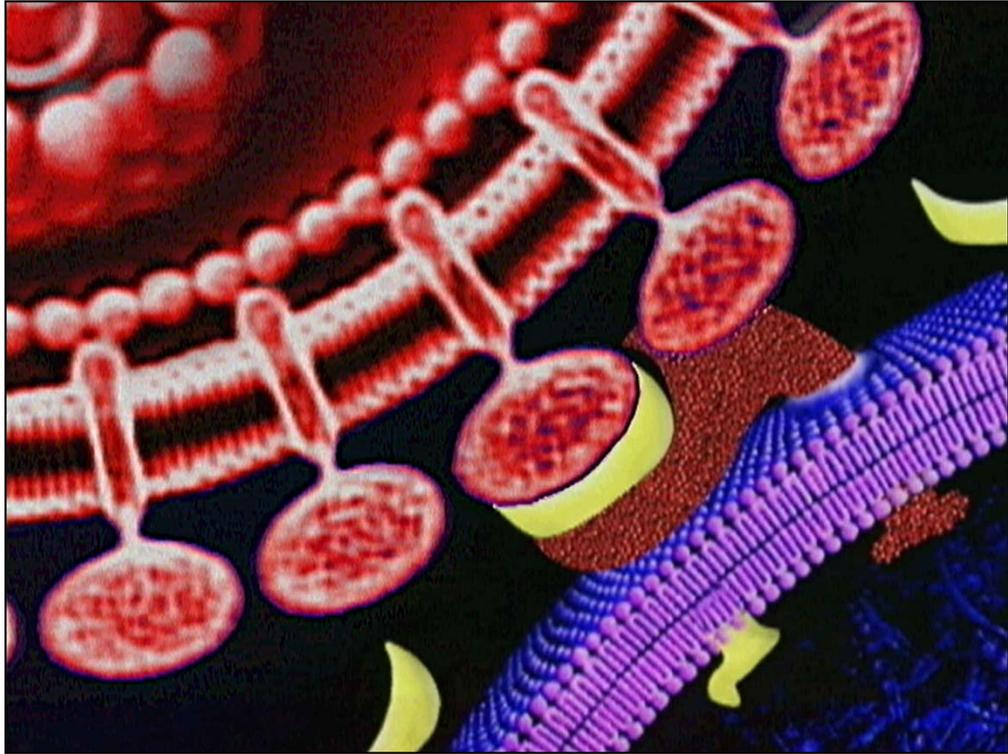
- HIV: A viral infection causing gradual depletion of T4 lymphocytes (a key WBC) by using them for replication and in the process killing them
- AIDS: A diagnosis given when T4 count reaches 200 (normal is 1000), defined by CDC as point where Opportunistic Infections are likely to occur

## How Does HIV Harm the Human Immune System?

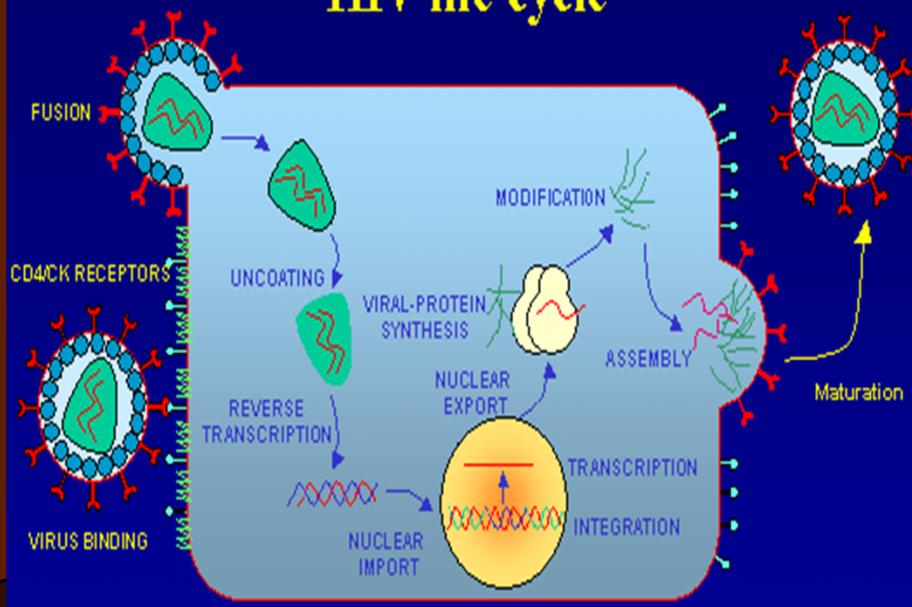
- The Virus.....
  - It is a Pretty 'SMART' Virus: well packaged to replicate!
  - RNA genetic material: needs human cell DNA to replicate







# HIV life cycle



## The Irony.....

- Use of CCR5 and CXCR4 chemokines in human immune system to gain entry into CD4 cell
- Immune system tries to 'remember' HIV infection by scooping up pro-viral DNA
- BUT: These long-lived memory T-cells that hold pro-viral DNA live for 40-60 yrs.
- Sanctuary sites: brain, testes, gut: difficult to eradicate

Chemokines are family of small proteins secreted by cells that guide the migration of cells.

## Viral Dynamics

- Avg. total HIV viron production per day:  
*10 billion RNA strands*
- Avg. life span of infected T cell: 2.2 days
- Min. duration of HIV life cycle: 1.2 days
- Avg. HIV generation time: 2 days
- Memory T cells can live for 40- 60 years

## Summary of Viral Dynamics

- HIV uses T4 Lymphocyte DNA to make more of itself
- HIV virus carries with it the enzymes it needs to replicate
- The meds we use to slow the virus either block its entry into the T4 cell or block the use of the enzymes it needs to break itself down, insert itself into the T4 DNA, or reassemble itself to bud out new virions

## Summary continued

- In going through this replication process, the virus damages the T4 lymphocyte and it dies.
- The virus has amino acids on its surface which can mutate rapidly to provide resistance to drugs.
- Therefore, adequate drug levels are essential to keep replication from occurring

Vaccines have not been successful because of the ability of HIV cells to mutate.

## HIV: Death sentence or Chronic Disease?

- As of today, we have nothing that can kill HIV or completely rid the body of it's presence
- However, we can CONTROL it with 3 drug regimens
- KEY: Keeping blood levels up : almost perfect adherence!!!

## Towards a Cure

- International initiative:
  - Functional cure (immune control)
  - Eradication: 'Berlin' patient
  - Intensification treatment: early and strong
  - Multiple approaches in combination

Berlin HIV+ patient received a stem cell transplant in 2007 to treat his leukemia. His doctors announced in 2010 that he had been cured of HIV.

## PRIMARY HIV

Usually within 2-4 weeks of getting the virus; lasts 2-4 weeks

HIV Viral Load usually very high; at greatest risk for transmission

Negative mono-spot and symptomatic

Indeterminant or negative HIV serology or recent seroconversion

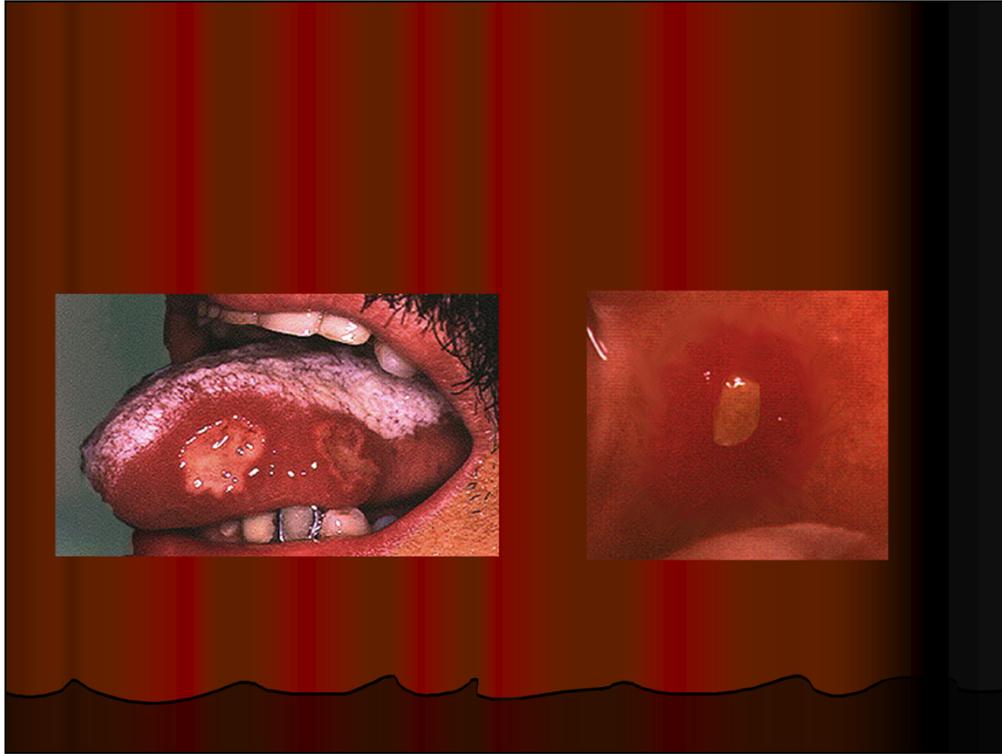
Seroconversion is the development of detectable specific antibodies to HIV in the blood serum.

## Acute HIV Syndrome/Primary HIV: A Flu-like illness

- Fever
- Sore throat
- Swollen lymph nodes
- Rash
- Headache
- Arthralgias/myalgias
- Lethargy/malaise
- Anorexia/weight loss
- Nausea/vomiting/diarrhea



Rash is acute HIV symptom.



Oral thrush, yeast infection in mouth.

## Diagnosis of HIV Disease

- Blood Test: (Gold Standard): ANTIBODY TEST
  - ELISA** for screening
  - Western Blot** for confirmation of (+) test
  - 99% sensitive and 97% specificity
- Rapid Tests: Saliva, blood, mucus membranes
  - ELISA ONLY
  - OraQuick HIV-1
  - OraSure Test
  - Still needs Western Blot confirmation if (+)
- HIV RNA PCR
  - Only used in acute viral syndrome; to test newborns born to HIV + mothers

Important to catch the disease early in order to keep the immune system healthy longer.

# Monitoring Disease Progression

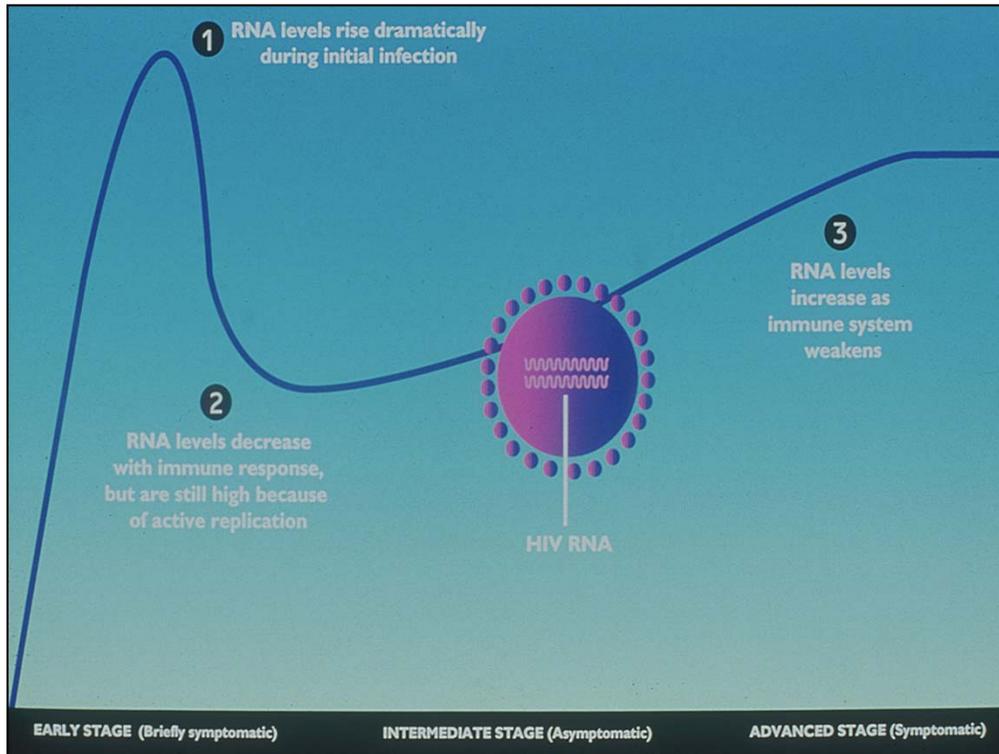
Special labs

## Essential Labs

- HIV-1 RNA Viral load
  - Ultrasensitive (<20 - >1 million copies/ml)
- CD4/T4 Lymphocyte Count
  - Normal= approx. 1000
  - AIDS dx. at 200
- HIV Genotype

## Viral Load

- Highest in initial infection
- Patient's 'set point' determines risks/rate of progression of infection
- Key to monitoring effectiveness of antiviral therapies

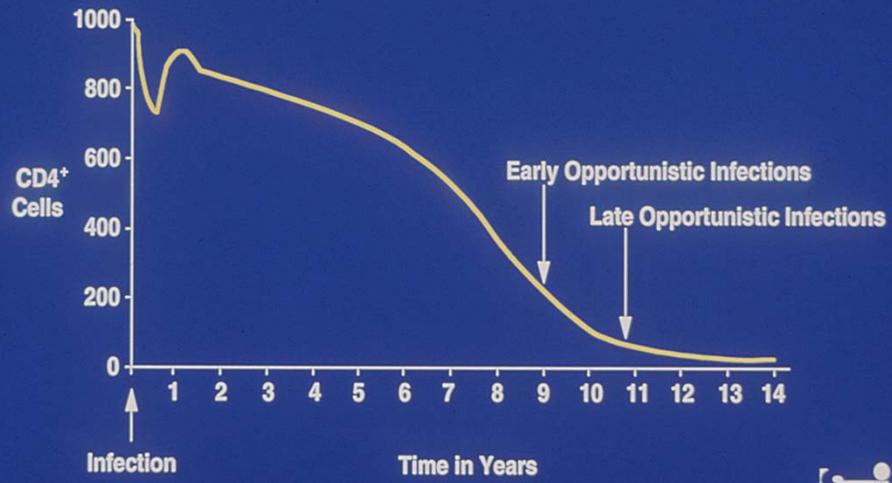


## T4 Lymphocyte Count

- Normal Count approx. 1000
- On average, with HIV lose approx. 50-100 cells a year (production vs. destruction)

# CD4<sup>+</sup> Cell Count

## Natural History of Untreated HIV-1 Infection



## HIV Virus Mutation

- Occurs with every viral life cycle
- Involves shifts in amino acid condons on the virus
- Can be transmitted
- Occur in the presence of drug if levels not adequate

## Goals of Treatment: Viral Suppression

- Viral Suppression
- Preserve /improve immune function:  
Increase in T4 cell count/strengthen immune function
- Delay/abort disease progression

## Viral Suppression: Then Improved Immune Function

- All the drugs control viral replication:
- By suppressing virus, allows immune system to recover, make naïve T4 lymphocytes

But ONLY if drugs taken exactly right

- EVERY DAY, EVERY DOSE

## Problems With Low T4 Lymphocyte Counts

- <200 : AIDS Diagnosis
- Susceptibility to Opportunistic Infections:
  - PCP
  - MAI
  - Toxoplasmosis
  - Thrush
  - Skin rashes
  - Cancers

PCP = Pneumocystis pneumonia, caused by a yeast-like fungus

MAI (or MAC)= Mycobacterium avium complex, bacterial infection, related to germ that causes TB

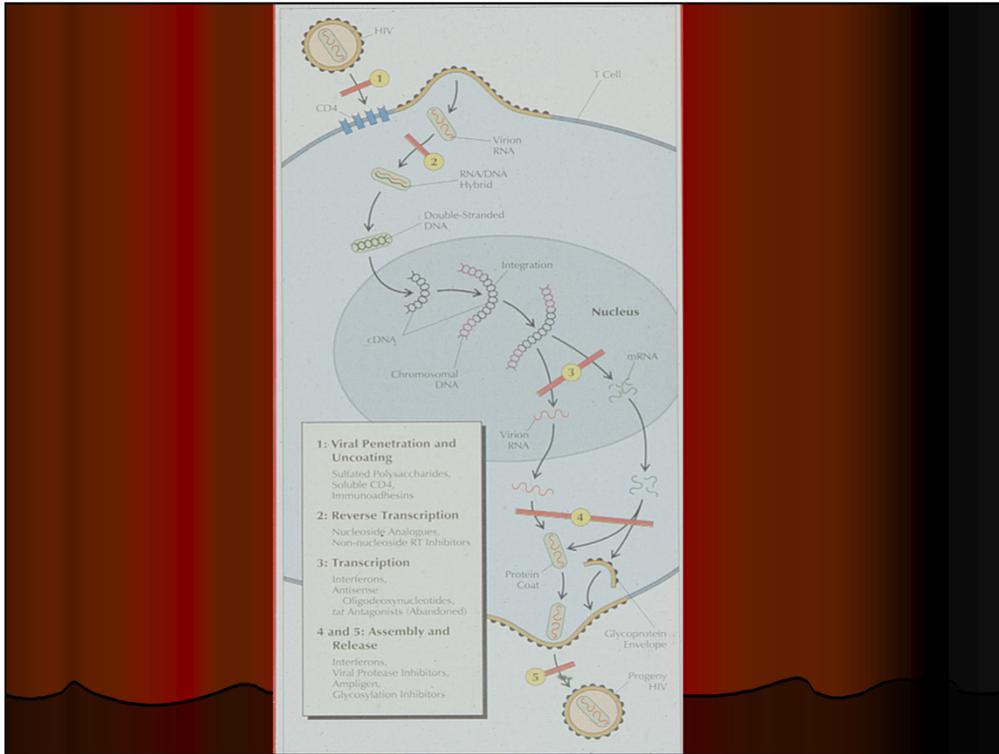
Toxoplasmosis– Protozoal, brain infection

Thrush – yeast infection in mouth

Kaposi's Sarcoma - cancer

# The Antiviral Medications

Where and How They Work



# Classes of HIV Antiviral Drugs

- Reverse Transcriptase Inhibitors: RTIs
  - Nucleoside analogs/Nucleotide analogs
  - Non-nucleoside analogs

## Antiviral Drugs cont'd

- Protease Inhibitors
- Fusion Inhibitors
- Entry Inhibitors
- Integrase Inhibitors

## When Treatment Is Started

- CD4 Count ~ 500
- Viral load >5,000-10,000
- Symptomatic
  
- Post-occupational exposure
- Post-sexual exposure
- Pre-sexual exposure: PrEP: 'Treatment as Prevention'

Post-occupational exposure – treat within 72 hours.

\*Professionals feel the only way to eliminate HIV is by pre-sexual exposure.

## What Meds to Take?

- STANDARD of CARE:
  - 3 antivirals at all times
  - Use of at least 2 classes

3 drug treatment must be used

Approximately \$3,000 a month – 1 pill per day

## Problems With HIV Antivirals

**Drug/drug interactions** (Cytochrome P-450 interactions)

Multiple drug **side effects/toxicities**: vary from person to person

Need for nearly **perfect adherence for years, ? lifetime**

Heart disease, high cholesterol, liver/kidney damage, diabetes susceptibility

## Monitoring Antiviral Therapy

- ADHERENCE
- CD4 and Viral Load
  - 3-4 wks after start therapy
  - Every 4-8 weeks until undetectable
  - Every 3 months after stabilization
- RESISTANCE TESTING
  - At diagnosis
  - With viral rebound

Continuous visits to doctor's office

## Assessing Resistance

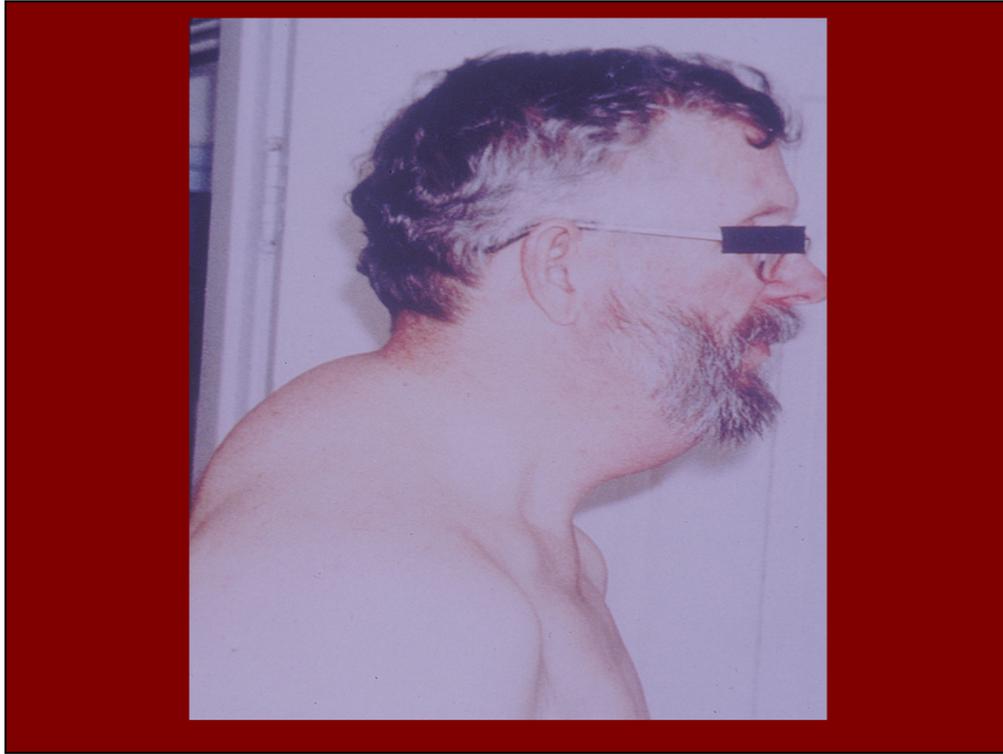
- Genotype  
Essential to target correct antivirals
- Phenotype  
Used for difficult resistance decisions

## HIV Antiviral Side Effects: These are not unsafe medications!

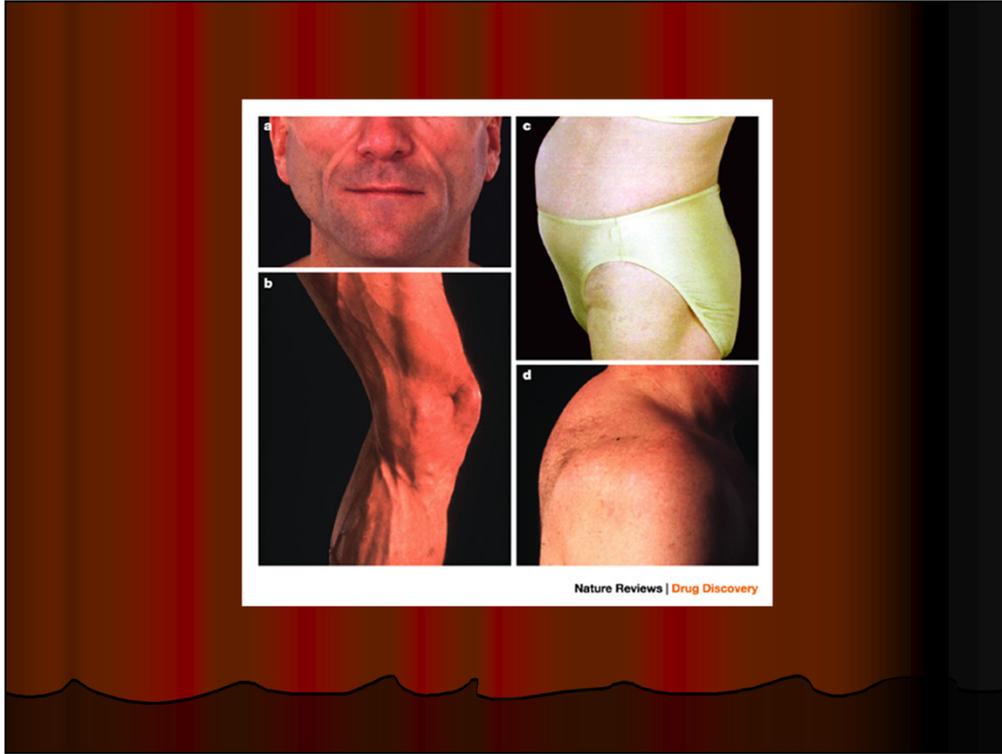
- Lactic Acidemia
- Lipid abnormalities
  - Triglycerides/Cholesterol
- Glucose intolerance/Insulin Resistance
- Body fat composition abnormalities
  - Lipodystrophy
  - Lipoatrophy

An example of Lipodystrophy – redistribution of fat on the back.

Lipoatrophy – localized loss of fat tissue, example in the face, arms, legs



Lipodystrophy



Lipoatrophy

## More Side Effects: Neurologic Complications

- CNS opportunistic infections
  - Toxoplasmosis
  - Cryptococcal meningitis
- Primary CNS lymphoma
- Progressive multifocal leukoencephalopathy (PML)
- Peripheral neuropathy (15-50%)
- Myelopathy (degeneration of nerves in spinal cord (22-55%))

## Why Do We Still See AIDS in the US a Decade Post HAART??

- “Late testers”: 50% present with AIDS
- Inability to adhere to antiviral regimens (for whatever reason: denial, psychiatric disease, substance abuse, chaotic lives, etc.)
- Development of multi-resistant HIV

## New Testing Guidelines

- CDC New Testing Guidelines:
  - Routine testing adults ages 13-64
  - Annual testing in those at risk
  - "Opt out" provision: implied consent vs. written informed consent
- Rapid Diagnostic Tests: 4 approved
  - "Point of care"
  - Home testing

Maine recently passed a law requiring all pregnant women be tested for HIV

## Continuing HIV Treatment Challenges 2012

- Antiviral meds must be continued indefinitely
- Must be adhered to at a high level
- Requires 3 active agents
- Significant side effects may occur
- Drug interactions are common
- Drug resistance is common
- Co-infections are common and complicate treatment
- Early aging and more chronic conditions for HIV+

## Co-infections/complications of HIV

- Hepatitis C Co-infection
- Hepatitis B Co-infection
- TB
- Cancers
- GI disturbances
- Cardiac Issues
- Osteoporosis
- Kidney problems
- Brain issues

## Biggest Challenge

- Belief that YOU are not at Risk
- Therefore, NOT GETTING TESTED
- GOAL: Everyone be "Safe"
- GET TESTED

Oldest HIV + patient in Maine is 89

Recently diagnosed is a 76 year old man

# Hepatitis

- A: Virus that causes liver inflammation and damage;
  - Preventable by vaccine
- B: Virus that causes liver inflammation and damage; can last for life. Cause scarring of liver, liver cancer, liver failure, death
  - Preventable by vaccine
- C: Virus that causes inflammation of liver; identified in 1989 (before called non-A non-B)
  - NO vaccine for this

## Hepatitis A

- “Infectious” Hepatitis: very contagious
- Causes acute hepatitis
- Liver repairs itself within 6 months
- Does not cause chronic liver disease
- Can be fatal, esp in older adults
- Transmitted through person to person contact via fecal-oral route

# Hepatitis B

- Transmitted by blood, semen, saliva
- A "hardy" virus
- Not transmitted by casual contacts
- In US: sex and IVDU: easier to transmit than HIV
- Transmitted during childbirth (in Africa, Asia esp.)
- Can cause acute hepatitis: can be silent ("flu") or extra-hepatic

## Hep B cont'd

- Can resolve on own
- Can be chronic (failure to clear): silent
- 2% increase/year in probability will develop cirrhosis
- Increased risk of liver cancer
- Treatment can get DNA to undetectable levels

# Hepatitis C

- RNA virus; after exposure, 10-20% clear the infection; rest develop chronic hep. C
- Prevalence 1.6% ( 4 million); 3.2 with chronic HCV
- Greatest risk factor: IVDU
- Progresses to cirrhosis 5%-25%; to liver failure 1%-7%
- Co-infection with HIV: 3x rate of progression to cirrhosis, liver failure, and carcinoma
- Treatment depends on genotype, amount of inflammation and scarring
- Current treatment meds look like HIV med evolution 15 years ago

HIV, STD's Hepatitis are Here To  
Stay.....

PREVENTION  
of Transmission  
is the ONLY WAY !!!!  
Get Tested; Be Safe  
Get Vaccinated; No IVDU