

When to Start ART

- Exact CD4 count at which to initiate therapy not known, but evidence points to starting at higher counts
- Current recommendation: ART for all patients with CD4 count of <500 cells/ μL
 - Randomized control trial (RTC) data support benefit of ART if CD4 count ≤ 350 cells/ μL
 - No RTC data on benefit of ART at CD4 counts of >350 cells/ μL , but observational cohort data exist
 - Reduction in AIDS- and non-AIDS-associated morbidity and mortality
 - ? Reduction in HIV-associated inflammation and associated complications
 - » i.e. CV disease, neuro, etc
 - Reduction in HIV transmission

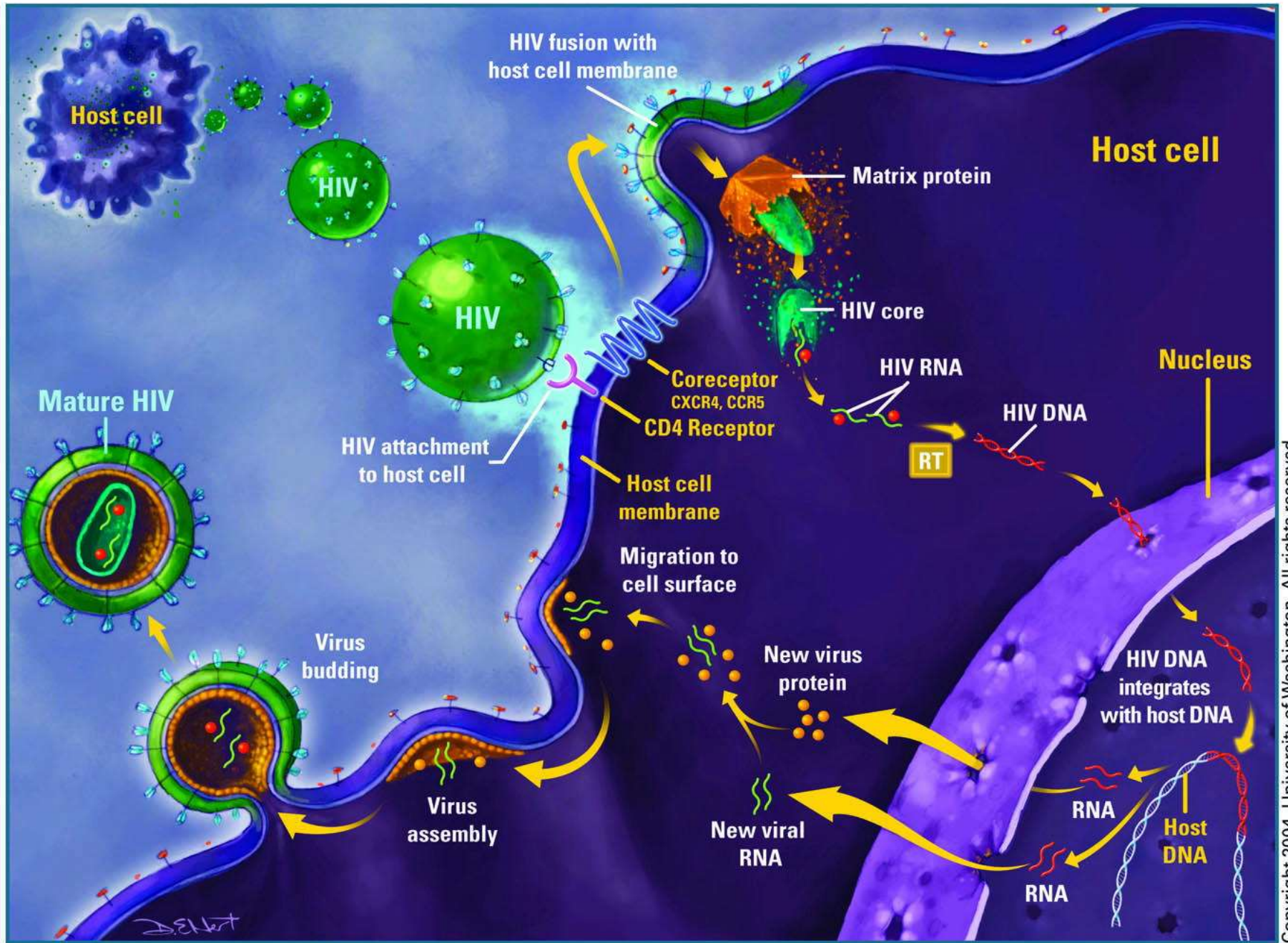
Recommendations for Initiating ART (DHHS 2011)

Clinical Category or CD4 Count	Recommendation
<ul style="list-style-type: none"> ■ History of AIDS-defining illness ■ CD4 count <350 cells/μL ■ CD4 count 350-500 cells/μL ■ Pregnant women ■ HIV-associated nephropathy (HIVAN) ■ Hepatitis B (HBV) coinfection, when HBV treatment is indicated <p><small>*Treatment with fully suppressive drugs active against both HIV and HBV is recommended.</small></p>	<h2>Initiate ART</h2>

Clinical Category or CD4 Count	Recommendation
<p>CD4 count >500 cells/μL, asymptomatic, without conditions listed above</p>	<p>50% of the Panel favors starting ART; 50% views ART as optional</p>

Recommendations for Initiating ART

- “Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence.”
- Patients may choose to postpone ART
- Providers may elect to defer ART, based on patients’ clinical or psychosocial factors
 - When there are significant barriers to adherence
 - If comorbidities complicate or prohibit ART
 - “Elite controllers” and long-term nonprogressor



Current ARV Medications

NRTI

- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (AZT, ZDV)

NNRTI

- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)

PI

- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

Fusion Inhibitor

- Enfuvirtide (ENF, T-20)

CCR5 Antagonist

- Maraviroc (MVC)

Integrase inhibitor (II)

- Raltegravir (RAL)

Current ARV Medications Coformulations

- Zidovudine + lamivudine – Combivir
- Tenofovir + emtricitibine - Truvada
- Abacavir + emtricitibine – Ezicom
- Zidovudine + lamivudine + abacavir - Trizivir
- Lopinivir + ritonavir – Kaletra

- Sustiva + tenofovir + emtricitibine - Atripla



Coming soon.....

- Rilpivirine
 - NNRTI
 - in process FDA
 - As effective as EFAVIRENZ
 - Coformulation with TRUVADA **ANOTHER ONE PILL TREATMENT**
- Elvitegravir
 - Integrase inhibitor
 - Successfully coformulated with emtracitabine/tenofivir/GS-9350 (a booster)
 - **QUAD PILL ONCE DAILY**
 - Smaller than current once daily pills

Choice of initial regimens

- 3 main choices
 - NNRTI + 2 NRTI
 - Boosted PI + 2 NRTI
 - II + 2 NRTI
- Few clinical end points to guide choices
- Advantages and disadvantages to each type of regimen
- Individualize

- **Preferred Regimens** (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use) The preferred regimens for nonpregnant patients are arranged by order of FDA approval of components other than nucleosides, thus, by duration of clinical experience.
- **NNRTI-Based Regimen**
 - • Efavirenz/Tenofivir/FTC (AI)
(Atripla)
- **PI-Based Regimens (Protease inhibitor)**
 - Atazanavir/ritonavir + TDF/FTC (AI)
 - Darunavir/ritonavir (once daily) + TDF/FTC (AI)
- **INSTI-Based Regimen (Integrase inhibitor)**
 - Raltegravir + TDF/FTC (AI)
- **Preferred Regimen for Pregnant Women**
 - Lopinavir/ritonavir (twice daily) + ZDV/3TC (AI)
- **Comments**
- EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.

Choice of initial regimens : PI vs NNRTI

- PI
 - Higher genetic barrier to resistance
 - PI resistance uncommon with failure
 - Metabolic C/O
 - Lipodystrophy, IR
 - GI intolerance
 - DRUG INTERACTIONS (CYP450)
 - Especially RTV
- NNRTI
 - Lower genetic barrier to resistance (1 mutation)
 - More transmitted resistance
 - Less metabolic toxicity
 - Rash, hepatotoxicity
 - Long half lives
 - Drug interactions (CYP450)

Integrase inhibitor- well tolerated

- potent
- fewer interaction

- twice daily

- low barrier to resistance
- less experience

Protease inhibitor drug interactions

- Statins
- Benzos
- Ca++ channel blockers
- ED agents
- Anticonvulsants
- Immunosuppressives
- Rifamycins
- Azoles
- Ergot derivatives
- Macrolides
- OCP
- Nasal steroids.....ETCETC

- BEWARE REYATAZ + PPI

The best regimen is the one your patient will take

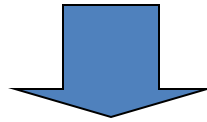
TOLERABILITY

ADHERENCE

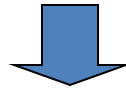
Complications of HIV

Immune activation and HIV disease

HIV is not only a disease of immune suppression but also of immune activation



INFLAMMATION



??health problems that are not typically “HIV related”
“accelerated aging”

NEUROLOGIC DISEASE

DIABETES

BONE DISEASE

HEART DISEASE / STROKE

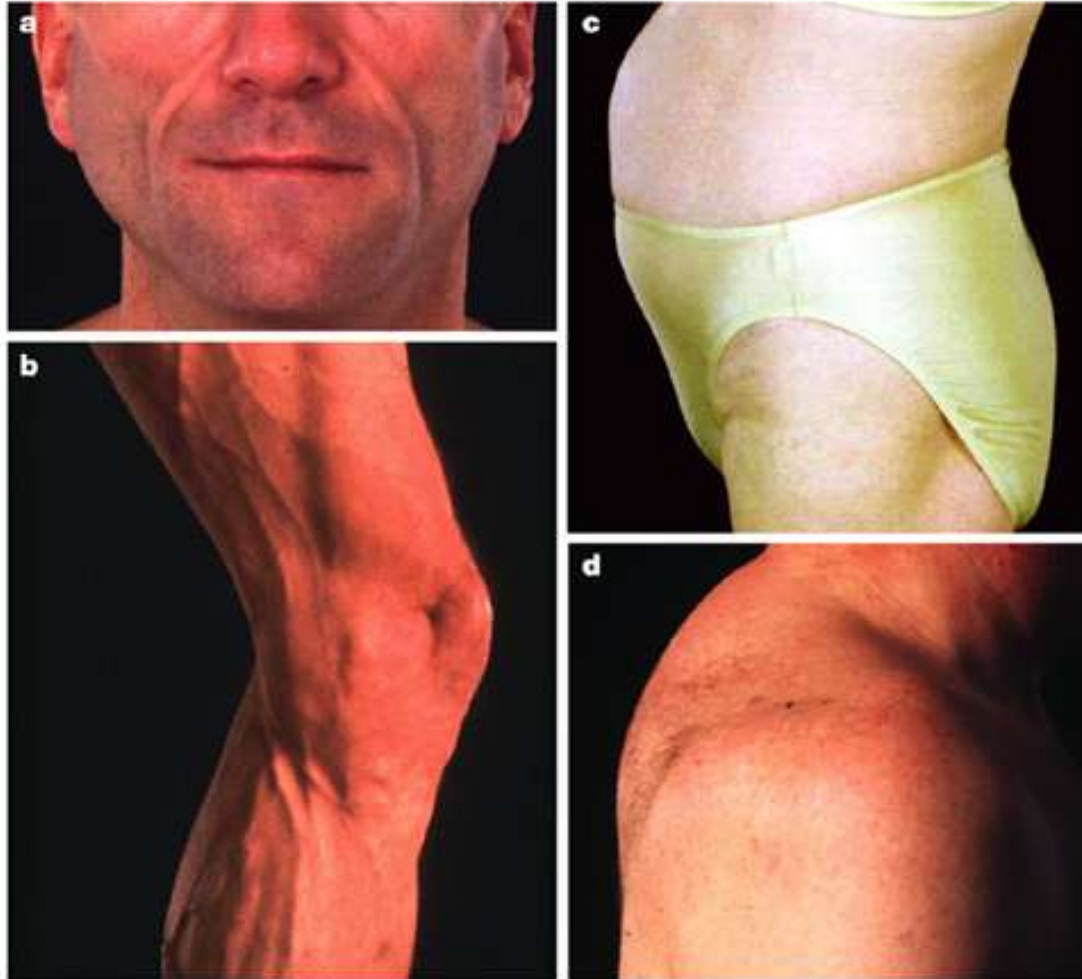
KIDNEY DISEASE

CANCERS

HIV Complications

- **Insulin resistance/DM**
 - DM 2-4X higher than general population
 - Treatment: same as non-HIV
 - ?switch HIV meds
- **Hyperlipidemia - Role for all HIV drug classes**
 - Target LDL as for non-HIV
 - Treatment
 - Risk factor modification
 - Pharmacologic – remember interactions!
 - ?switch HIV meds
- **Lipodystrophy**
 - **Lipoatrophy - Fat loss face, extremities, buttocks (Not HIV wasting)**
 - Mitochondrial toxicity of meds
 - Treatment
 - Avoid d4t, AZT
 - Cosmetic procedures
 - **Fat accumulation - “buffalo hump”, “Protease paunch”, excess breast tissue**
 - Multifactorial
 - Treatment
 - Exercise
 - Consider change HAART
 - Liposuction
 - R/O breast tumor, hypogonadism

“LIPO”



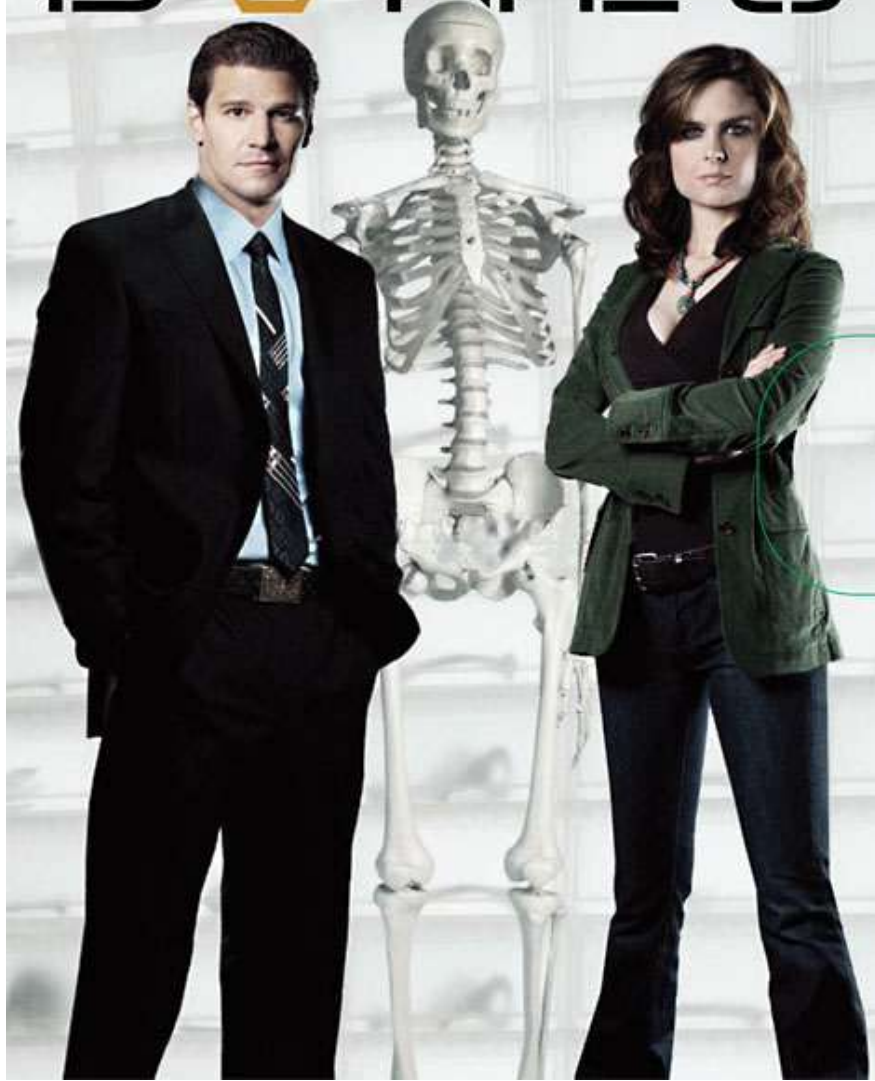


HIV COMPLICATIONS 2011

Neurologic effects of HIV

- Hoped HAART neurologic disease would go away – NOPE
- Increasing problems neurocognitive dysfunction in chronically infected persons
 - The brain is affected early in infection
 - Brain changes seen in early infection (2-12months)
 - Brain are changes seen in patients on stable ARV with controlled virus
 - ? Less problems if start ARV earlier
 - People with lower CD4 nadirs have more problems
 - ? Better outcome with antiretrovirals that get into the central nervous system
 - Some studies ys others no
- Ongoing studies of who is at more risk, how to best identify them & most importantly what to do about it

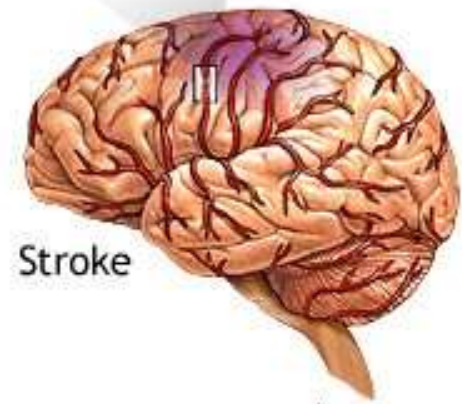
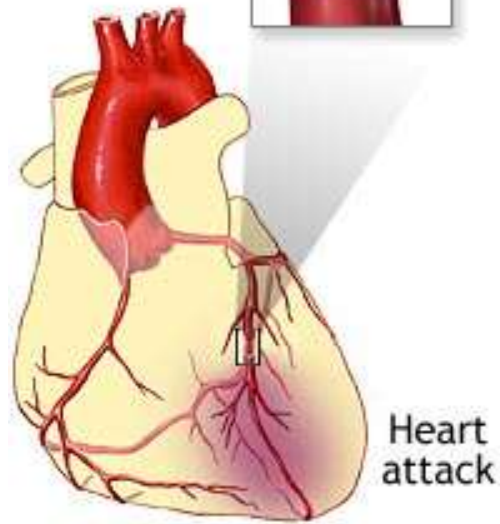
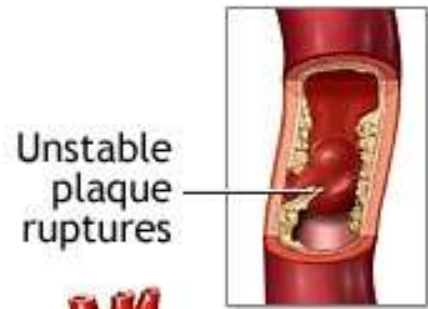
BONES



HIV COMPLICATIONS: BONE DISEASE

- Osteopenia/osteoporosis
 - 10-15% prevalence in HIV
 - high for a relatively young population
 - Etiology
 - Effects of chronic HIV infection
 - ↓ subcutaneous fat
 - Low testosterone
 - Long term survivors
 - Effects of ARV :
 - seen within weeks of starting therapy
 - PI's
 - Tenofovir
 - Traditional causes of low BMD
 - Low BMI
 - Smoking
 - Alcohol use
 - Advanced age
 - Diabetes
 - Hepatitis B and/or C
 - Opiate use

Treatment - ? Role for intervention when starting ARV
- modifiable risk factors
- screening guidelines (DEXA)



HIV COMPLICATIONS

ATHEROSCLEROSIS

- Atherosclerosis increased in HIV
- Etiology
 - HIV itself - lipo
 - Inflammation - DM
 - Genetics - Lifestyle – tobacco, EtOH
 - Other
- Even in elite controllers see signs of early atherosclerosis
- VA study presented at CROI
 - HIV itself increased risk of coronary artery disease & stroke 2 fold
THE SAME AS HAVING DIABETES
- ? Some suggestion things look better with early HAART



Non-AIDS Malignancy

- Incidence of non-AIDS related CA ↑ in HIV patients vs non HIV
 - ♂ > ♀
 - Greatest risk with anal CA, HD, skin, liver
 - Also lung, probably colon, H&N
- Incidence increasing over time -> 3X 1998
 - Prolonged survival
 - Aging
 - **Direct affect of HIV/inflammation**
 - Coinfection
 - Lifestyle
 - Genetics
 - Genomic instability?
- Manifest atypically
- Therapy more problematic

IMPORTANCE OF
lifestyle modification
vaccination
screening

What's next ?

- In 2011 we can stop viral replication with ART in *adherent patients!!!*
 - With adherence to medication:
 - No viral replication
 - No evolution of drug resistance
 - No failure
 - BUT THIS IS NOT CURING HIV

Can we think about curing HIV?

HOW COULD WE CURE HIV??????

Purge the body of HIV – including latent reservoirs

- we still need to figure out how the whole latency thing really works
- it will probably take a lot of drugs

OR

Manipulate the body's interaction with HIV

–prevent HIV from integrating into the host& alter the immune response

- Berlin patient
- Gene therapy

?toxic

? \$\$\$\$\$\$\$\$\$\$

BOTTOM LINE : NONE OF THIS IS COMING SOON.

The pipeline is not strong for salvage drugs

If a regimen that it is important to keep it working – for a long time

ADHERENCE

HIV Prevention

- Safe sex counseling; needle exchange etc
- Screening ->Diagnosing-> behaviour modification
- Prenatal screening to prevent MTCT
- **P**ost **E**xposure **P**rophylaxis
 - occupational & non-occupational
- **P**re-**E**xposure Prophylaxis
 - CAPRISA 004
 - 1% tenofivir vaginal gel in high risk o
 - 39% decrease in risk of HIV infection
 - iPrEx
 - Oral Truvada vs placebo in MSM
 - 44% decrease in risk of HIV acquisition
(\$12,000/year vs cost of condoms!!!)
 - FEM-PrEP
 - Daily oral Truvada in high risk **women** in Africa to prevent HIV – terminated
INEFFECTIVE IN PRELIMINARY ANALYSIS



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