

## HIV epidemiology since 1999

- 8% increase in HIV diagnoses
- Men who have sex with men (MSM) increased 14%
- Heterosexual increased 10%
- IVDU decrease about 30%
- Young Black MSM 15% incidence

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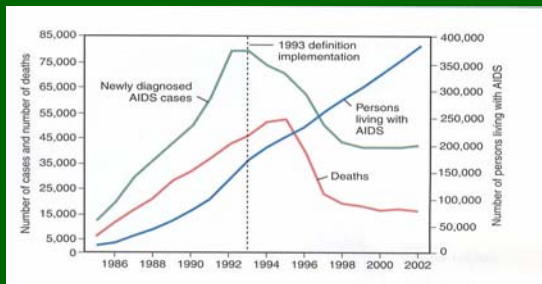
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## HIV in the United States



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## HIV Transmission

- 2/3 of HIV infected persons sexually active
- Interactive targeted counseling decreased STD's 30%
- Now about 100 perinatally transmitted cases per year

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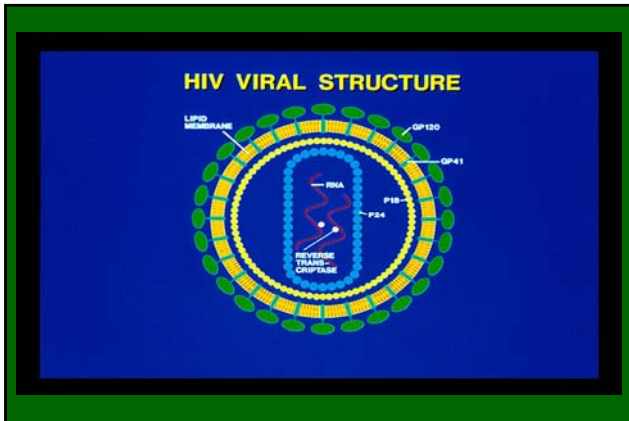
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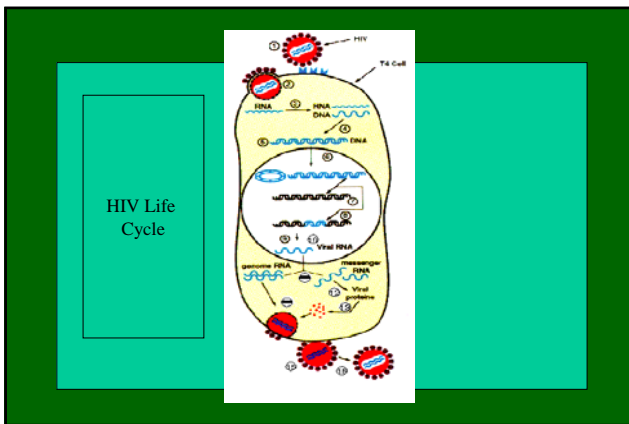
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**Retrovirus Family Characteristics**

1. Viral RNA makes DNA copy of itself (provirus) via reverse transcriptase
2. DNA provirus inserts into host Chromosome causing range of effects:
  - Latent infection
  - Cell damage
  - Malignant transformation
  - Cell death
3. Infection usually lifelong

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### Important HIV gene products

Gene	Product
gag	Nucleocapsid
	Capsid protein
	Matrix protein
pol	Reverse transcriptase Integrase
env	Transmembrane protein
	Surface glycoprotein

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### Important regulatory HIV gene products

Gene	Product
tat	Transcription activator
rev	Transport of mRNA
nef	Down regulates cell proteins
vpu	Facilitates virus production
vpr	DNA entry into nucleus of non dividing cells
vif	Virus infectivity

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### HIV

- CD4 receptor approximation with GP 120 (Attachment)
- Modulation of GP120 and P41 complex to bind with CCR5 or CXCR4 chemokine receptors (Co-receptor binding)
- Conformational folding of GP41 to bring virus in contact with the cell (Fusion)

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## Immunology

- CCR5
  - Influences migration
  - Apoptosis
  - Deficiency or mutation does not seem to cause immunosuppression or adverse outcomes
- In long term CCR5 mutant non-progressors have normal production of alpha interferon

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**TABLE II-Features in 12 Cases of Acute AIDS Virus Infection**

Characteristic	No (%)	Characteristic	No (%)
<i>Patient's Age (yr)</i>		<i>Selected Signs and Symptoms*</i>	
20-35	7 (58)	Fever/sweats	11 (92)
36-50	4 (33)	Myalgia/arthralgia	11 (92)
Over 50	1 (8)	Malaise/lethargy	10 (83)
Mean 35.4 (range 23-64)		Lymphadenopathy	9 (75)
<i>Duration of Illness (days)</i>		Sore throat	9 (75)
5 or less	4 (36)	Anorexia/nausea/vomiting	8 (67)
6-10	3 (27)	Headaches/photophobia	7 (58)
Over 10	4 (36)	Rash	6 (50)
Mean 8.1 (range 3-14)		Diarrhea	4 (33)

\*Others included shooting pains in arms and legs, desquamation of palms and soles, weight loss, and severe chest and back pains.

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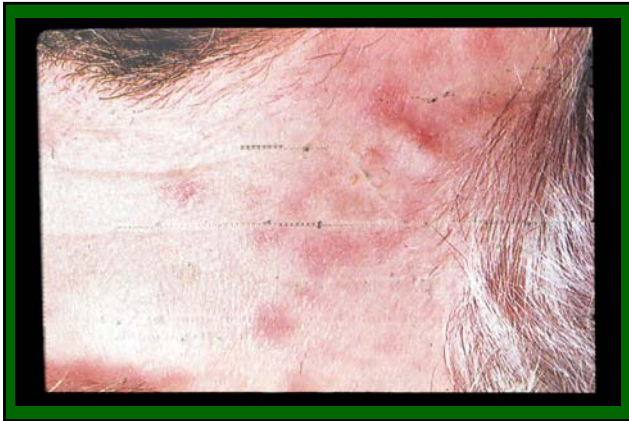
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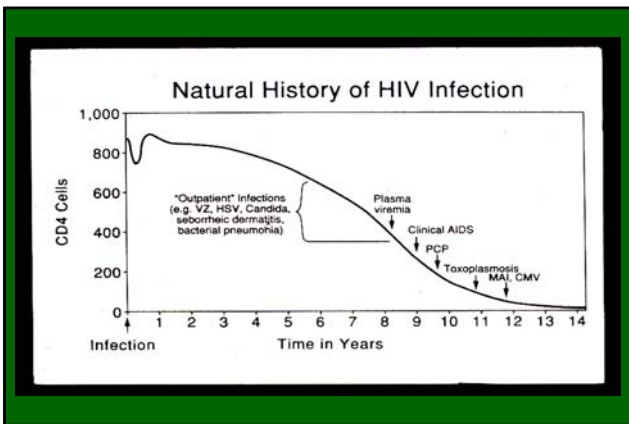
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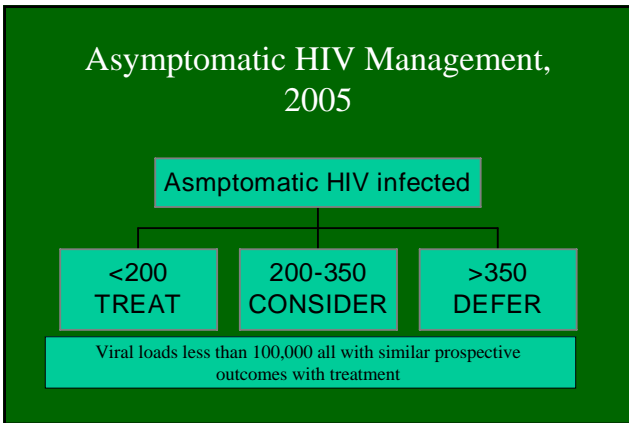
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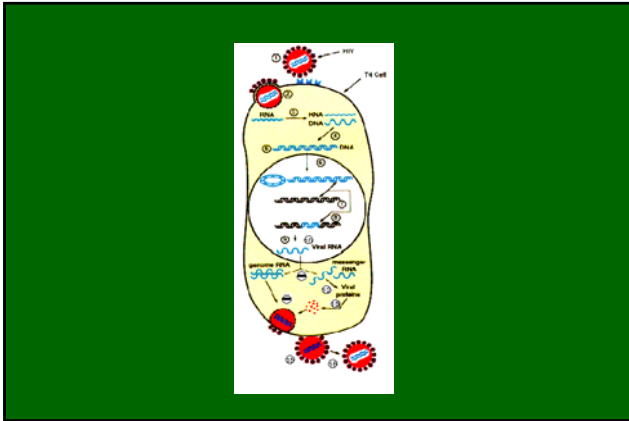
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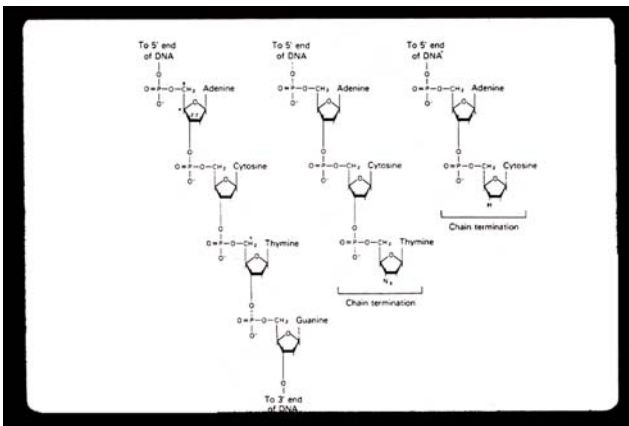
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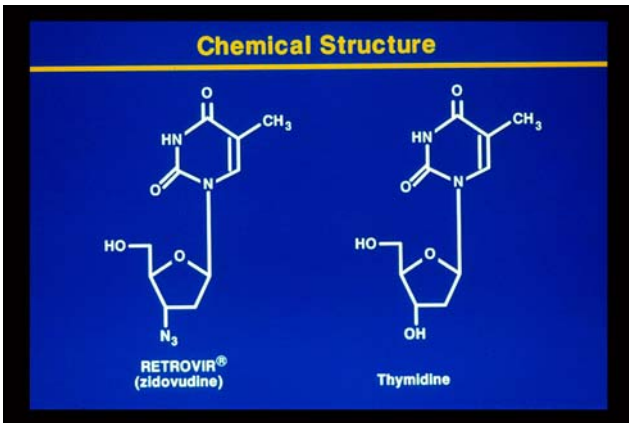
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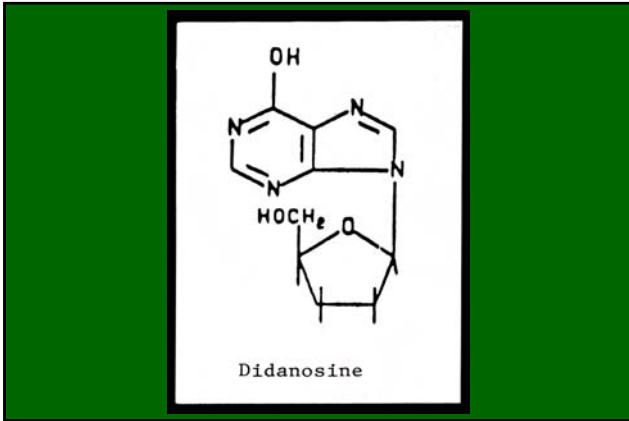
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Nucleoside Reverse Transcriptase Inhibitors

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Nucleic acid	HIV analog	Dosing
Thymidine	Zidovudine (ZDV, AZT)	300 mg bid
	Stavudine (d4T)	40 mg bid
	Tenofovir	300 mg daily
Adenosine	Didanosine (ddI)	400 mg q day
Cytidine	Lamivudine (3TC)	150 mg bid
	Zalcitabine (ddC)	.75 mg tid
	Emtricitabine (FTC)	200 mg daily
Guanosine	Abacavir (ABC)	300 mg bid

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### Common Side Effects of NRTI's

- Nausea (Abacavir 15%)
- Headache (Zidovudine 50%)
- Diarrhea (Didanosine 25%)
- Oral ulcers (Zalcitabine 15%)
- Hypersensitivity reactions (Abacavir 5%)
- Peripheral neuropathy (Didanosine 20%)
- Lactic acidosis

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### Mitochondrial DNA

- NRTI's inhibit mitochondrial DNA gamma DNA polymerase
- ddC > ddI > d4T > all the rest in in vitro inhibition
- Depletion of mitochondrial DNA in limb fat greatest in persons on d4t
- Reversed in 10/11 who stopped d4T
- No change in PBMC's mitochondrial DNA

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### Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI's)

- Work at non enzymatic site of HIV reverse transcriptase
- Competitive binders
- Conformational change in RT renders enzyme inactive

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## Non-nucleoside Reverse Transcriptase Inhibitors

Generic name	Trade name	Dose
Delaviridine	Rescriptor	400 mg tid
Efavirenz	Sustiva	600 mg hs
Nevirapine	Viramune	200 mg daily for 2 wks then 200 mg bid

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## Issues With NNRTI's

- Cross resistance
- No additive effects
- Rashes
- CNS effects
- Lipodystrophy

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## HIV Protease

- 90 amino-acid protein
- Monomers inactive
- Aspartyl protease
- Targets HIV gag-pol polyproteins

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## HIV Protease Inhibitors

- Developed through computer assisted drug design
- Synthetic analogs of phenylalanine-proline
- Difficult to synthesize
- No effect on cells already infected
- Prevents formation of mature viral particles

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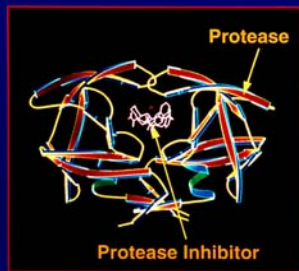
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### Pathogenesis and Treatment PROTEASE INHIBITORS Structure

1.054



IAEP<sub>96</sub>

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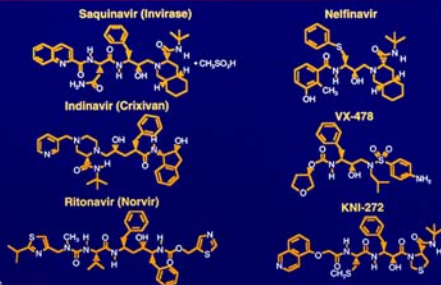
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### Pathogenesis and Treatment PROTEASE INHIBITORS Chemical Formulas

1.055



IAEP<sub>96</sub>

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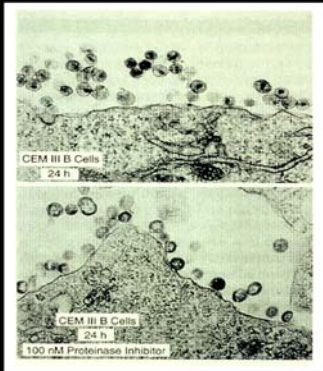
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### Protease Inhibitors

Generic name	Trade name	Dosing
Amprenavir	Agenerase	1200 mg bid
Indinavir	Crixivan	800 mg tid
Nelfinavir	Viracept	1250 mg bid
Ritonavir	Norvir	600 mg bid
Saquinavir	Fortovase	1200 tid
Lopinavir/ Ritonavir	Kaletra	3 capsules bid
Atazanavir	Reyataz	400 mg daily

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### Issues With Protease Inhibitors

- GI toxicity
- Drug-drug interactions
- Lipid abnormalities
- Lipodystrophy
- Myocardial infarctions
- Increased risk of diabetes

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Combivir One tab bid	Zidovudine 300 mg Lamivudine 150 mg	
Trizivir One tab bid	Zidovudine 300 mg Lamivudine 150 mg Abacavir 300 mg	
Truvada One tablet daily	Emtricitibine 200 mg Tenofovir 300 mg	
Atripla One tablet daily	Emtricitibine 200 mg Tenofovir 300 mg Efavirenz 600 mg	
Kaletra Two tablets bid	Ritonavir 100 mg Lopinavir 400 mg	

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**Fusion Inhibitors**  
**Enfuvirtide (T-20)**

- Blocks HIV CD4 cell fusion
- Protein
- Administered subcutaneously twice daily

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**Fusion inhibitors, 2004**

- Enfuvirtide
- Side effects
  - Inflammation at the injection site
  - Eosinophilia
  - Increased rate of bacterial pneumonias (? mechanism)

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## Enfuvirtide T-20

	ENF + Optimal therapy	Optimal therapy alone
Change in viral load (log)	-1.70	-0.76
Viral load less than 400 (%)	37%	16%
Change in CD4 count (absolute)	+76	+32

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## Tolerability of Fusion Inhibitors

- Injection site reactions<sup>1</sup>
- Rash, general allergic reactions<sup>1</sup>



*Moderate-to-severe injection site reaction*

<sup>1</sup> Lalezari JP et al. *AIDS*. 2003;17:691-698.

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## Enfuvirtide side effects

- Injection site reactions 75-95 %
  - 3% discontinuation in research trial
  - 10% required analgesics for pain control
- Hypersensitivity 2%
- Eosinophilia

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## Goal of Anti-Viral Therapy

- Maximal viral suppression (undetectable at 6 months)
- Regimen with good compliance and few side effects

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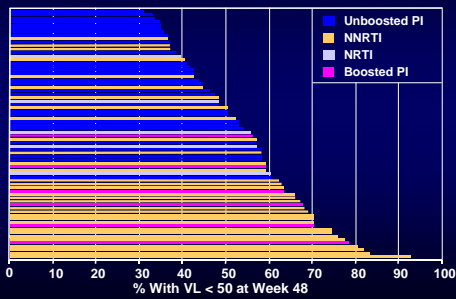
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## Collated Results of HAART Studies



Bartlett JA et al. 12<sup>th</sup> CROI. 2005; Boston, MA. Abstract #586.

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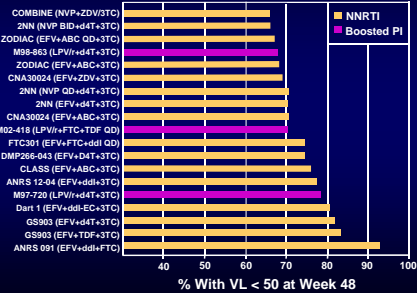
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## Potency of HAART: Studies with > 65% Response (VL < 50 at Wk 48)



Bartlett JA et al. 12<sup>th</sup> CROI. 2005; Boston, MA. Abstract #586.

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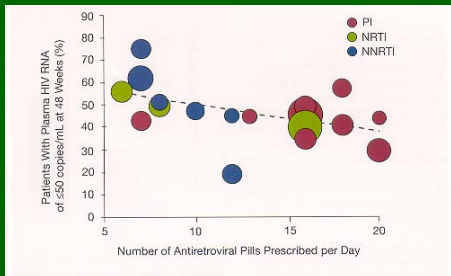
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**Figure 1.** Virologic response by daily pill burden in a meta-analysis of 23 clinical trials involving antiretroviral combination therapy in antiretroviral-naive HIV-infected adults ( $r = -0.57, P = .0085$ ). PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor. Note: Size of symbol is directly proportional to weight of the data point in the analysis. Modified from Bartlett JA, et al.<sup>4</sup>

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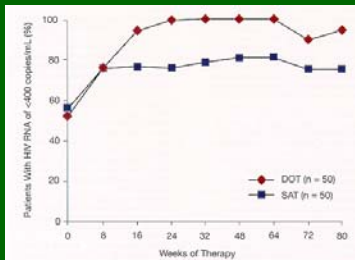
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**Figure 5.** Effect of directly observed therapy on virologic response. DOT, directly observed therapy; SAT, self-administered therapy. Adapted from Fischl M, et al.<sup>10</sup>

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## Metabolic Changes in Persons With HIV on HAART

- Stavudine (d4T) and protease inhibitors increase lipolysis in adipocytes
- Nelfinavir decreases glucose transport and phosphorylation in the liver
- Metabolic syndrome
- Insulin resistance
  - Lipodystrophy implies insulin resistance

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## Intimal Thickness With HAART

- Measured by B mode ultrasound
- Compare subjects on PI's (216 wks median) vs non-PI therapy vs HIV (-)
- No differences in cholesterol, LDL, BMI

	Thickness
Non PI	.69
PI	.71
HIV-	.69

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## CV Disease in Persons With HIV

- Case control study (7330 person yrs)
- CAD/Angina 6/1000 person yrs
- TIA/CVA 5/1000 person yrs
  
- NHANES would be 2-3/1000 person yrs

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## Risk of MI's on PI's

- Risk of 5-6 per 1000 person years at 4 yrs
- 1.26 increased risk per year of exposure
- Gender, age, smoking, prior cardiovascular disease greatest increase in risk
- Lipodystrophy with decreased risk of MI

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## Lipodystrophy

Regimen	% occurrence at 80 weeks
No therapy	5%
NRTI plus NNRTI	35%
NRTI plus PI	50-60%

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## Lipodystrophy

- No decline in incidence at 80 weeks
- Stoppage of therapy may not alter many of the metabolic parameters
  - Follow-up to 9 months do not show physical reversal of changes (change from PI to abacavir)
  - May not continue to worsen
- Use of statins and clofibrate have been associated with rhabdomyolysis (Pravastatin safest)

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## Osteoporosis/Osteopenia

- Effects 40-60% of HIV + patients on HAART
- 48 week study of alendronate 70mg q wk with Ca++ and Vitamin D
- Almost all men
- Bone mineral density in lumbar spine

	» Alendronate	No alendronate	
• % change	5-6%	2-3%	p<0.01

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### Choices for initial HIV therapy

- 2 nucleosides (nucleotides) plus a non nucleoside reverse transcriptase inhibitor
- 2 nucleosides (nucleotides) plus a boosted protease inhibitor regimen
- 2 nucleosides (nucleotides) plus a non boosted protease inhibitor regimen

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**Thank You**

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