

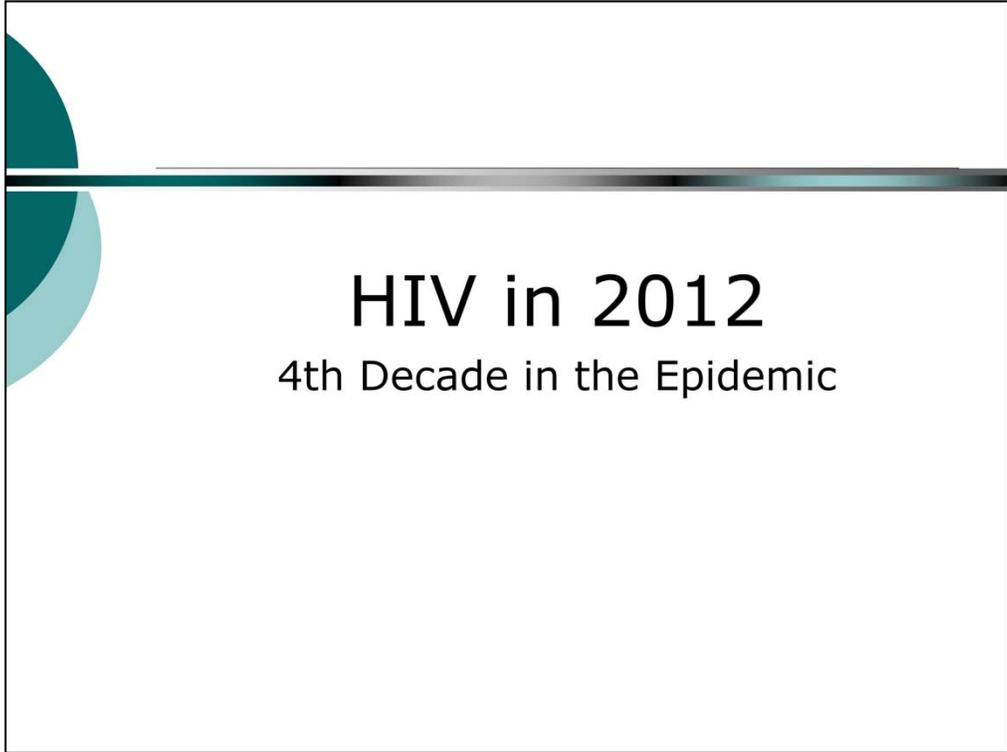


Virology Treatment Center
AIDS Consultation Service
Maine Medical Center

Consultation Team

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HIV in 2012

4th Decade in the Epidemic



World Pandemic

- >43 million people living with HIV or AIDS, 68% in sub-Saharan Africa
- Approximately 2 million deaths in 2010 (5500/day), 72% in sub-Saharan Africa
- 8000 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
- 11-12 million orphans under age 18 in sub-Saharan Africa



U.S. Demographics

- 1.1 million people living with HIV; >500,00 deaths
- One fifth of infected unaware of HIV infection
- 48,100 new infections each year (incidence rate stable)
- 73% new infections in men; 27% in women
- 45% of new infections in African Americans; 35% in whites
- 34% in ages < 30 years
- Death rate dropped 70% post 1996

People infected with HIV are living much longer today because of the combined use of 3 separate cocktails



Maine HIV

- Median year new cases: 52;
- 1,616 cases of HIV living in Maine 2011
 - 71 deaths in 1993
 - 10-16 deaths/yr in 2002-2010 (Dramatic drop with HAART)
- Est. 404 HIV undiagnosed cases
- Approx 800 under care and treatment now: 85% male; 15% female
- MSM – 64.8 % of cases over-all
- IDU – 15.8 %
- Heterosexual – 11.4%
- Pediatric: <1
- Growing number of STD's and new HIV cases, esp. in MSM pop. bet. ages of 25-40.
- Maine ranks 42nd of 50 states in cumulative AIDS cases

HAART = highly active antiretroviral therapy



Maine HIV Stats

- 2010: New Diagnoses:
 - 51 % have AIDS diagnosis at time of + test
 - 49% have HIV diagnosis
 - HIV 9th leading cause of death
 - 84% male; 16% female
 - 78% of all diagnoses > 30 yrs old
 - 82% of new diagnoses >30
 - 0.2% of new cases 40-49 yrs old
 - 87.1% white; 10.7% black; 4.8% Spanish; 0.8% Native American; Asian 0.3%; unknown 1.1%



Maine HIV Distribution

- Maine by Region:
 - Cumberland county 562
 - York County 238
 - Western (ox, Frank, andros) 184
 - Central (somenset, Kenneb) 161
 - Mid Coast (Linc, Knox, Waldo, Sagadahoc) 114
 - Penquis (Pisc, Penob) 113



2010 funding for HIV

○ HIV Prevention:	\$1,786,725
○ Ryan White Part B:	\$1,658,908
○ ADAP:	\$898,597
	(plus \$760,311 from B)
○ Part C:	<u>\$1,038,298</u>
	TOTAL: \$5,382,528

The US Centers for Disease Control (CDC) has been reducing funding to low incidence states like Maine (rank 42 out of 50 states for cumulative HIV cases)



Maine STD Data

- HIV
- 2011: 54
- Avg: 52
- Hepatitis C
- 2011: 1184
- Overall: 26,000
- Gonorrhea
- 2011: 273
- Avg: 135
- Syphilis
- 2011: 19
- Avg: 16
- Chlamydia
- 2011: 3101
- Avg: 2543

YTD = year to date Avg = average for the past 5 years



Milestones of HIV Treatment

- 1981 – first cases of AIDS reported
- 1985 – HIV antibody test
- 1987 – AZT approved (1st 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

- 1996-2012 - Continuing drug research: 6 classes of drugs now approved; 26 individual agents
- Vaccine trials still not successful, but some hope with trial from Thailand (use of 2 early vaccines together gave 30% immunity over 3 years)

HIV+ German patient given 2 bone marrow transplants for treatment of leukemia has no verifiable viral load for HIV



Where and How Did HIV Arise?

- Molecular epidemiology:
 - HIV-1....SIVcpz
 - HIV-2....SIVsm

- Emergence of HIV-1 in humans:
 - Time frame (1914-1941)
 - Where: Central/SubSaharan Africa
 - How?? Bushmeat trade (likely)

In 2005, scientists report that HIV most likely originated in the jungles of Africa in wild chimps. The virus was transferred to humans through monkey bites or eating meat and brains of infected chimps. Viruses that jump from one animal species to another usually are more destructive in the second species



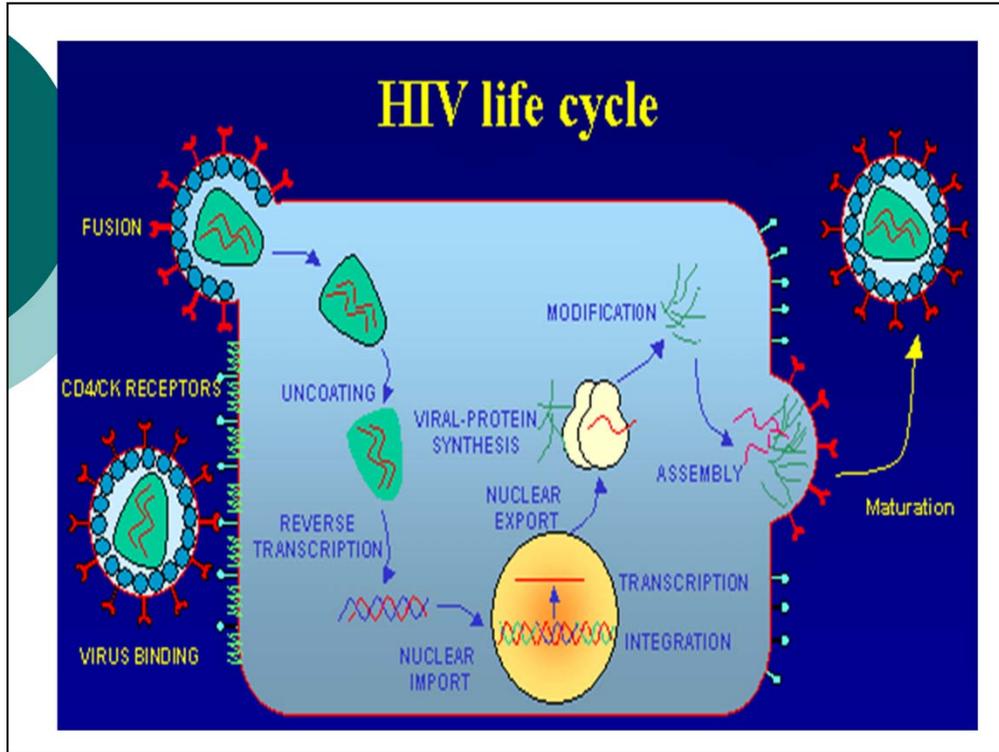
HIV/AIDS: What is the Difference?

- 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 cell DNA to replicate



For more complete explanation go to: aidsinfo.nih.gov/contentfiles/HIVLifeCycle



The Irony.....

- Our 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.

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

The essential piece of treatment is to keep HIV from replicating



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



HIV: Death sentence or Chronic Disease?

- Nothing to 'cure' HIV yet
- But we can control viral replication by blocking how it works
- KEY: Keeping blood levels up: almost perfect adherence!!!



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

Mono-spot is a test for mononucleosis. A person presenting with fever and swollen glands is given this test. Seroconversion is the development of detectable specific antibodies to microorganisms in the blood serum as a result of infection. A person may not yet test positive for HIV but can still transmit the virus to others

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

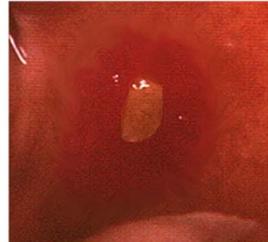
- Fever
- Sore throat
- Swollen lymph nodes
- Rash
- Headache
- Arthralgias/myalgias
- Lethargy/malaise
- Anorexia/weight loss
- Nausea/vomiting/diarrhea

Arthralgia = joint pain myalgia = muscle pain



This is a picture of the skin rash which may occur during initial infection

Thrush, aphthous ulcers



Thrush is a yeast infection in the mouth and aphthous ulcers are also known as canker sores. Both can occur in a person with a weakened immune system



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

HIV+ pregnant women taking medication have a 1% chance of transmitting HIV to baby. If they are not on medication, the risk increases to 25%



Monitoring Disease Progression

There are several key variables:

Variables include viral load, T4 Lymphocyte count, and HIV RNA genotype (HIV 1 is most virulent and originated with chimps; HIV 2 is much less common and not as destructive and comes from a type of monkey called a sooty mangabey)



Essential Labs

- HIV-1 RNA Viral load
 - Ultrasensitive (<48 - >1 million copies/ml)

- CD4/T4 Lymphocyte Count
 - Normal=1000
 - AIDS dx. at 200

- HIV RNA Genotype

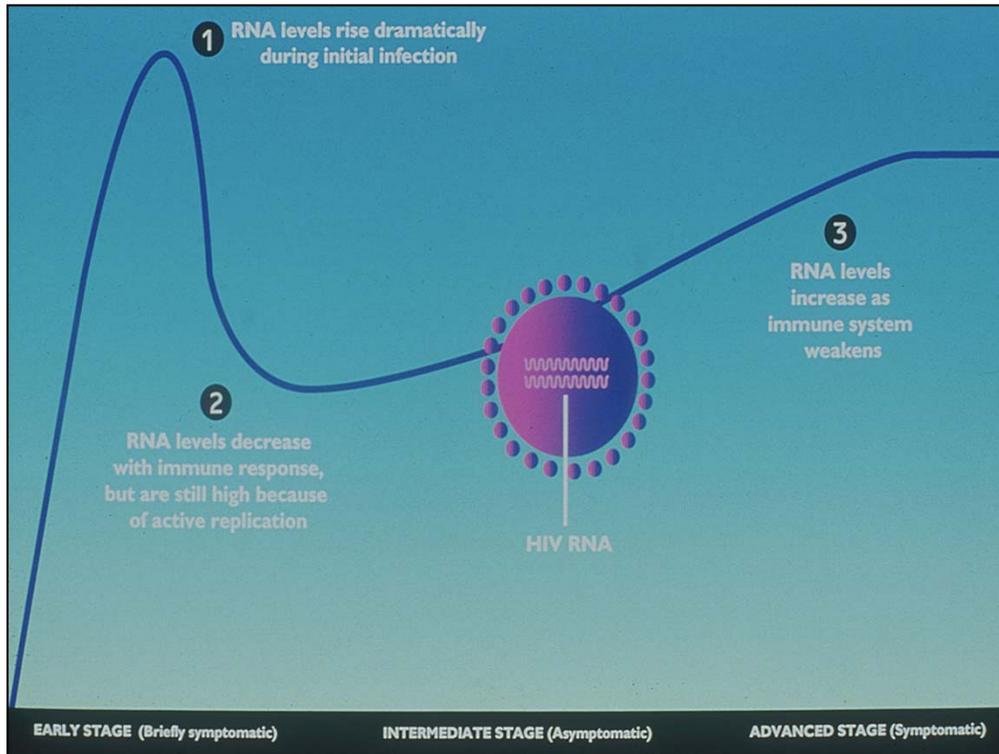
The viral load test measures the amount of HIV in the blood and shows how actively the virus is reproducing in the body. There are 9 different HIV subtypes and each responds differently to medication



Viral Load

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

Viral load greater than 100,000 in initial diagnosis indicates a greater likelihood of developing AIDS within 5 years



A person is very infectious in the early stage

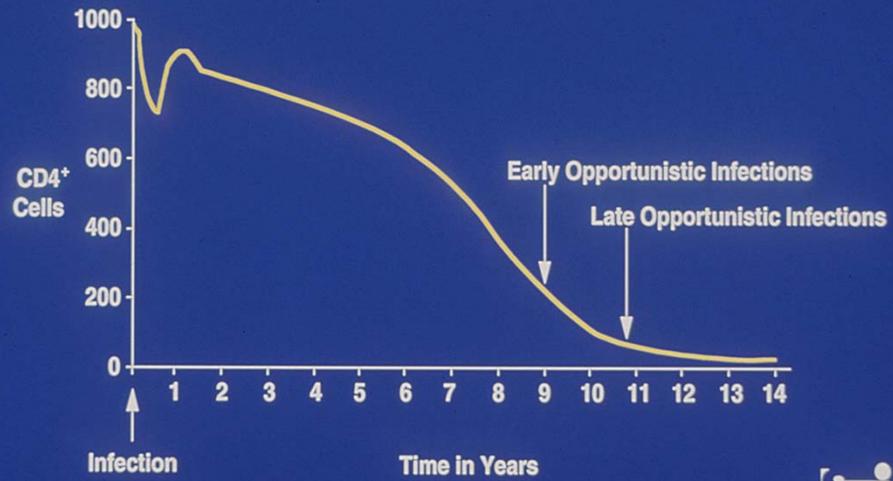


T4 Lymphocyte Count

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

CD4⁺ Cell Count

Natural History of Untreated HIV-1 Infection



In Maine, people diagnosed as HIV+ typically progress to AIDS within a few years, which means that they have had undiagnosed HIV for a number of years



HIV Virus Mutation

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

This mutation is why development of a vaccine has not happened to date



Assessing Adherence

- Finding a regimen patient's can take
- Developing a routine
- Carrying meds with them if schedule is unpredictable
- Need for near 100% adherence, commitment 'for life'

In order for HIV to not progress, patients must strictly follow a treatment medication regimen. Missing just a single dose can result in mutation of the virus, making the original medication no longer work



Goals of Treatment: Viral Suppression

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



No Cure: Just Viral Suppression: Then Improved Immune Function

- All the drugs control viral replication:
 - They DO NOT KILL HIV
- 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

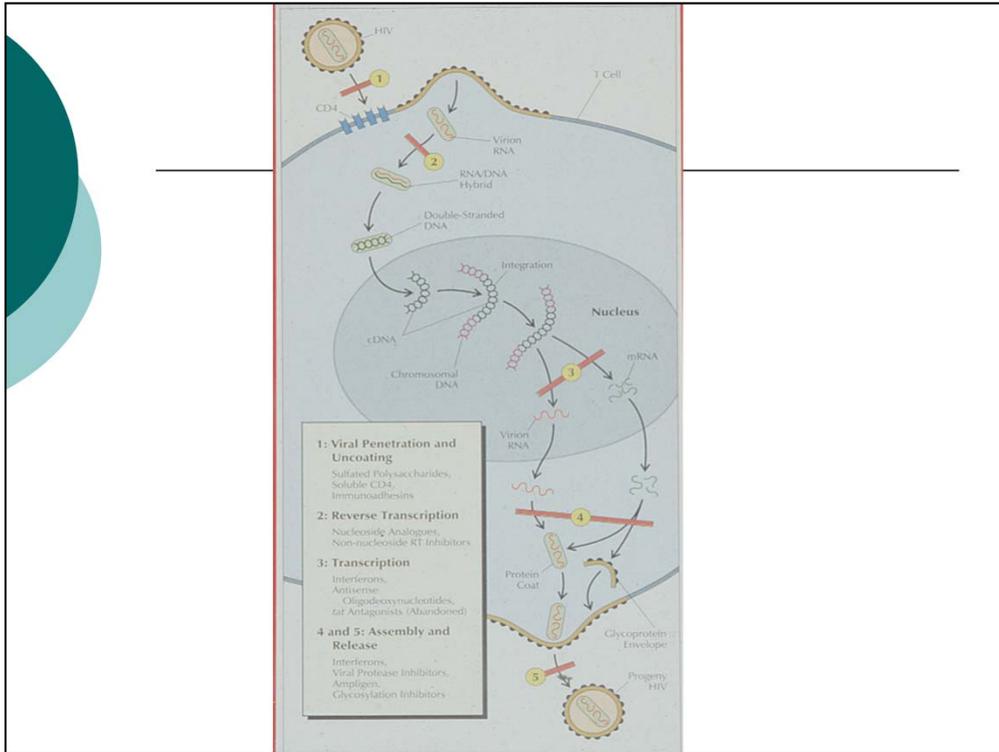
- <200: AIDS Diagnosis
- Susceptibility to Opportunistic Infections:
 - PCP
 - MAI
 - Toxo
 - Thrush
 - Skin rashes
 - Cancers

PCP = pneumocystis pneumonia (caused by fungus) MAI = atypical mycobacterial infection (such as encephalitis) Toxo = toxoplasmosis (protozoal disease)
Karposi's sarcoma is a type of 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: At time of diagnosis
- Viral load: at time of diagnosis
- Symptomatic infection: asap!

- Post-occupational exposure
- Post-sexual exposure PrEP
- Pre-sexual exposure PrEP

PrEP stands for Pre-Exposure Prophylaxis, a new HIV prevention method in which people who do not have HIV take a daily pill to reduce their risk of becoming infected



What Meds to Take?

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



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**



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

HIV is "resistant" to a drug if it keeps multiplying rapidly while you are taking the drug. Resistance testing helps health care providers make better treatment decisions for their patients



Assessing Resistance

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

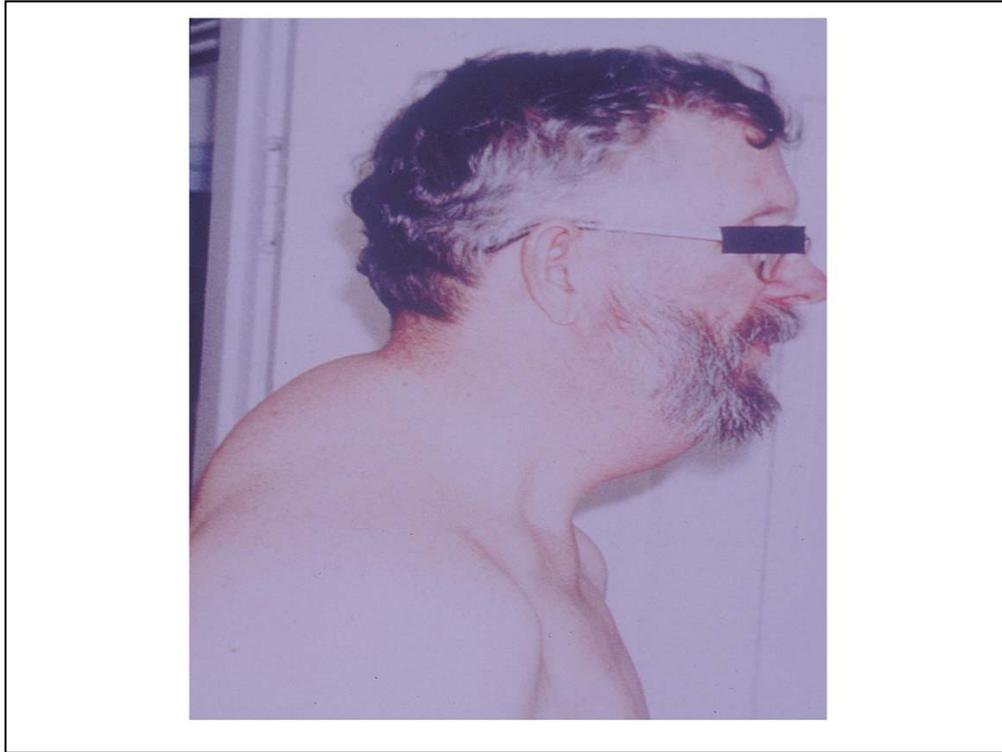
Genotype = genetic makeup of a cell Phenotype = outward, physical manifestation of the organism



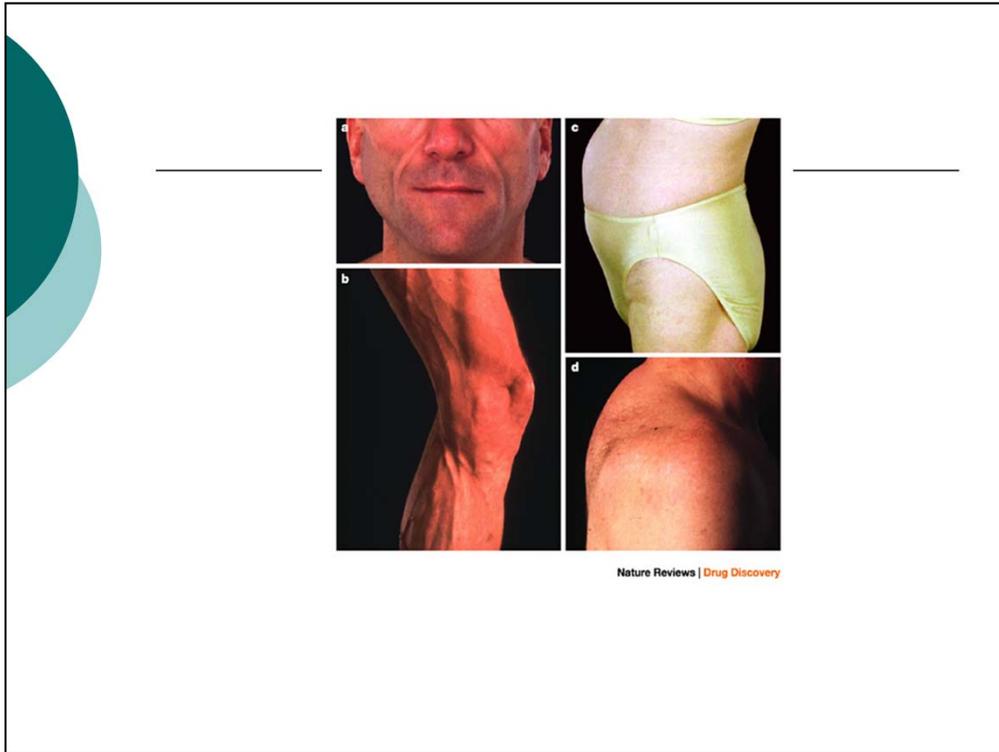
HIV Antiviral Side Effects: These are not unsafe medications!

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

Lactic acidemia is too much lactic acid in the blood. Lipoatrophy involves fat redistribution. The next slide shows a picture of an individual with “buffalo hump” fat deposits in the upper back. Lipodystrophy is fat loss in the face, buttocks, arms, and legs



“Buffalo hump” fatty deposits



This slide also illustrates fat redistribution



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%))

CNS = central nervous system PML = viral disease characterized by progressive damage or inflammation of the white matter of the brain



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

HAART = highly active antiretroviral therapy HAART involves taking 3-4 different classes of antiretroviral drugs



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 now available in drug stores: results in 30 minutes



Continuing HIV Treatment Challenges 2012

- Antivirals 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 can occur if don't adhere
- Co-infections are common and complicate treatment
- Early start of therapy: first regimen is key
- Antivirals used as prevention (Truvada)
- Many new drugs: now 4 different 'start' choices



Co-infections/complications of HIV

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

TB = tuberculosis



Biggest Challenge

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



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



Hep 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



Hep 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 extrahepatic

Extrahepatic = happening outside the liver



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%; cause of 50% of liver cancer cases
- 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**