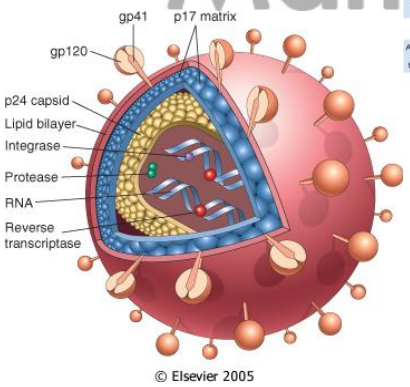
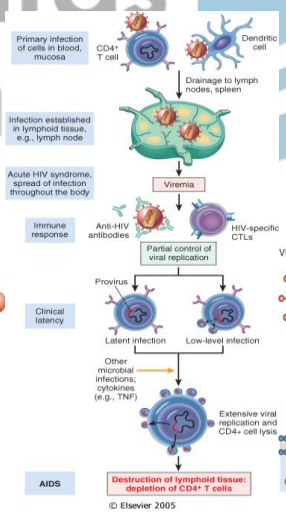
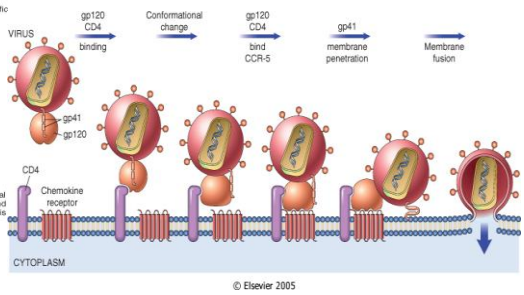
Human Immunodeficiency Virus (HIV) & Auto Immune Deficiency Disorder (AIDS)

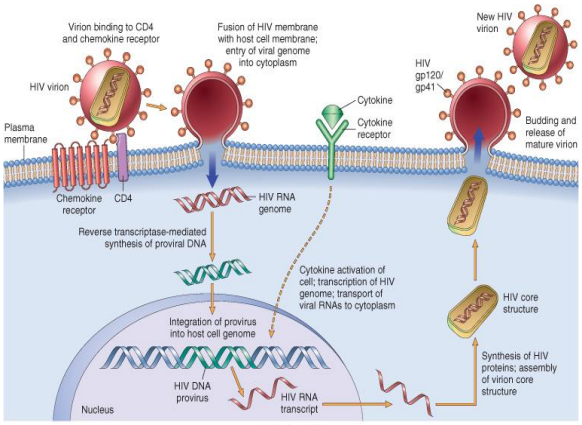
General

- Mech: HIV → Immune System Dysfunction → Opportunistic Infections & Neoplasms
- RFs: IVDU ("Rule of Threes": If you get pricked by IV you have a 30%, 3%, 0.3% chance of getting HBV, HCV, HIV), sex (increased in the presence of STD ulcers), vertical, transfusions, NOT via physical contact or insect bite
- Virology: ssRNA Virus, there are two type of HIV virus (1 = US, Europe, Central Africa and 2 = West Africa, India) they are basically the same but 2 progresses to AIDS more slowly but is resistant to many meds
    - Genes
        - *gag* and *pol* gene products are translated as one peptide which must be cleaved by viral protease to yield functional proteins (protease inhibitors which are the mainstay of HIV drug therapy act here)
        - *gag* gene product is then cleaved into **p17** (matrix protein), **p24** (capsid protein), and **p6** and **p7** (nuclear capsid protein)
        - *pol* gene product is then cleaved into **protease** and **reverse transcriptase**
        - *env* gene product is cleaved into **gp120** and **gp41**
        - interestingly the part of the genome that codes for envelope proteins has a high mutation rate; this is unfortunate b/c our humoral defense is targeted against these envelope proteins
    - HIV is trophic for cells that are CD4+ (not just found on T-Cells but also on Macrophages, Dendritic Cells, etc)
        - Step 1: gp120 on HIV binds CD4 on host cell (these are antigen receptors)
        - Step 2: gp41 inserts into host cell membrane and stimulates fusion of the enveloped virus with the host cell
        - Step 3: HIV ssRNA genome is released into cytoplasm and undergoes reverse transcription into cDNA
        - Step 4: cDNA remains free in linear form when host cell is quiescent, but when host cell divides the cDNA incorporates into host genome and remains there for years *but not as a latent infection b/c virus is continually being produced*
        - Step 5: when the body is faced with something foreign the foreign antigen stimulates T-cells to activate to fight this foreign intruder (NORMAL IMMUNE FUNCTION) BUT THE PROBLEM IS THAT THE SAME STIMULUS FOR T-CELL ACTIVATION IS THE SAME STIMULUS FOR THAT TRIGGERS HIV TO EMERGE FROM LATENT PHASE AND ENTER LYTIC PHASE WHERE IT PRODUCES MANY VIRIONS WHICH EVENTUALLY LYSE THE T-CELL
        - Step 6: the worst part about it is that by destroying T-cells you allow for more infections which in turn activate those remaining (however infected) T-cells while also activating more HIV production resulting in a vicious cycle that ends up destroying all T-cells and resulting in AIDS
        - Step 6: because T-cells are destroyed there is also dysregulation of B-cells









Dx (obtain informed consent, recommended that high-risk pts, pregnant women, active TB pts, hospitalized pts 15-55yo if community seroprevalence rate exceeds 1% or AIDS cases are >1/1000, donors, health care workers)

- **1st ELISA Screen** (high sensitivity low specificity, enzyme-linked Ab to HIV-1-Ab which is against p24, + w/in 2-3mo of acquisition therefore check PCR of **D**NA to make Dx in ARS and it just tells you "yes or no" it doesn't give you a number like in VL, a screening test is being developed that can produce results in 20min)
- **2nd Western Blot Confirmation** (low sensitivity high specificity, fluorescent coded Ab to ≥2/3 HIV-Ags p24, gp41, gp120, NB indeterminate test is one which is + ELISA but only 1/3 Western)
- NB the chance that both ELISA and Western Blot is false-positive is 1/140,000 esp in blood transfusions, organ transplants, etc and false-negative is 1/? esp in pts with very advanced HIV as pts cannot form Ab b/c immune system is so damaged and very early HIV as Ab have not formed yet)

Monitoring

- **Viral Load** (PCR ssRNA Assay = inaccurate <400 copies/mL but an "Ultrasensitive Assay" exists which is accurate to <40copies/mL, assess effectiveness of HAART and gives you an idea of the rate of CD4 destruction (goal should be complete remission aka 0 viral load) NB this is different than PCR of HIV DNA used to dx early infections
- **CD4 T-Cell Count** (not sensitive nor specific for dx, foretell type of clinical problems, it is also good to check % of total Lymphocytes that are CD4 w/ <14% being bad)

Initial Evaluation

- Teaching: Psych Issues, Support System, Safe Sex Ed, General HIV Ed
- Labs (baseline unless stated otherwise): VL/CD4, TB (yearly), VDRL/RPR, Toxo IgG, CMV IgG, HepA/B/C, GC/CH, Pap (yearly), HIV resistance testing, CXR

Acute Retroviral Syndrome (ARS)

- Epidemiology: self-limited illness often disregarded as a viral syndrome that appears in only 70% of pts ~1 month after exposure and lasting for 2 weeks
- S/S: "Mono + Rash" (1° F, pharyngitis from oral thrush, lymphadenopathy, rash, 2° HA, malaise, weight lose, myalgia/arthralgia, GI symptoms, meningitis, encephalitis, peripheral neuropathy, myelopathy, ulceration)
- Labs: pancytopenia (esp lymphopenia), elevated LFTs
- DDx: (1) CMV (2) EBV (3) Rubella (4) HSV (5) Hepatitis Virus (6) Secondary Syphilis (7) Group A Strep (8) Toxoplasmosis

Chronic Infection

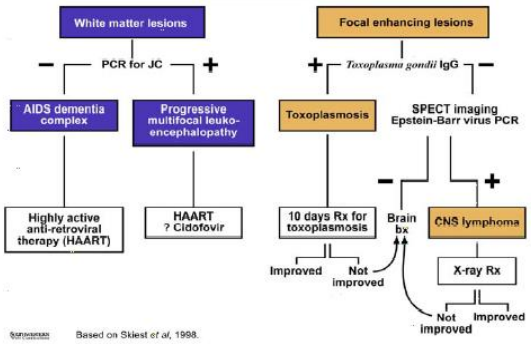
- This phase reflects the equilibrium reached b/t the virus and the host after the initial battle resulting in a steady-state between viremia (positive viral load but low) and CD4 count (low CD4 but >500)
- The exact steady state (number of viruses vs. number of CD4 cells) is a predictor for the rate of progression of HIV disease
- 10% of pts do not enter a chronic infection of clinical latency but rather go into full blown AIDS
- S/S: constitutional Sx, thrush, shingles, diarrhea

AIDS

- **Def: AIDS Defining Illness (infection or malignancy) OR Asymp but CD4 <200 OR CD4% <14% of total lymphocytes**
- Eventually the immune system decompensates (~10yrs) and AIDS manifest as T-cells drop accompanied by very high viremia
- Pt presents with long-standing (>1mo) F, weight loss, and night sweats (classic "B" symptoms of cancer) followed by a series of opportunistic infections (accounting for most of the deaths), secondary neoplasms and/or neurologic disease

>500 **(infections similar to non-HIV pts)**	**<500** **(infections similar to non-HIV pts but esp increased r/o Strep pneumonia, HSV, TB)**	**<200** **(Fungi)**	**<50** **(CMV, MAC, Aspergillus, Lymphoma)**

CNS • 90% of AIDS pts at autopsy have neurologic involvement, 50% of AIDS pts have clinically apparent neurologic dysfunction • Four areas of infection: peripheral nerves, meninges, CNS, spinal cord	• Peripheral Neuropathy: **HAART** • Meninges: **Ordinary Bugs, HSV, TB** • CNS: **Neurosyphilis, Abscess** • Spinal Cord: **Abscess**	• Peripheral Neuropathy: **HIV** • Meninges: **Crypto** (refer) • CNS: **Progressive Multifocal Leukoencephalopathy** (JCV infects oligodendrocytes, multiple white matter lesions, CSF PCR for JCV, Tx: HAART), **Toxoplasmosis** • Mech: animals eat meat containing cysts which invade GI tract and then live in skeletal muscle, myocardium, and brain, cysts are then released into GI lumen which are then excreted into feces and then form spores, humans ingest undercooked meat esp pork/lamb containing cysts or contaminated food w/ cat feces, organ transplantation, blood transfusions, transplacental transmission from infected mother, NB overall 30% of US adults have been infected • S/S: immunocompetent (asymptomatic but sometimes there is a mono-like illness or ocular toxo w/ yellow retinal lesions and scarring), immunocompromised (multiple small ring enhancing lesions develop in the 1° CNS (basal ganglia and grey-white jxn) and 2° heart, lungs, etc due to reactivation of latent infection acquired as a child (50% of HIV pts w/ +IgG will develop active toxo)), congenital infection (spontaneous abortion but if the a baby is delivered then necrotizing chorioretinitis results w/ subsequent retinal scarring and mental retardation) • Dx: rising IgG and + IgM, rarely are Bx done anymore but if they are then you will see cysts/trophozoites, occasionally you see cysts/trophozoites in CSF, +IgG w/ clinical picture, MRI and response to Tx is usually how diagnosis is made • Tx: usually not needed if healthy and not pregnant but if healthy pt w/ ocular toxo or immunocompromised pt w/ CNS toxo then Pyrimethamine + Leucovorin + Sulfadiazine/Clinda/Spiramycin x4-6wks	• Peripheral Neuropathy: **CMV** • Meninges: **CMV** • CNS: **Primary CNS NHL** (refer below), **HIV Dementia** (generalized white matter atrophy), **CMV**, **Nocardia** • Eye: **CMV Retinitis** (most common CMV infection, 4F's: "floaters, flashes, field defects, failing vision", clinical Dx only for eye but for any other organ you need tissue, NB no pain/redness, white puffs on fundoscopy, induction Tx and then maintenance forever until CD4 >100 x6mo, NB never start HAART during an acute CMV infection b/c of high r/o IRIS) • Spinal Cord: **Lymphoma, Vacuolar Myelopathy**

			
Pulm • b/f HAART PCP was the main admitting diagnosis b/c CD4 was often <200 after HAART bacterial pneumonias become the main admitting diagnosis b/c CD4 is usually >200 (bug never identified → normal bugs → PCP → fungi → mycobacterium) if CD4 <200 take the following approach ○ respiratory isolation b/c of possible TB ○ obtain blood (60% sens) & sputum induced w/ hypertonic saline (70% sens) for Gram Stain / Cx for Bacteria, Ziehl-Neelson Stain / Cx for TB, Direct Fluorescent Ab Stain / Cx for PCP ○ if sputum unrevealing then BAL (80% Sensitive) ○ if BAL unrevealing then begin empiric therapy for bacterial pneumonias and PCP not TB unless + stain/Cx • pattern of infiltration on CXR is not pathogen specific • 50% of time HIV pts w/ pneumonia are just treated for PCP and bacterial pneumonias once TB has been ruled so as to not subject them to BAL (this approach is discouraged)	• **TB** (remember +PPD is >5, often atypical presentation) • **Strept** (HIV pts are at an extraordinarily high risk)	• **Endemic Mycosis** • **PCP :** NB was Pneumocystis carinii (PCP) but now Pneumocystis jiroveci (PJP), S/S (Atypical CAP w/ F, non-prod cough, hypoxemia out of proportion to CXR which is nl early on and then diffuse interstitial infiltrates later on, NB it was called pneumocystis b/c on CT there is a fine groundglass infiltrate then when looked at closely is cystic and if severe it can begin to look like emphysema), Dx (high LDH, PCP Ags and Methanamine/Giemsa Silver or Toluidine-Blue O stain of BAL ?% sens AND Sputum 50% sens), Complications (5% PTX), Tx (x21d, 1° Bactrim 2° Trimethoprim+Dapsone or Clindamycin+Primaquine or Atovaquone, if A-a Gradient >35 or PaO2 <70 and NO other infection exists then add prednisone 40 BID starting before Bactrim and tapering after 5d, NB even though PCP is a fungus antifungals do not work b/c PCP does not have ergosterol in its membrane and that is why prior to 1988 PCP was considered a bacteria)	• **Aspergillus** • **CMV** • **HSV** • **Kaposi** • **Nocardia** • **Rhodococcus** • **Lymphoma**
Derm	• HSV/ VZV • Squamous Cell Carcinoma (not consider AIDS defining but occurs at much greater frequency than BCC) • Seborrheic Dermatitis • Nasopharyngeal Carcinoma or Oral Hairy Leukoplakia		• Disseminated Bartonella (Bacillary Angiomatosis) • Kaposi Sarcoma (KS) ○ **Four Epidemiologic Groups**: (1) **"Classic"** elderly men of Eastern European and Jewish Ancestry (indolent cutaneous only dz on LE)

	2/2 EBV • HPV Cervical/Anal SCC/Warts • Molluscum Contagiosum • Eosinophilic Pustular Folliculitis (EPF, looks just like acne but more generalized, Tx the same way) • Prurigo Nodularis • Scabies • Cutaneous Candidiasis • Psoriasis		first described by Moritz Kaposi, (2) **"Endemic"** young men in Equatorial Africa (aggressive disseminated dz w/ significant LAD), (3) **"Iatrogenic"** immunosuppressed pts after solid-organ transplant, (4) **"Epidemic"** homosexual men w/ HIV/AIDS ○ Incidence: 1/100,000 (general pop) → 1/20 (HIV) → 1/2 (homosexual male w/ AIDS off HAART w/+HHV-8) NB higher the lower the CD4 ○ Mech: HHV-8 infects circulating endothelial precursor cells → impaired immune system → cells localize to sites of inflammation (Koebner Effect) and proliferate mediated by specific cytokines (IL-1, TNF-α, IFN-γ) elevated in HIV ○ HHV-8 Dz: Castelman's Dz, Primary Effusion Lymphoma, Kaposi Sarcoma ○ S/S: Skin (red elliptical patches,diffuse to localized (1° face/neck esp tip of nose) arranged along skin tension lines, indolent (non-HIV type) to rapid (HIV-type), generally painless and non-pruritic, lesions tend to develop or exacerbate with the use of systemic steroids and development of opportunistic infections) vs Visceral Involvement (seen in 10% of skin causes, usually GI (more common in proximal than distal GI tract), pharynx, lungs, generally asymptomatic but can bleed) ○ Dx: no Bx unless rapid onset, atypical or systemic Sx, histology shows spindle shaped cells infected w/ HHV-8, leaky neovascularization w/ extravasated RBCs, inflammatory infiltrate ○ Tx: **Immune Reconstitution w/ HAART (50% effective) → If HAART does not resolve dz then additional Tx is needed** ▪ Local therapy to palliate Sx caused by specific bulky lesions or for cosmesis (Large Lesions → XRT vs Small Lesions → Intralesional

			Chemo (Vinblastine), Topical Agents (Aliretinoin, Imiquimod), Cryotherapy, Surgery) ▪ Systemic therapy if widespread cutaneous, visceral involvement, IRIS (Systemic Chemo w/ doxorubicin and paclitaxel)
CV	• Dilated CM • Increase r/o ACS from use of PIs		
Endo	• **Hypogonadism** • **Adrenal Insufficiency** • **Lipodystrophy** (central obesity w/ wasting of extremities + metabolic syndrome)		
Heme Onc • chronic B-cell stimulation leading to increased r/o genetic mutation, 100x increased risk compared to non-HIV population, there are three types of lymphoma, , generally aggressive, also increased risk of HL but not considered an AIDS defining illness, HAART is part of the Tx of lymphoma along w/ chemo, unlike other CNS tumors PCNSL is not treated w/ surgery b/c multiple and often surrounding vessels (NB Rituxan gives increased response but also increased r/o infectious complications therefore give prophylactic abx), XRT/steroids for CNS, NB always check LP for leptomeningeal involvement in HIV pts w/ systemic/effusion NHL b/c they often have asymptomatic dz	• **Pancytopenia** • **Hyperglobulinemia** • **Primary Systemic NHL** (Large Cell/Burkitt's) 40% associated w/ EBV, can be seen in anus/rectum	• **Primary Effusion NHL** (Large Cell) 100% associated w/ HHV-8, in pleura / pericardium / peritoneum / synovium	• **Primary CNS NHL** (Large Cell) 100% associated w/ EBV, solitary ring enhancing lesion, periventricular and thus can lead to leptomeningeal dz, ocular involvement is common, Dx: CSF PCR of EBV, PET Scan
Renal	• **Collapsing FGS**		

OI	**Indication** (how about prior infection???)	**OI Prophylaxis** (stop when CD4 above threshold for 3mo)
TB	+PPD >5mm OR Exposure	1° Isoniazid + Vitamin B6 x9mo 2° Rifampin + Pyrazinamide x2mo
PCP	CD4<200 OR CD4% <14% OR Thrush OR FUO >2wks	1° Bactrim 2° Dapsone or Atovaquone or Pentamidine
Toxo	CD4<100 AND +IgG	1° Bactrim 2° Dapsone + Pyrimethamine + Leucovorin
MAC	CD4<50	1° Azithromycin or Clarithromycin 2° Rifabutin
Influenza Pneumococcal HepA HepB	All pts	Immunizations (generally wait until CD4>200, no live vaccines) • Influenza (note that vaccination actually promotes HIV replication for up to 3mo) • Pneumococcal (Q5yrs) • HepA (if HepA Ab neg then vaccinate b/c HIV pts are at higher risk of fulminant hepatitis if they become superinfected with

		HepA while being HepC positive) • HepB (if HepB Ab neg then vaccinate)
HSV Candida CMV Crypto Endemic Fungals	NONE	NONE

(2) Highly **A**ctive **A**nti**R**etroviral **T**herapy **(HAART)**
"Triple Drug Cocktail" never mono/dual therapy
[2 Nucleos/tide RTIs + 1 Protease Inhibitor] eg. Atripla
[2 Nucleos/tide RTIs + 1 Non-Nucleoside RTI]
[3 Nucleos/tide RTIs]

1st Symptoms	2nd CD4 (#/mm3)	3rd Viral Load (copies/mL)	Treatment
Symptomatic Pregnant HIVAN HBV Coinfection	NA	NA	Treat
Asymptomatic	<350	NA	Treat
	>350	>100k	Treat
		<100k	Watch

- HAART began in mid-1990s, now regimens are down to one pill a day <$10k/yr
- goal is that viral load become undetectable after therapy, once this occurs never stop HAART b/c even though viral load decreases to zero latent cells exist (you can never be cured of HIV), keep on checking viral load Q3mo
- **Immune Reconstitution Inflammatory Syndrome (IRIS)**: can occur when any type of infection (HIV, TB, leprosy, etc) that affects the immune system is appropriately Tx (HAART, RIPE, etc) resulting in reconstitution of immune system and subsequent worsening clinical state as the body is now able to mount an inflammatory process and fight other infections (esp Zoster, TB, MAC, CMV, Crypto), onset is variable from days to months, Tx: continue HAART, RIPE, etc, treat infection, steroids 1mg/kg/d w/ rapid taper over 10-14d
- always check resistance
- if Tx needs to be held hold ALL HAART not just part of it to minimize development of resistance
- if on HAART VL should decrease by 1 log copies/mL per month
- <5k VL = near normal CD4 and minimal disease progression vs >30K VL = opposite
- treatment failure defined as (1) <log reduction of viral load 4-6wks after starting a new HAART regimen, (2) failure to reach an undetectable viral load after 4-6mos of treatment, (3) new detection of viral load after viral load became undetectable, and (4) persistent CD4 decline or clinical decline despite Tx = do resistance testing and change HAART regimen
- resistance testing, check pts starting Tx and those who are failing Tx
- always check for interactions between antiretrovirals (extensive tables exist) and with other drugs (b/c of extensive P450 interactions)
- given the metabolic SEs below there is concern for CV risks down the road
- there have been 56 cases of health care acquisition while there are 600,000 cases of exposure per year, percutaneous worse than mucus membrane, start Px (2 drugs) w/in hrs of exposure and continue x4wks, check HIV at baseline/72hrs/6wks/3mo/6mo), no sex/transfusions/transplants for 3mo, 50% will experience SEs

Nucleosides (inhibit at active site)	Mechanism • prodrug (psuedonucleoside) is converted by host kinases to psuedonucleotide which in turn directly inhibit reverse transcriptase or incorporate into DNA but prevent elongation General Side Effects • Lipodystrophy Syndrome: fat from limb/face/buttocks moves to ab/back giving pts a distinctive/stigmatizing cachectic appearance, Tx w/ surgery, DM/DL meds • Lactic Acidosis w/ Liver Steatosis (Nucleo**s/t**ides) 70% Morality, Tx: riboflavin/thiamine/L-carnitine, RRT • Hepatitis (**NON**-Nucleo**s**ides) • Rash (**NON**-Nucleo**s**ides)	zidovudine-AZT/ZDV (Retrovir) • used during pregnancy b/c found to reduce risk of fetal transmission • first drugs	BM Suppression Macrocytosis Myopathy
		stavudine-d4T (Zerit)	Pancreatitis Peripheral neuropathy
		didanosine-ddI (Videx)	Pancreatitis Peripheral Neuropathy
		zalcitabine-ddC (Hivid)	Peripheral Neuropathy Stomatitis
		emtricitabine-FTC (Emtriva)	Minimal Toxicity
		lamivudine-3TC (Epivir)	Minimal Toxicity

Nucleotides (inhibit at active site)	• Steven-Johnson Syndrome (**NON**-Nucleo**s**ides) Synergism abacavir+lamivudine (Apzicom) abacavir+lamivudine+zidovudine (Trizivir) emtricitabine+tenofovir (Truvada)	abacavir-ABC (Ziagen)	Fatal Hypersensitivity (check for HLA B-5701)
		tenofovir-TDF (Viread)	Minimal Toxicity
NON-Nucleosides (inhibits at allosteric site)		nevirapine-NVP (Viramune)	Hepatitis Inhibits CYP450
		delavirdine-DLV (Rescriptor)	HA Inhibits CYP450
		efavirenz-EFV (Sustiva)	CNS effects False + UTox (Cannabinoid) Inhibits/Induces CYP450
Protease Inhibitor (PI)	Mechanism • inhibits protease from splicing protein to make gp120/41 and p17/24 General Side Effects • Lipodystrophy Syndrome • Inhibits CYP450 • GI Problems • Hyperglycemia • Bleeding Diathesis esp in Hemophiliacs • Hyperlipidemia esp Hypertriglyceridemia (but do not use statins in Tx) Synergism lopinavir+ritonavir (Kaletra)	indinavir-IDV (Crixivan)	Nephrolithiasis Increased Indirect Bilirubin
		ritonavir-RTV (Norvir)	
		saquinavir-SQV (Fortovase)	Hepatitis
		nelfinavir-NFV (Viracept)	Diarrhea
		amprenavir (Agenerase)	
		lopinavir-LPV (Kaletra)	
		fosamprenavir-fAPV (Lexiva)	Rash GI Problems
		atazanavir-ATZ (Reyataz)	Increased Indirect Bilirubin
Fusion Inhibitors (FI)	• SC injection	Enfurvitide-T20 (Fuzeon) Maraviroc (Selzentry)	Injection site rxn
Integrase Inhibitors (II)		Raltegravir (Isentress)	