HIV Management

Updates in HIV Primary Care

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No Financial Disclosures

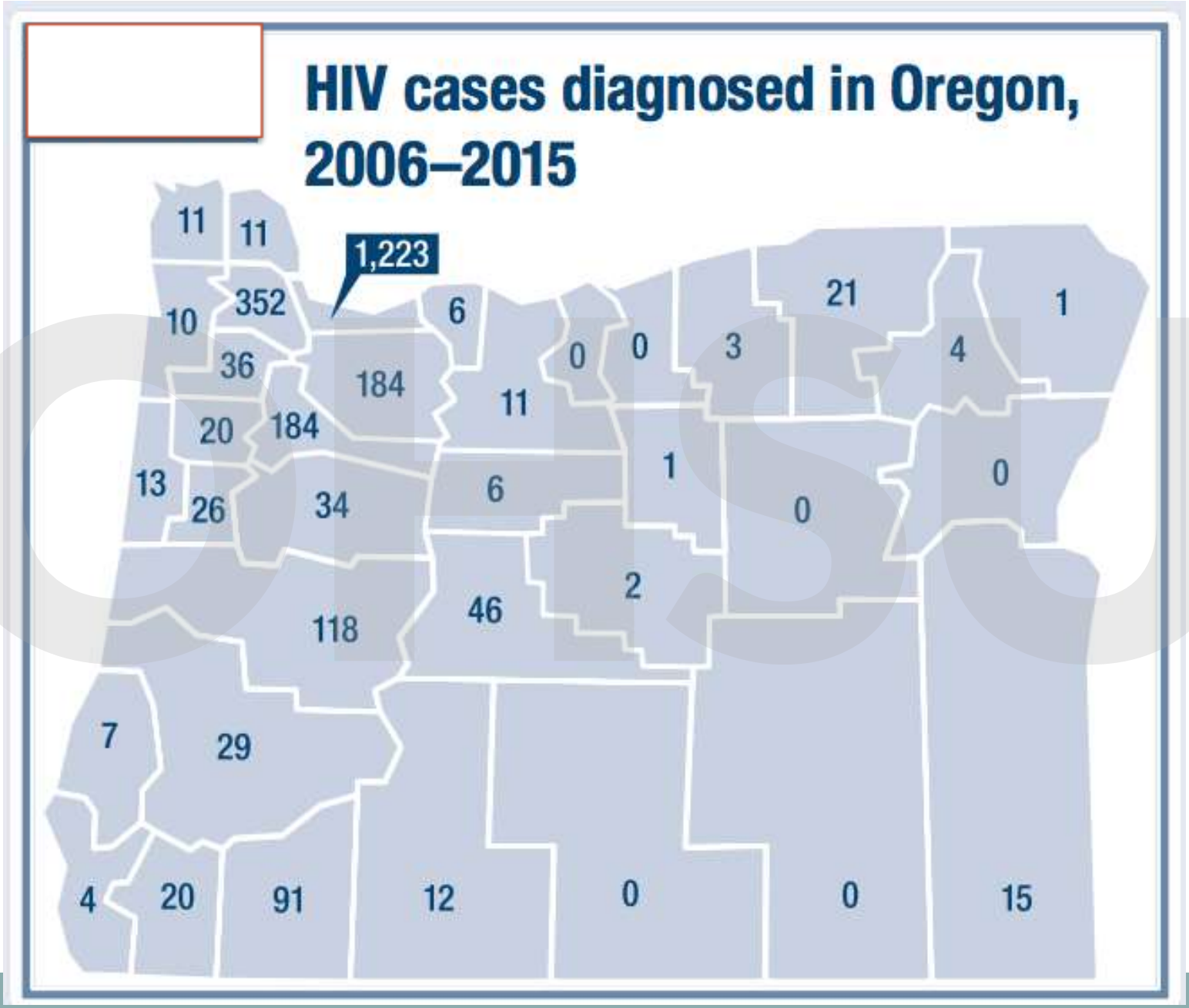
Learning Objectives

- Understand the role of role of **Primary Care** in HIV
- Understand the epidemiology of HIV in the United States
- Appreciate the multiple comorbidities in patients living with long term HIV infection
- Understand current guidelines and screenings for the health maintenance of HIV patients
- Understand the role of Pre Exposure Prophylaxis (PreP) in at risk patients for HIV
- Appreciate the future science of an HIV Cure

HIV Testing Recommendations

- USPSTF recommends that clinicians screen adolescents and adults 15-65 years and all pregnant women for HIV infection (Grade A)
  - Younger adolescents and older adults who are at increased risk should also be screened
  - Repeat screening should be considered for those known to be at risk for HIV infection
- Rationale for updated recommendations:
  - ART reduces progression to AIDS, AIDS-related events and death and substantially reduces transmission of HIV
  - Data support earlier initiation of ART, and routine testing helps identify patients earlier

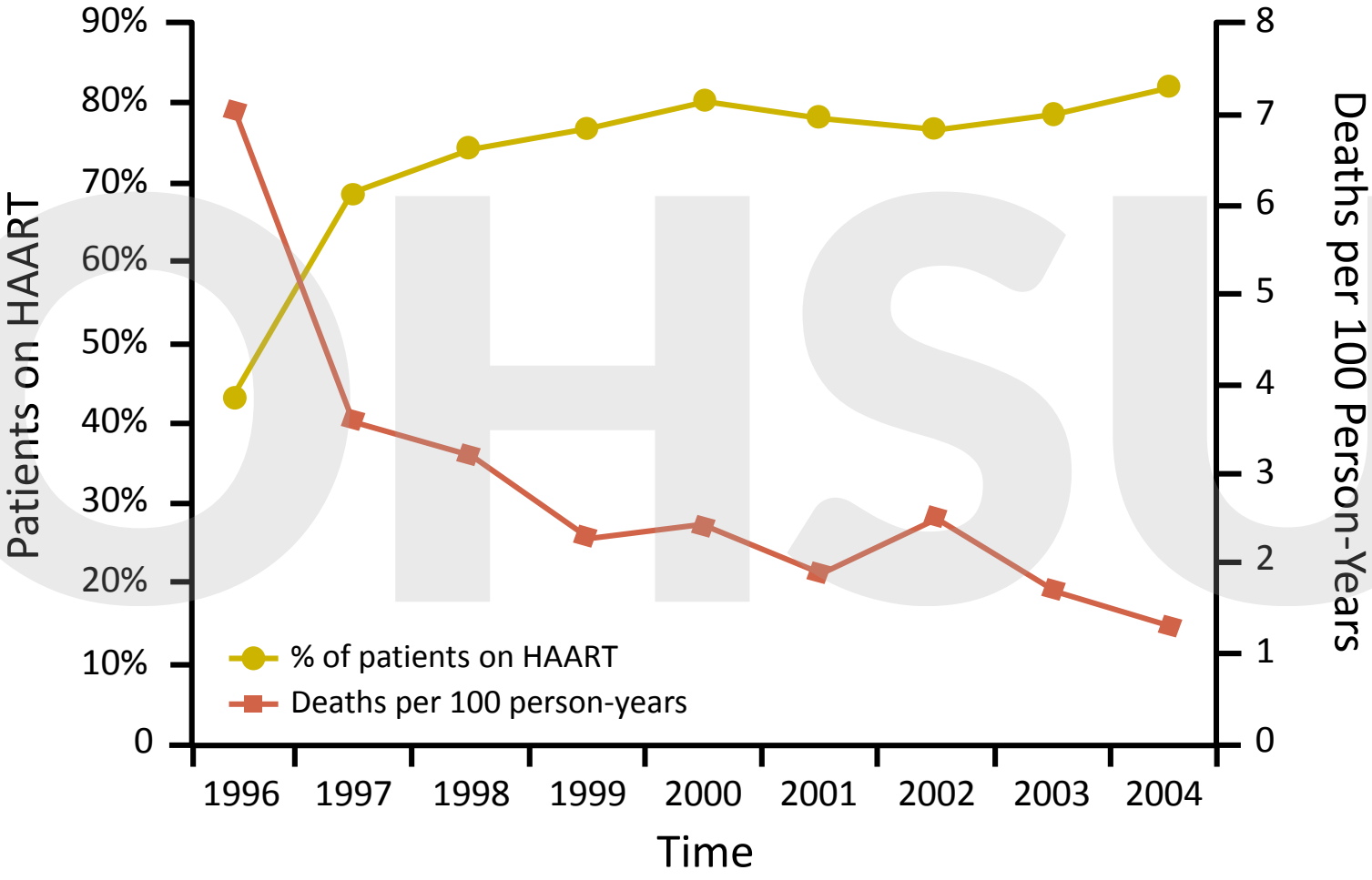
Moyer VA. Screening for HIV: U.S. Preventive Services Task Force Recommendation. Ann Intern Med 2013;159 (1):1-10, w1-


HIV cases diagnosed in Oregon, 2006–2015
11
11
1,223
10
352
6
21
1
36
184
0
0
3
4
20
184
11
13
26
34
6
1
0
0
2
46
118
7
29
4
20
91
12
0
0
15

Late Diagnosis of HIV in Oregon

- 41% of Oregon adults have ever been tested for HIV
- 2008 – 2012 (39%) of Oregonians newly diagnosed with HIV infection had severe enough immune suppression to meet AIDS criteria within 12 months of diagnosis
- Most have likely had been infected for ≥7 years
- These individuals reported missed opportunities for testing, often because they didn't recognize or report their HIV risks.

Mortality and HAART Over Time



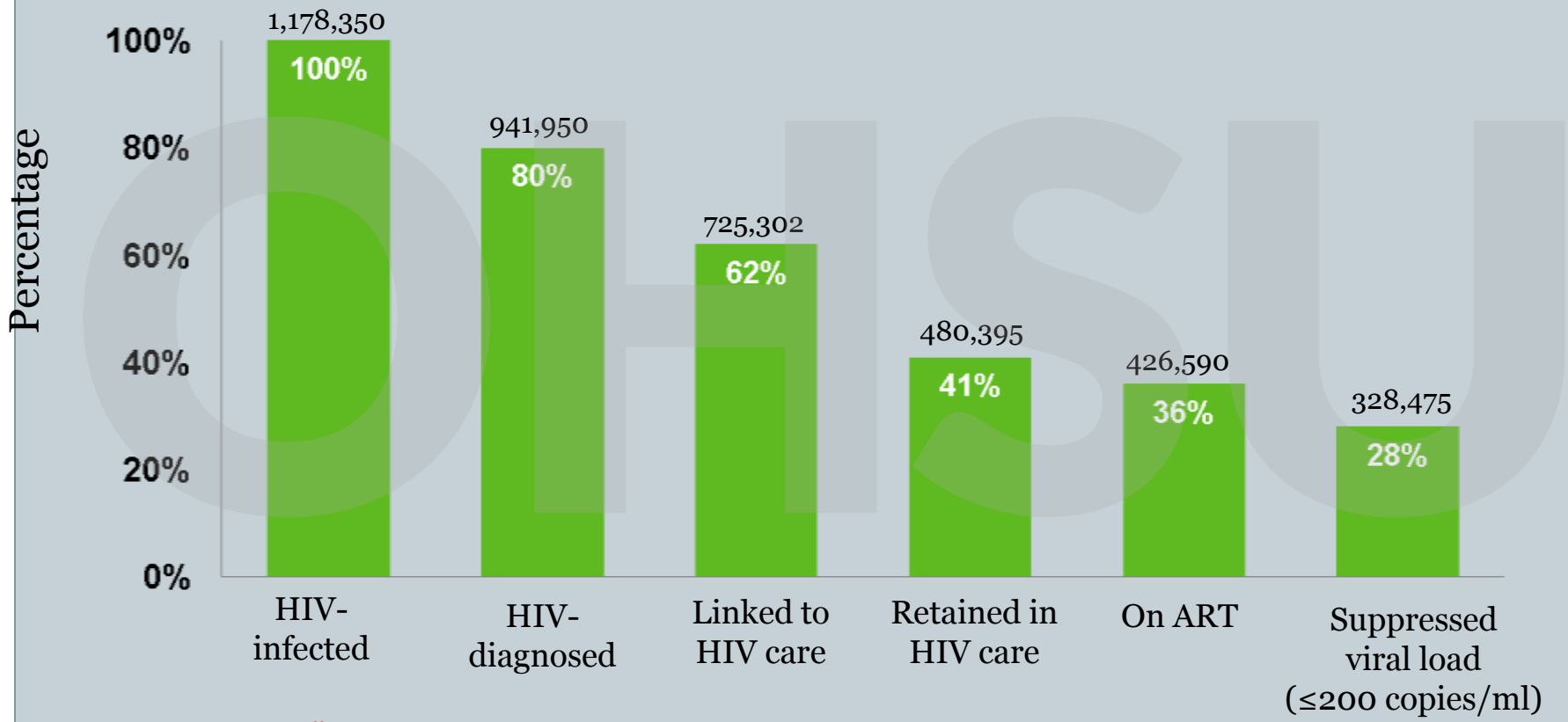
Palella FJ Jr, Baker RK, Moorman AC, et al; *J Acquir Immune Defic Syndr*. 2006;43:27-34.

Life Expectancy is Not "Normal"

At HAART Initiation	CD4 Cell Count (mm^3)		
	<100	100-199	≥200
A 20 yr old will live to	52	62	70
A 35 yr old will live to	62	65	72
% Remaining Life Lost (all ages)	46%	27%	14%

Adapted from *ART-CC, Lancet 2008;372:293-99* by adding additional expected survival to age at treatment initiation.

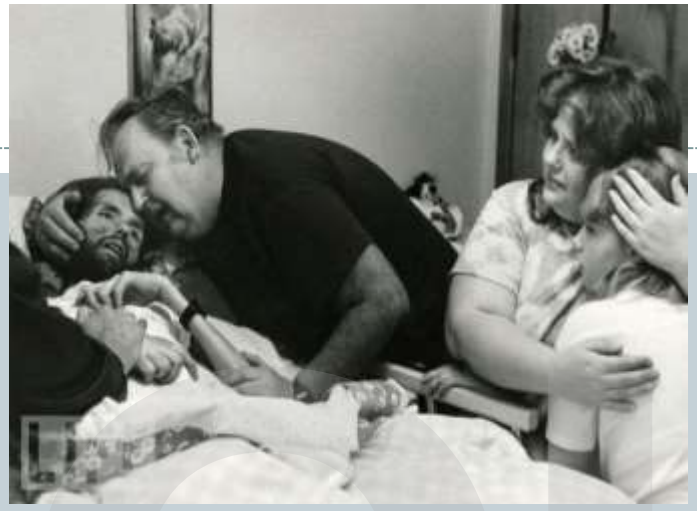
The Continuum of HIV Engagement in care



"Only 28% of all persons with HIV have a suppressed viral load because the best possible levels have not been reached for 1) testing, 2) ongoing HIV medical care, and 3) adherence."

Adapted from CDC, MMWR 2011;60:1618-1623

HIV…The Early Years



David Kirby 1990 Life magazine Picture

1981 June 5;30:250–2

Pneumocystis Pneumonia – Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

HIV Care Today

Jimmy Mack

Southhampton, N.Y
Diagnosed1987

Marama Pala

Waikanae, New Zealand
Diagnosed: Oct. 1993

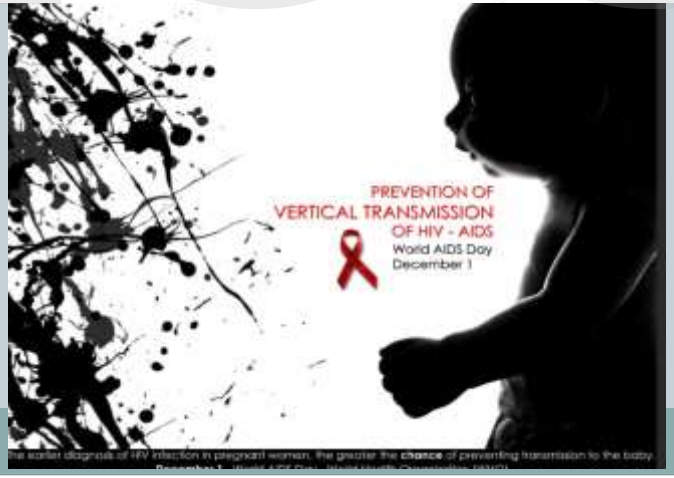
Keith Green

Chicago, Ill
Diagnosed 1994

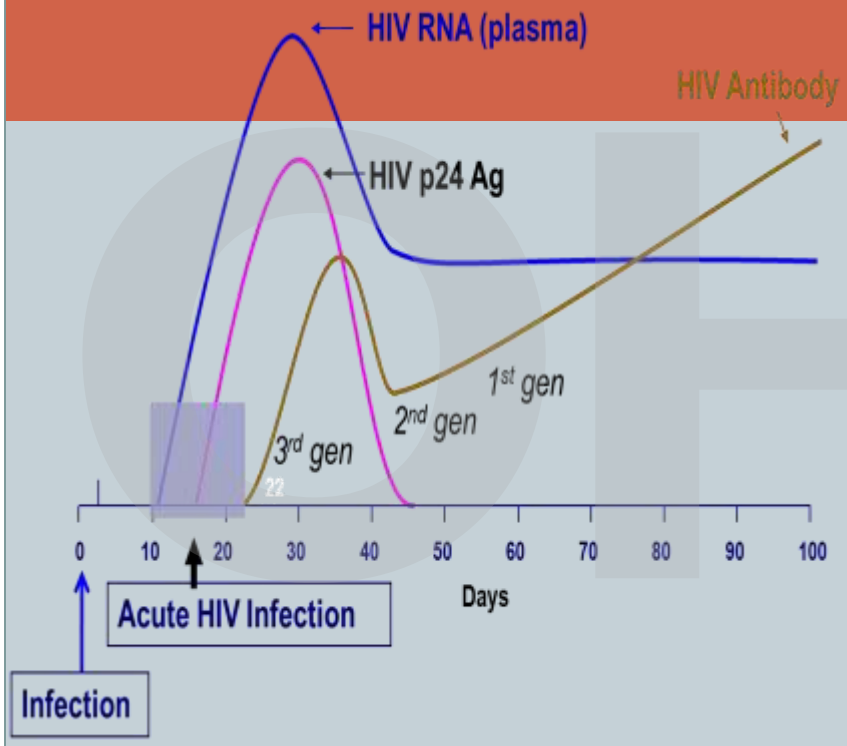
James Nicacio

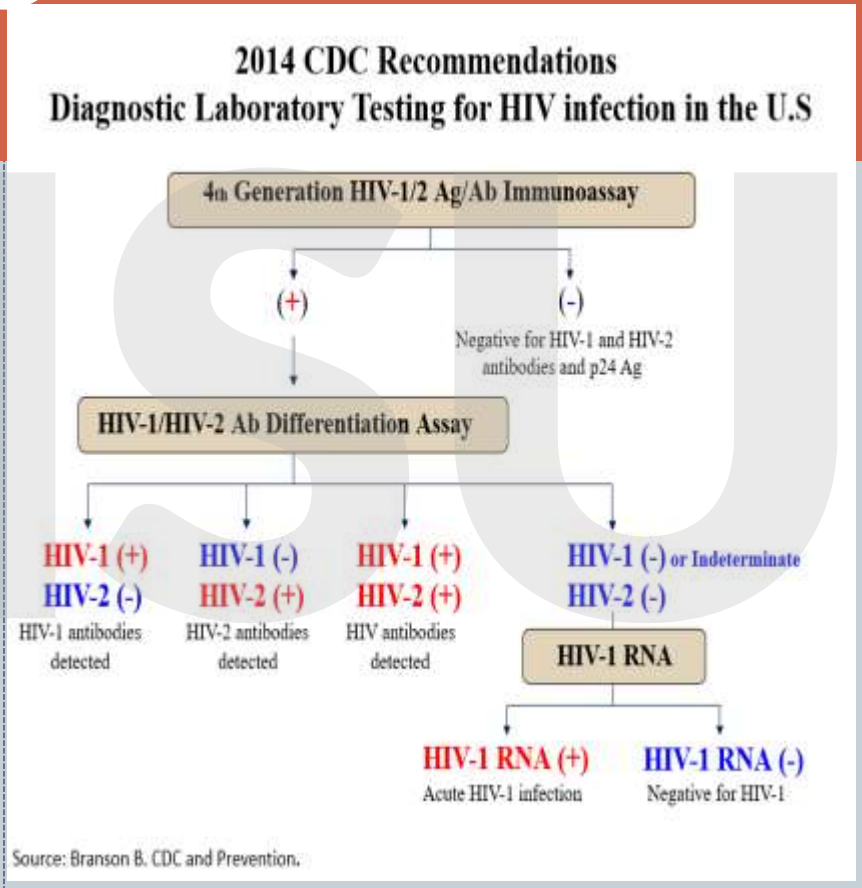
Selma, Calif
Diagnosed in 2001

Credit: POZ Magazine



Window Period and HIV Infection





Busch MP, et al. *American Journal of Medicine*. 1997; 102(5B):117-124. Modified diagram based on first iteration in stated source and updated using several publications since 1997.

Starting HAART Early

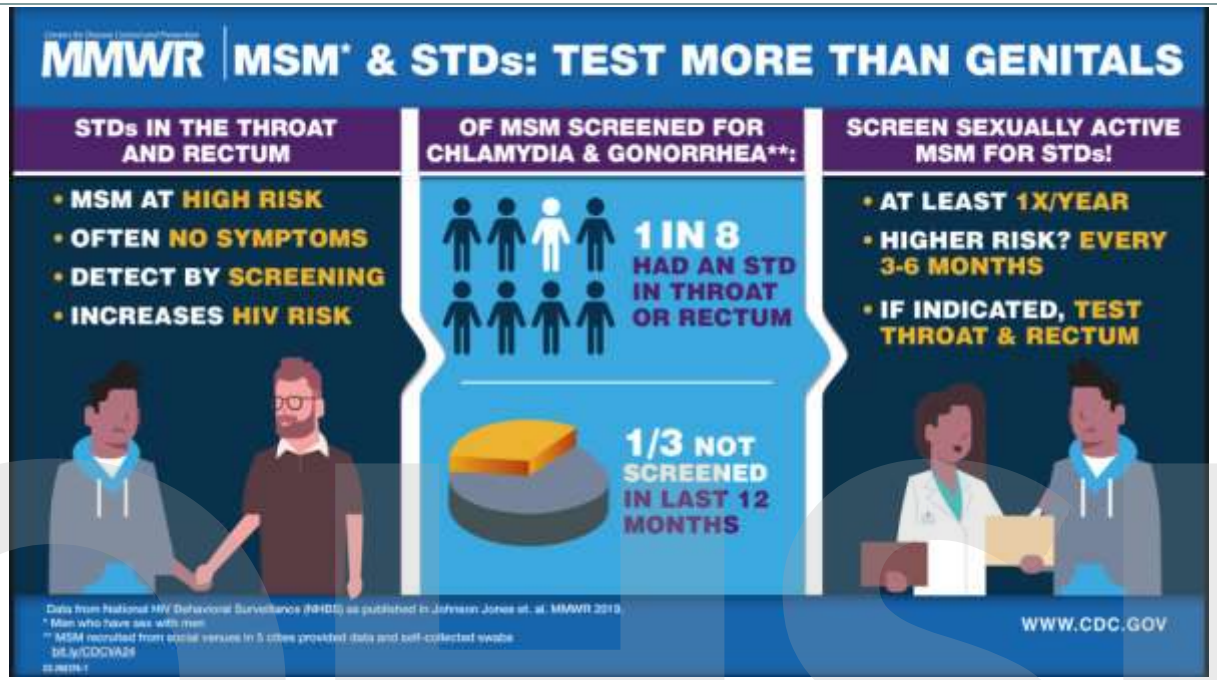
- **START trial**
  - Subjects who initiated ART with a CD4 > 500 cells/mm3 experienced statistically significant reduction in
  - Risk to Death
  - Cancer
  - Tuberculosis
  - Other serious health end points
- **HPTN-052**
  - Early use of HAART (CD4+ cell count >350 cells/mm3) was show to decrease transmission between partners by 93%

- CD4 + cell recovery directly associated with CD4 count nadir at initiation on HAART

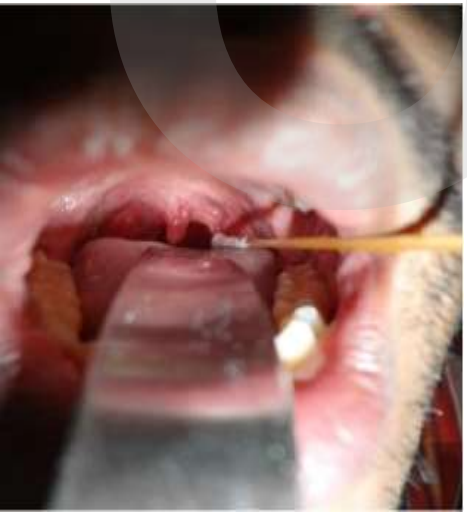
INSIGHT/START Group. N. England J Med. 2015;373: 795-807. Cohen MS. El al N. Engl J Med. 2011;365:293-505
Cohen MS, et al. IAS 2015. Abstact MOAC0101LB. Cohen MS, et al N Engl J Med. 2016, 275:830-839

HIV – Initial Clinic Visit and Labs

- CD4 Count
- HIV viral RNA PCR
- CMP and CBC with diff
- Lipid Panel
- HIV Resistance Testing (GENOTYPE)–selected patient
- Hepatitis A, B & C serology
- Tuberculin skin testing or IGRA (QuantiFERON Gold)
- Sexually transmitted disease (GC/chlamydia + RPR) 3 point testing in MSM
- Toxoplasma serologic test
- HLA-B5701 if considering Abacavir

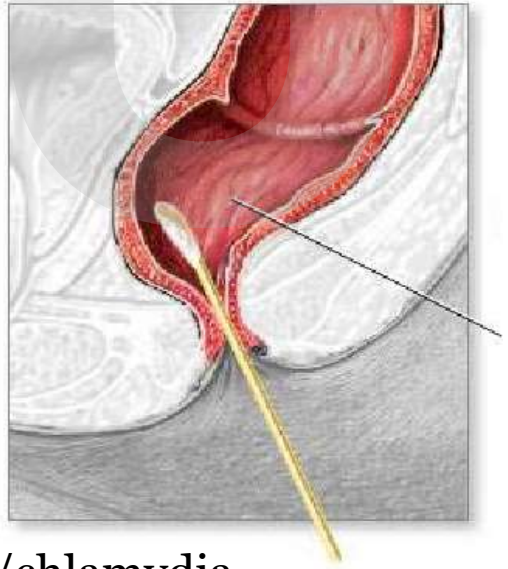


Pharyngeal



Aptima swab

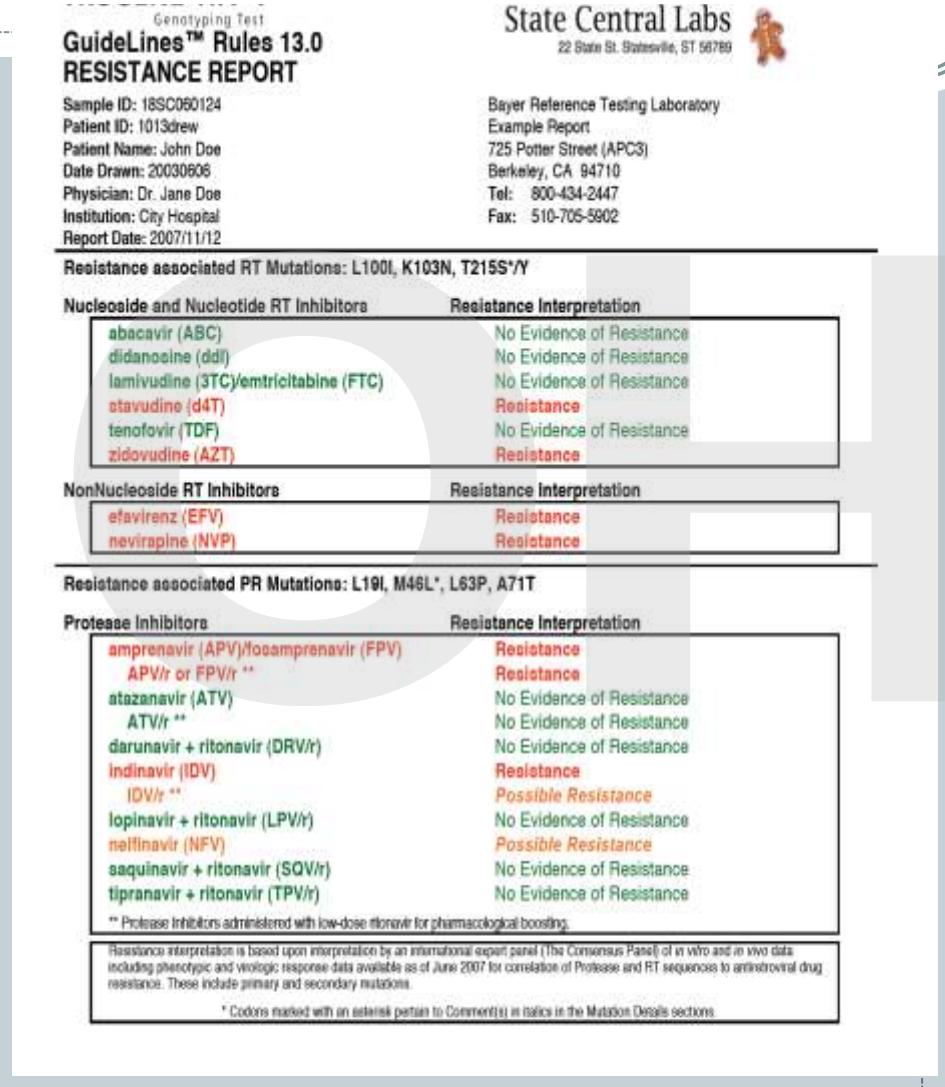
Rectum



3 point testing: Especially in MSM and asymptomatic disease GC/chlamydia

http://emedicine.medscape.com/article/212100
4-overview#aw2aab6b4. https://www.scripps.org/articles/907-rectal-culture

Genotype Report (GART)



Genotyping Test
GuideLines™ Rules 13.0
RESISTANCE REPORT

State Central Labs
22 State St. Statesville, ST 56789

Sample ID: 18SC060124
Patient ID: 1013drew
Patient Name: John Doe
Date Drawn: 20030606
Physician: Dr. Jane Doe
Institution: City Hospital
Report Date: 2007/11/12

Bayer Reference Testing Laboratory
Example Report
725 Potter Street (APC3)
Berkeley, CA 94710
Tel: 800-434-2447
Fax: 510-705-5902

Resistance associated RT Mutations: L100I, K103N, T215S*/Y

Nucleoside and Nucleotide RT Inhibitors	Resistance Interpretation
abacavir (ABC)	No Evidence of Resistance
didanosine (ddI)	No Evidence of Resistance
lamivudine (3TC)/emtricitabine (FTC)	No Evidence of Resistance
stavudine (d4T)	Resistance
tenofovir (TDF)	No Evidence of Resistance
zidovudine (AZT)	Resistance

NonNucleoside RT Inhibitors	Resistance Interpretation
efavirenz (EFV)	Resistance
nevirapine (NVP)	Resistance

Resistance associated PR Mutations: L19I, M46L*, L63P, A71T

Protease Inhibitors	Resistance Interpretation
amprenavir (APV)/fosamprenavir (FPV)	Resistance
APV/r or FPV/r **	Resistance
atazanavir (ATV)	No Evidence of Resistance
ATV/r **	No Evidence of Resistance
darunavir + ritonavir (DRV/r)	No Evidence of Resistance
indinavir (IDV)	Resistance
IDV/r **	*Possible Resistance*
lopinavir + ritonavir (LPV/r)	No Evidence of Resistance
nelfinavir (NFV)	*Possible Resistance*
saquinavir + ritonavir (SQV/r)	No Evidence of Resistance
tipranavir + ritonavir (TPV/r)	No Evidence of Resistance

** Protease Inhibitors administered with low-dose ritonavir for pharmacological boosting.

Resistance interpretation is based upon interpretation by an international expert panel (The Consensus Panel) of in vitro and in vivo data including phenotypic and virologic response data available as of June 2007 for correlation of Protease and RT sequences to antiretroviral drug resistance. These include primary and secondary mutations.

* Codons marked with an asterisk pertain to Comment(s) in italics in the Mutation Details sections.

Before Starting :

- Transmitted resistance in 6-16% of HIV + patients

Failing medications:

- Perform while patient is taking ART, or ≤4 weeks after stopping therapy

- **NRTI, NNRTI AND PI**
  - GENOTYPE
  - PHENOTYPE
  - Genotype Archive – DNA, virologically suppressed.
- **INTEGRASE INHIBITORS**
  - GENOTYPE
  - PHENOTYPE
- **Co-Receptor Tropism Assay**
  - RNA
  - DNA

Antiretroviral Therapy
What to Start in 2019

- **Nucleoside and nucleotide RTIs (NRTI)**
  - Zidovudine, AZT
  - Abacavir, ABC
  - Lamivudine, 3TC
  - Didanosine, ddI
  - Stavudine, d4T
  - Tenofovir, TDF
  - Emtricitabine, FTC
  - AZT/3TC
  - AZT/3TC/ABC
  - ABC/3TC (HLA B5701 testing)
  - TDF/FTC
  - TAF/FTC
- **CCR5 receptor blocker**
  - Maraviroc
- **Integrase inhibitor (INSTI)**
  - Raltegravir, RAL
  - Elvitegravir, EVG
  - Dolutegravir, DTG

- **Non nucleoside NRTIs: (NNRTI)**
  - Delavirdine (DLV)
  - Nevirapine, NVP
  - Efavirenz, EFV
  - Etravirine
  - Rilpivirine
- **Fusion inhibitors:**
  - Enfuvirtide, ENF or T20

Protease inhibitors (PIs):

- Indinavir, IDV
- Saquinavir, SQV
- Nelfinavir, NFV
- Amprenavir, APV
- Atazanavir, ATV
- Fosamprenavir, FPV
- Lopinavir/ritonavir
- Tipranavir
- Darunavir
- Darunavir/cobicistat
- Atazanavir/cobicistat

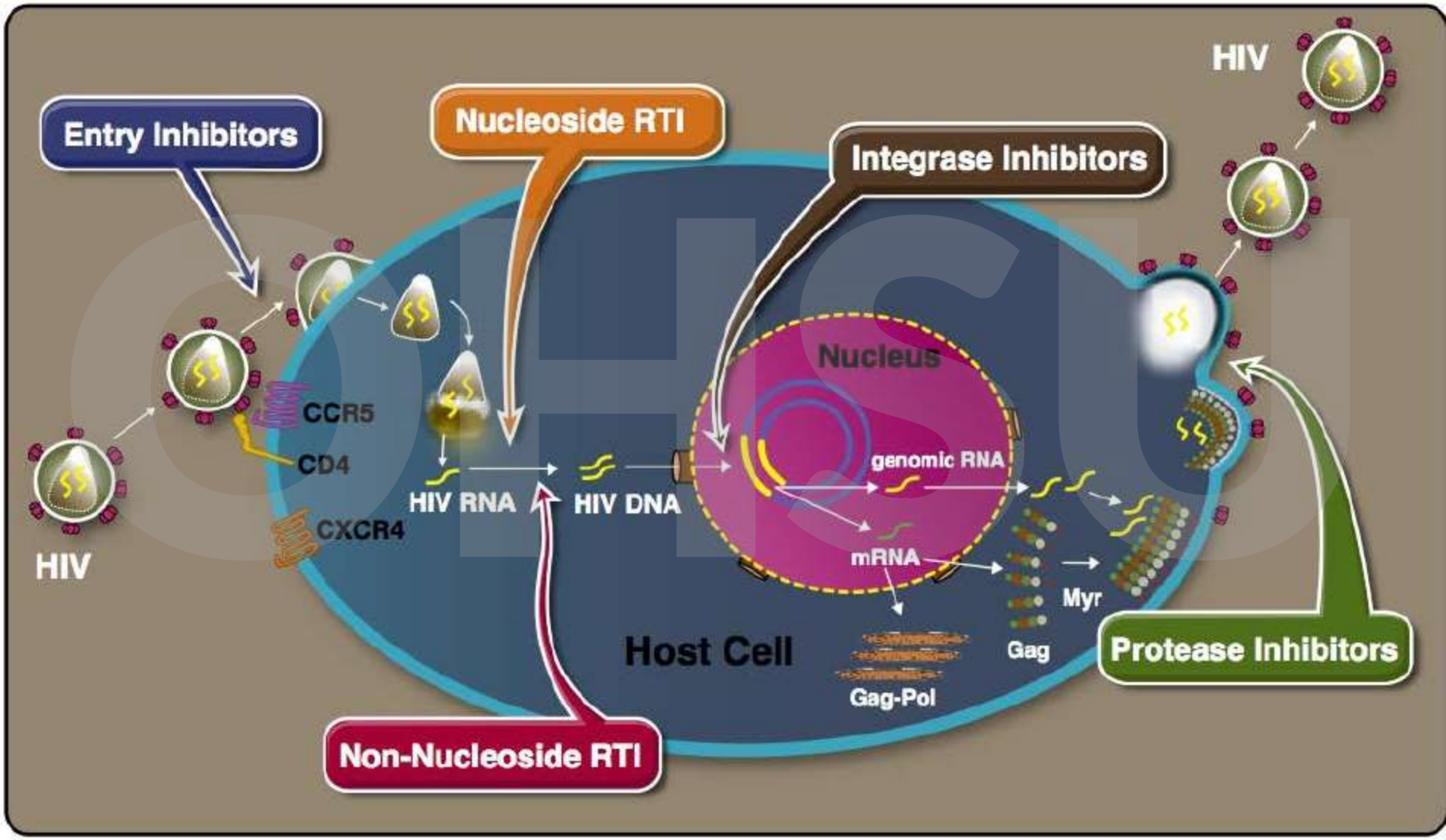
Red – combination agents

Single pill regimens

- EFV/FTC/TDF
- RPV/FTC/TDF
- EVG/cobi/FTC/TDF
- DTG/ABC/3TC
- EVG/cobi/FTC/TAF
- Rilpivirine/FTC/TAF
- Bictegravir/FTC/TAF
- DRV/c/TAF/FTC

Picture Credit: https://www.choice.com.au/health-and-body/medicines-and-supplements/prescription-medicines/articles/the-dangers-of-mixing-medicines

HIV Drug Targets



Antiretroviral Therapy
What to Start in 2019?

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

DHHS, IAS-USA, EACS, and WHO guidelines include recommended first-line ART regimens

	US DHHS [1]	IAS-USA [2]	EACS [3]	WHO [4]
INSTI	▪ BIC/TAF/FTC* ▪ DTG/ABC/3TC* ▪ DTG + TDF/FTC or TAF/FTC ▪ EVG/c/TDF/FTC* ▪ EVG/c/TAF/FTC* ▪ RAL + TDF/FTC or TAF/FTC	▪ DTG/ABC/3TC* ▪ DTG + TAF/FTC ▪ EVG/c/TAF/FTC* ▪ RAL + TAF/FTC	▪ DTG/ABC/3TC* ▪ DTG + TDF/FTC or TAF/FTC ▪ EVG/c/TDF/FTC* ▪ EVG/c/TAF/FTC* ▪ RAL + TDF/FTC or TAF/FTC	▪ TDF+ 3TC (or FTC) + EFV
Boosted PI			▪ DRV/r or DRV/c + FTC/TAF or FTC/TDF	
NNRTI			▪ RPV/TDF/FTC* ▪ RPV/TAF/FTC*	

*Single-tablet regimens.

- Recommendations may be altered based on baseline HIV-1viral load, CD4+ count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, and osteoporosis status

Recommended Regimens

Integrase inhibitor + 2 NRTI	Bictegravir/TAF/FTC Dolutegravir/abacavir*/3TC Dolutegravir + TDF/FTC or TAF/FTC Elvitegravir/cobi/TDF (or TAF)/FTC Raltegravir +TDF/FTC or TAF/FTC

HLA-B5701 Testing needed for ABC – HSR (If negative safe to use ABC).
Chronic Hepatitis B, consider using TAF or TDF based regimens

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

HIV medications
Patient Characteristics & Considerations

Patient Characteristics	Regimen Considerations
• Cardiovascular disease • Hyperlipidemia • Renal Disease • Osteoporosis • Chronic Hepatitis B • Psychiatric illness • Substance Use	• Genetic Barrier to resistance • Food requirements for absorption • Elimination /metabolism • Once daily vs twice daily • Drug interactions !!!!!!!

Monitoring Labs

Laboratory	On HAART
CD4 & HIV RNA	q 3-6 months
BMP & LFT (with total bilirubin)	q 3-6 months
CBC w/differential	q 3-6 months
Fasting Lipid Panel	q 6-12 months
Fasting BG	q 3-6 months
Urinalysis	q 6 months (if HIVAN) or q 12 months (if on Tenofovir [TDF])
*for patients who have just started a new regimen, VL and safety labs should be checked 2-8 weeks following ARV initiation	

CD4 count monitoring for those on *ART for at least 2* years with consistent viral suppression:

- CD4 count between 300 and 500 cells/mm3: CD4 count monitoring every 12 months
- CD4 count >500 cells/mm3: CD4 count monitoring is optional

Common Drug Interactions

Anticonvulsants

- Protease inhibitor/PKE
- phenytoin, carbamazepine, phenobarbital-monitor levels
- Oral contraceptives
- PI/PKE, nevirapine, efavirenz

Miscellaneous

- methadone-some Protease inhibitors/PKE
- sildenafil, vardenafil-most Protease inhibitors/PKE
- warfarin-most Protease inhibitors/PKE, efavirenz
- Fluticasone, Protease inhibitors/PKE (Cushings)
- Antacids, rilpivirine and ATV (lowers HIV medication levels)

Opportunistic Infection Prophylaxis for Adults with HIV

	Criteria for Initiating Primary Prophylaxis	Criteria for Discontinuing Primary Prophylaxis	Criteria for Restarting Primary Prophylaxis	Criteria for Initiating Secondary Prophylaxis	Criteria for Discontinuing Secondary Prophylaxis	Criteria for Restarting Secondary Prophylaxis
PCP	CD4 < 200 or oral candidasis	CD4 > 200 for 3 mos	CD4 < 200	Prior PCP	CD4 > 200 for 3 mos	CD4 < 200
Toxoplasmosis	+ serum IgG CD4 < 100	CD4 > 200 for 3 mos	CD4 < 100 – 200	Prior toxoplasmic encephalitis	CD4 > 200 sustained and completed initial therapy and is asymptomatic	CD4 < 200
MAC	CD4 < 50	CD4 > 100 for 3 mos	CD < 50 – 100	Documented disseminated disease	CD4 > 100 sustained and completed 12 mos of MAC tx and asymptomatic	CD4 < 100
Cryptococcosis	none	n/a	n/a	Documented disease	CD4 > 100 – 200 sustained and completed initial therapy and asymptomatic	CD4 < 100 - 200
Histoplasmosis	none	n/a	n/a	Documented disease	No criteria recommended for stopping	n/a
CMV	none	n/a	n/a	Documented end-organ disease	CD4 > 100 – 150 sustained and no evidence of active disease and regular exams	CD4 < 100 - 150

HIV & Cancer Screening

- Breast Cancer
  - HIV Primary Care recommend that HIV + women follow the same breast cancer screening guidelines as for the general population.
- Colon Cancer
  - HIV infection may have a slightly higher risk for developing colon cancer. No additional screening recommendations
- Prostate Cancer
  - Men with and without HIV infection have a similar risk of prostate cancer. No additional screening

Cervical Cancer Screening in Women with HIV

- Abnormal cervical cytology is nearly x 11 times more common with HIV compared to HIV negative female population
- < 30 years
  - Cervical pap smear at the HIV diagnosis
  - If normal, repeat every 12 months
  - If 3 consecutive apps are normal →every 3 years
  - Co-testing (Pap and HPV) not recommended
  - Refer for colposcopy if ACUS on pap and reflex HPV test positive or if pap result LSIL or worse

https://aidsinfo.nih.gov/contentfiles/lvguidelines/glchunk/glchunk_343.pdf

Cervical Cancer Screening in Women with HIV

- >= 30 years
  - Pap alone or pap with HPV co-testing

<u>Pap alone</u>:

- At time of HIV diagnoses, then annually
- If 3 consecutive pap smears normal, then every 3 years

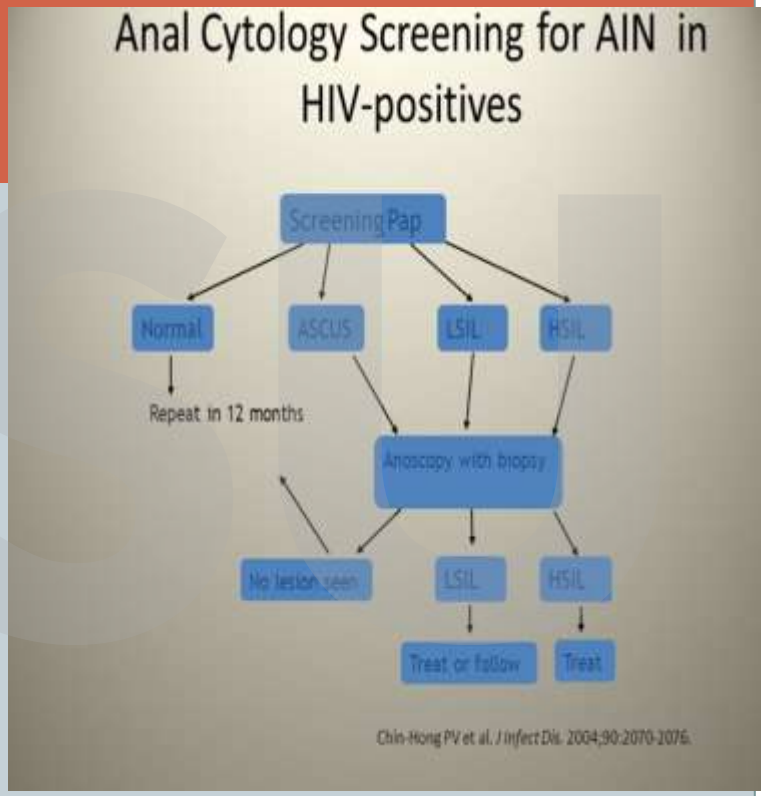
<u>Pap with HPV co-testing</u>

- If pap and HPV negative, screening every 3 years
- If pap normal and HPV positive, repeating testing in 1 years' if HPV
- Type 16 and 18 positive, refer for colposcopy
- If ASCUS and HPV positive, refer to colposcopy
- For LSIL or worse, refer for colposcopy

https://aidsinfo.nih.gov/contentfiles/lvguidelines/glchunk/glchunk_343.pdf

HIV & Anal Cancer

- Anal cancer incidence among HIV+ MSM has been estimated to be 2x that of HIV negative MSM (131/100,000)
- Anal Pap smears (Controversial) in MSM & women with a history of receptive anal intercourse OR abnormal cervical Pap test results, AND all individuals with HIV infection who have genital warts with DRE



Daling JR, et al. N Engl J Med. 1987;317(16):973.

JA Aberg Et al. Clinical Infectious Diseaes. 2014 Jan;58(1):e1-34. doi: 10.1093/cid/cit665. Epub 2013 Nov 13.

Recommendations for vaccination in HIV-infected adults

Vaccine	Age group (years)					CD4 cell count (cells/microL)	
	13 to 18	19 to 26	27 to 59	60 to 64	≥65	<200	≥200
Influenza*	1 dose annually					1 dose annually	
Tetanus, diphtheria, acellular pertussis (Tdap)/ tetanus, diphtheria (Td)¶	1 dose Tdap, then Td booster every 10 years					1 dose Tdap, then Td booster every 10 years	
Measles, mumps, rubella (MMR)Δ	2 doses if CD4 cell count ≥200					Contraindicated	2 doses if born in 1957 or later
Varicella (VAR)◇	2 doses if CD4 cell count ≥200					Contraindicated	2 doses
Herpes zoster (HZV)§						Contraindicated	
Human papillomavirus (HPV)¥	3 doses					3 doses through age 26 years	
Pneumococcal conjugate (PCV13)‡	1 dose					1 dose	
Pneumococcal polysaccharide (PPSV23)‡	2 doses				1 dose	Up to 3 doses depending on age	
Hepatitis A (HepA)†	2 or 3 doses depending on vaccine					2 or 3 doses depending on vaccine	
Hepatitis B (HepB)**	3 doses					3 doses	
Meningococcal (MenACWY)¶¶	2 doses, then booster every 5 years					2 doses, then booster every 5 years	
Meningococcal B (MenB)¶¶	2 or 3 doses depending on vaccine					2 or 3 doses depending on vaccine	
Haemophilus influenzae type b (Hib)ΔΔ	1 or 3 doses depending on indication					1 or 3 doses depending on indication	

Recommended for adults and adolescents with HIV infection

Recommended for adults and adolescents with HIV infection and other indications

Contraindicated

No recommendation

Adapted from the Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for adults and adolescents. These immunization schedules are available at https://www.cdc.gov/vaccines/schedules/hcp/index.html. Detailed information on these and other vaccines can be found at https://www.cdc.gov/vaccines/hcp/acip-recs/index.html.

HIV & Pneumococcal Vaccine

Invasive pneumococcal infection x 20 higher

- No History of Pneumococcal vaccine
  - PCV-13 followed by PPV 23 at least 8 weeks later
  - 5 years later, revaccinate with PPSV-23
- Previously Received PPSV23
  - Give PCV 13 x 1 dose 1 year later
  - PPSV-23 given 5 years later
    - booster at 65 years old

HIV & Meningococcal Vaccine

- Meningococcal vaccine is x 5 - 14 times greater in HIV than the general population
- (Greatest risk if CD4 is low and HIV viral load high)
  - 2 dose of meningococcal conjugate vaccine MenACWY-CRM (Menveo) or MenACWY-D (Menactra) at least 2 months apart
  - Booster every 5 years
  - Serotype B if indicated (Outbreaks or Asplenia)

ACIP. Recommended. Adult immunization Schedule US 2017

HIV & HPV vaccine

- Recommended for females and males with HIV from 9 to 26 years
  - 9 valent vaccine, 3 doses, at 0, 1-2 and 6 months
  - For those who have completed vaccination with bi or quadrivalent vaccine, may consider additional vaccine with the 9 valent
  - Pick up additional serotypes associated with some cancers in men and women.

HIV & the Zoster vaccine

- Live zoster vaccine (Zostervax)
  - CD4 < 200 Contraindicated
  - CD4 > 200 – no recommendation
- Recombinant Vaccine (Shingrix)
  - >90 % efficacy at prevention
  - Immunocompetent adults aged > 50 years, irrespective or prior zoster vaccine live (ZVL) o previous zoster
  - 2 doses, 2-6 months apart
  - Local and systemic reactions reported > 10%
  - Data on immunocompromised host coming
    - Recommended if low dose immunosuppression (< 20 mg/d prednisone)

Adapted from the Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for adults and adolescents. These immunization schedules are available

HIV & Hepatitis Vaccine (A + B)

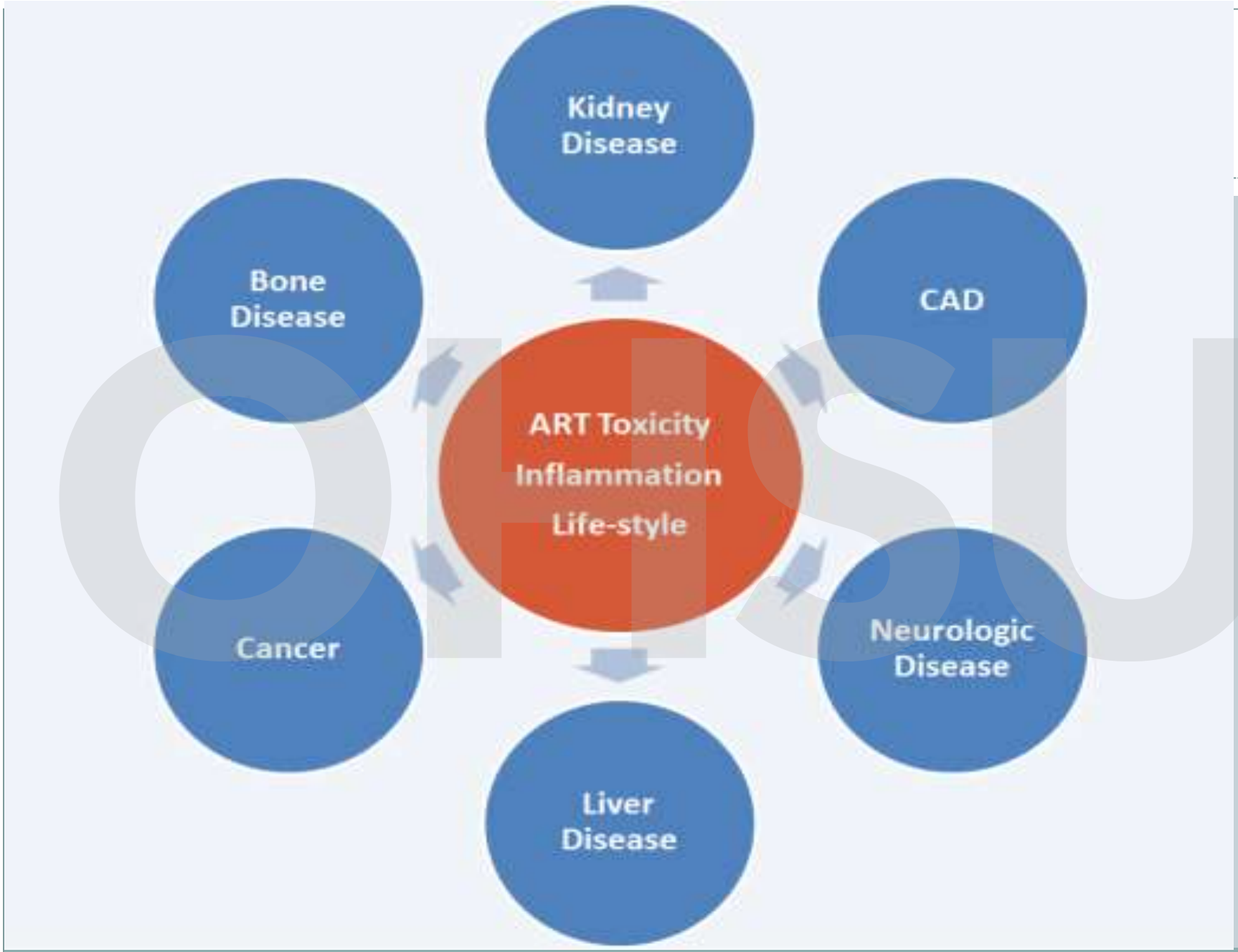
- Hepatitis A vaccine (MSM population)
- All HIV + patient should be screened for HBV
  - If non-immune give vaccine, 0, 1, 6 months
  - If vaccine series is interrupted don't restart.
  - Give 2nd & 3 doses at least 8 weeks apart
- Check anti-Hep B s after completing series
  - If non-immune- 2nd series Hep B vaccine
  - Consider revaccinating with double dose (Stop)
- Isolated Hep B core (common in HIV +)
  - Check Hep B DNA to rule out occult Hep B (rare)
  - If negative consider vaccine

http//www.cdc.gov/hepatitis/HBVfaq.htm

HIV & Influenza vaccine

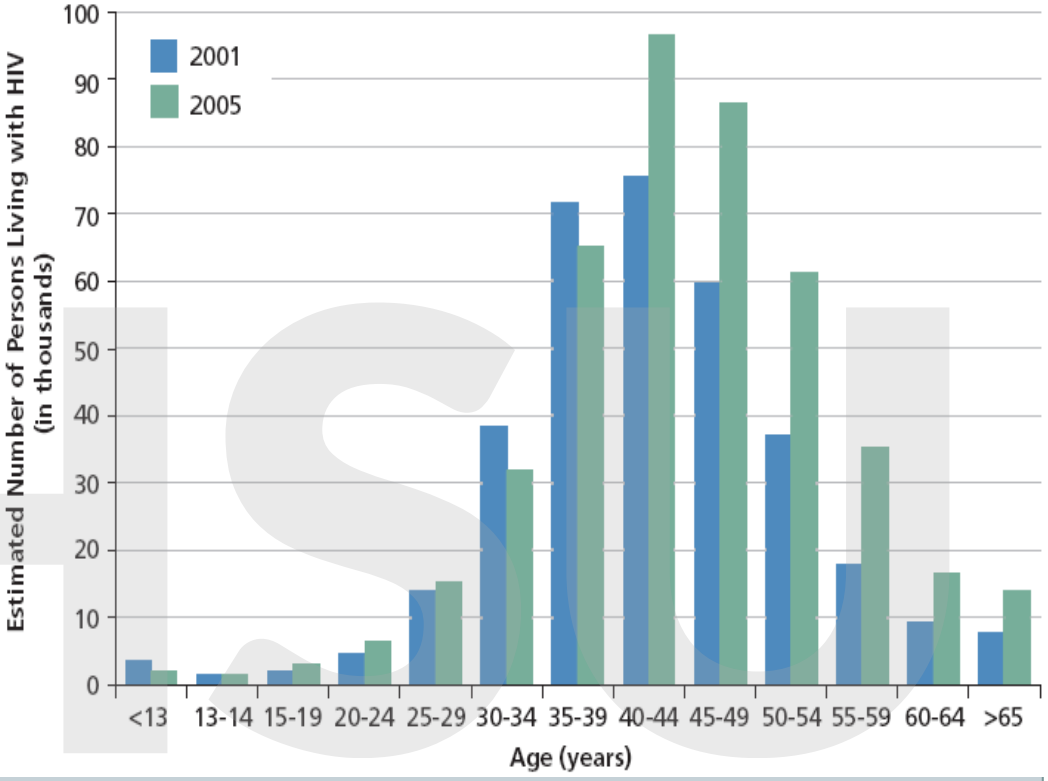
- All persons with HIV infection should receive a annual dose influenza vaccine [inactivated] (trivalent or quadrivalent)
  - **Contraindicated Vaccine**: No live attenuated influenza
- Lower CD4 count with poorer response
- More studies need for the efficacy of the high-dose influenza vaccine in HIV-infected adults
- > **65 years**: Adults with HIV infection aged 65 years or should get standard-dose or high-dose inactivated influenza vaccine.

Yamanaka et al J Acquir Immune Defic Syndr. 2005;39(2):167.



Reference: Chang et al., Archives of Gerontology and Geriatrics, 2012

Another Kind of AIDS Crisis…

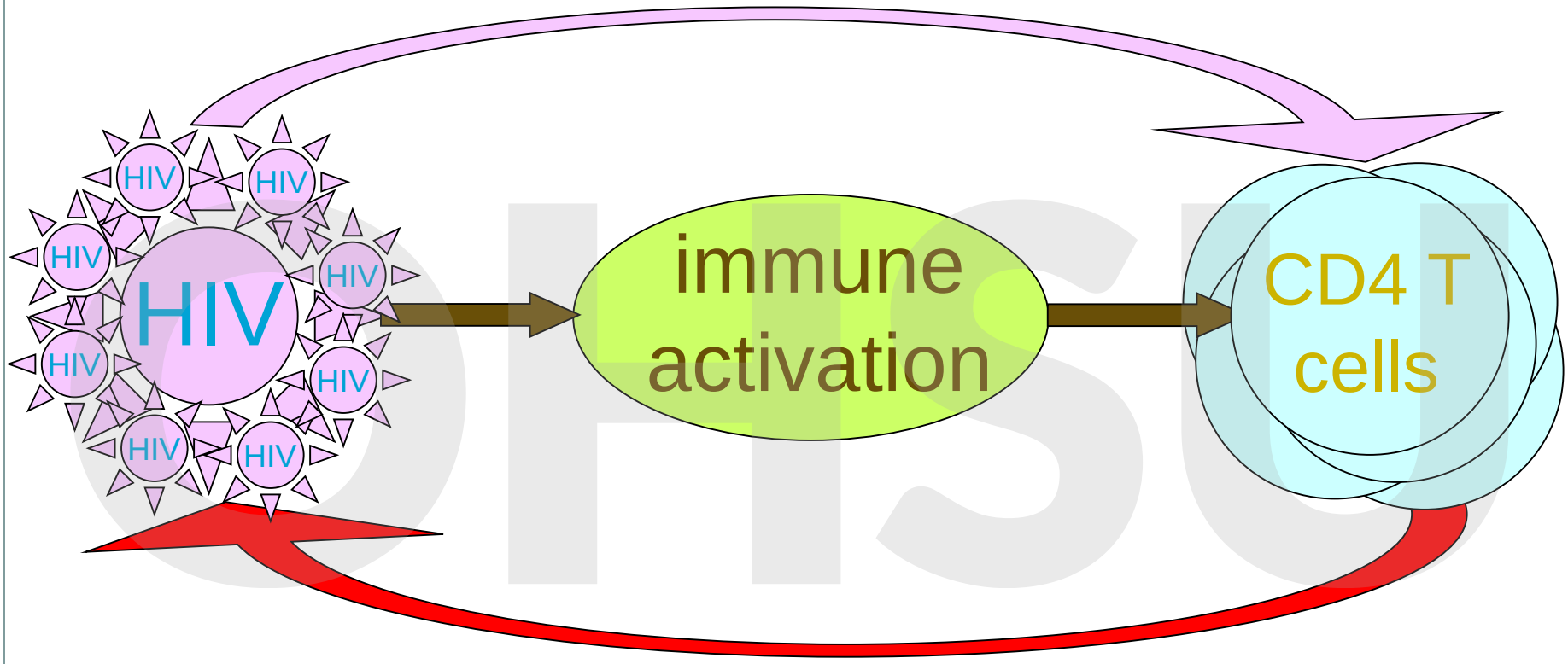


Left: **Russell Steinke**. Age: 56 / HIV: 23 years / Has suffered from: memory loss, nerve damage in feet, lipodystrophy, fatigue.
Right: **Enrico McLane**. Age: 52 / HIV: 17 years / Has suffered from: short-term memory loss, two hip replacements.

(David France, published Nov 1 2009. New York Magazi

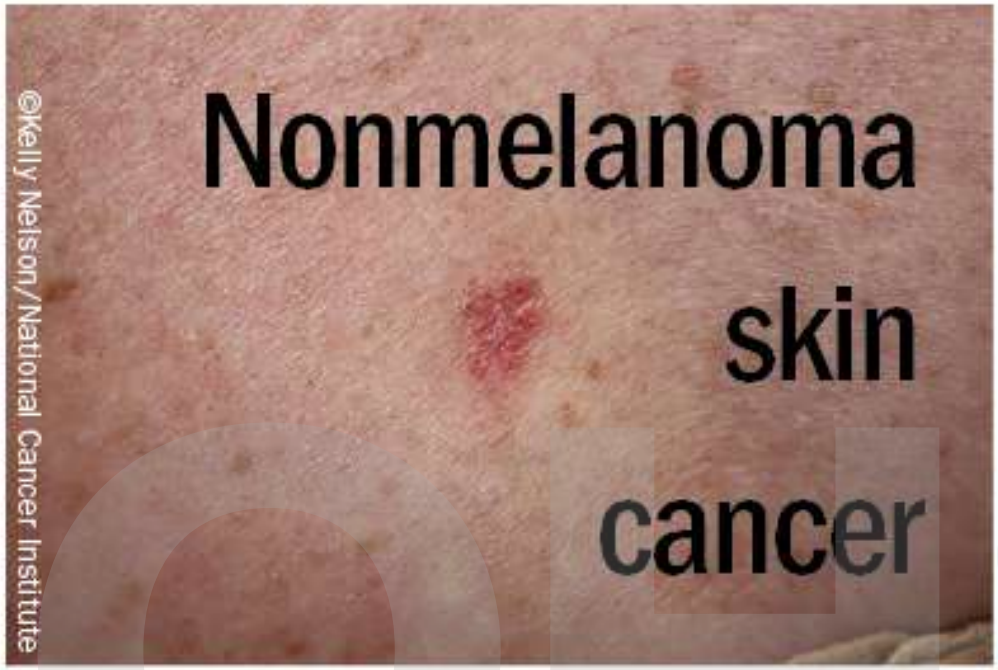
2015 > 50% of HIV patients in the USA are > 50 years old

Immune Activation Drives HIV Replication



- HIV drives a cycle of immune activation, CD4 T-cell infection and death, and more virus
- Inflammatory markers like CRP may not improve with HAART

Slide courtesy D Douek, MD, PhD, at New York, NY: March 13, 2009, IAS–USA.
Shikuma, et al, AIDS Res Hum Retroviruses. 2010 Sep 23.



Risk higher in HIV patients

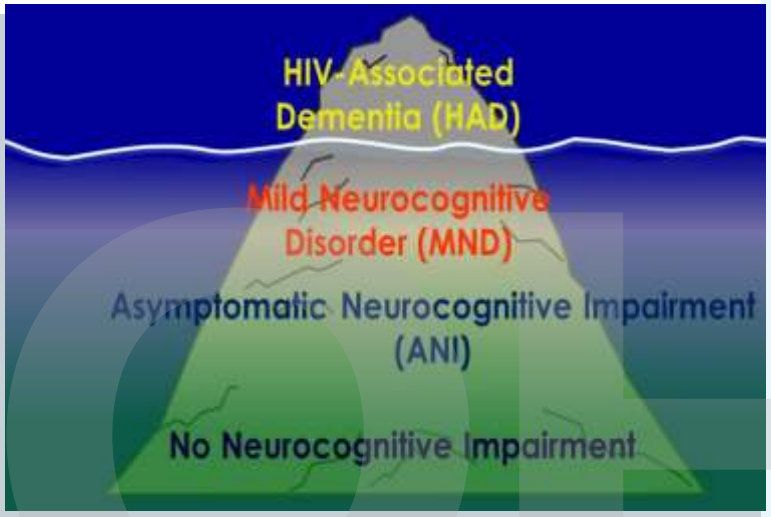
Carcinoma incidence rate ratios, compared with HIV-negative subjects:

Basal cell	Basal cell	Squamous cell
1.79	**2.3**	**5.4**
All HIV-positive patients	Men who have sex with men	All HIV-positive patients

Source: Omland S et al. J Am Acad Dermatol. 2018 Mar 24. pii: S0190-9622(18)30475-4.

INCREASED RISK of Non-AIDS Defining Cancers

HIV-associated neurocognitive disease



The CNS Penetration-Effectiveness Score may reflect better efficacy in CNS[1,2]

	4	3	2	1
NRTIs	▪ Zidovudine	▪ Abacavir ▪ Emtricitabine	▪ Didanosine ▪ Lamivudine ▪ Stavudine	▪ Tenofovir ▪ Zalcitabine
NNRTIs	▪ Nevirapine	▪ Delavirdine ▪ Efavirenz	▪ Etravirine	
PIs	▪ Indinavir/r	▪ Darunavir/r ▪ Fosamprenavir/r ▪ Indinavir ▪ Lopinavir/r	▪ Atazanavir ▪ Atazanavir/r ▪ Fosamprenavir	▪ Nelfinavir ▪ Ritonavir ▪ Saquinavir ▪ Saquinavir/r ▪ Tipranavir/r
Entry/Fusion Inhibitors		▪ Maraviroc		▪ Enfuvirtide
Integrase Inhibitors	▪ Dolutegravir	▪ Raltegravir	▪ Elvitegravir/cobi	

Changes in memory, concentration, attention, and motor skill issues
Progression by history & exam or by neuropsychological testing
Deficits cannot be fully explained by alternate conditions

<u>HAND</u>

- Asymptomatic neurocognitive impairment (ANI)
- HIV-associated mild neurocognitive (MND)
- HIV-associated dementia (HAD)

Thompson Neuroimaging Laboratory, UCLA (2005(Ellis et al., 2003) J. Neurovirology 2011 Feb; 17(1): 3–16. Letendre SL. Et al Top HIV Med. 2010; 18, 45-55. Letendre SL et al HIV management 2014. The New York Course.

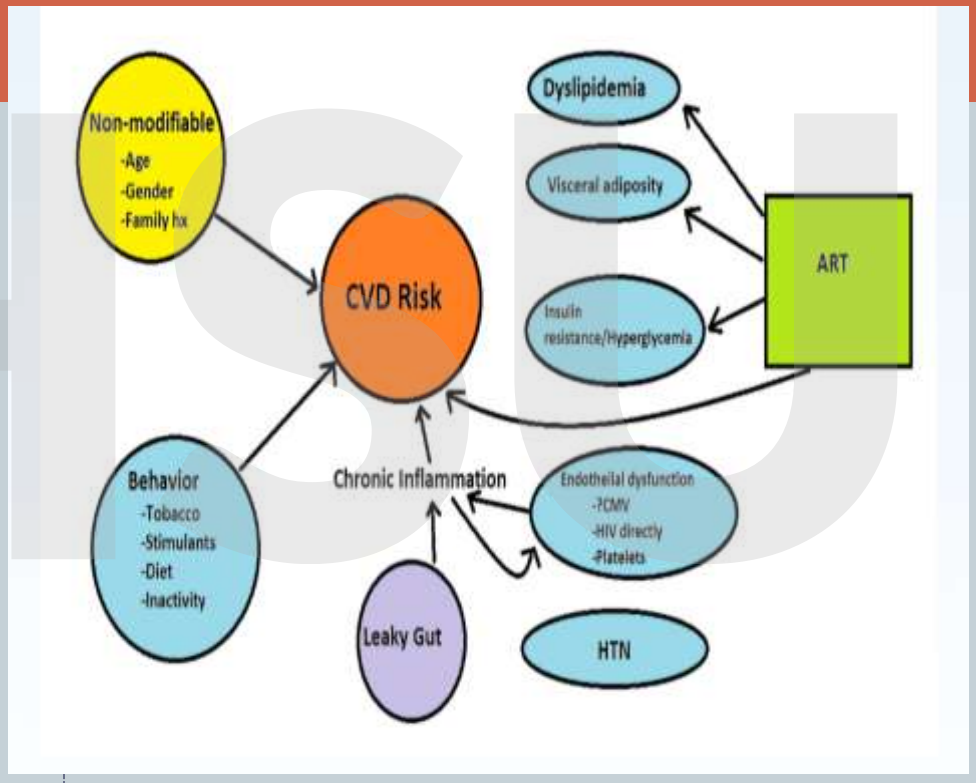
HIV and Heart Disease
Chronic inflammation

HEALTH | Heart Trouble Early and Often in H.I.V. Patients

Heart Trouble Early and Often in H.I.V. Patients

By DONALD G. McNEIL Jr. JUNE 18, 2012

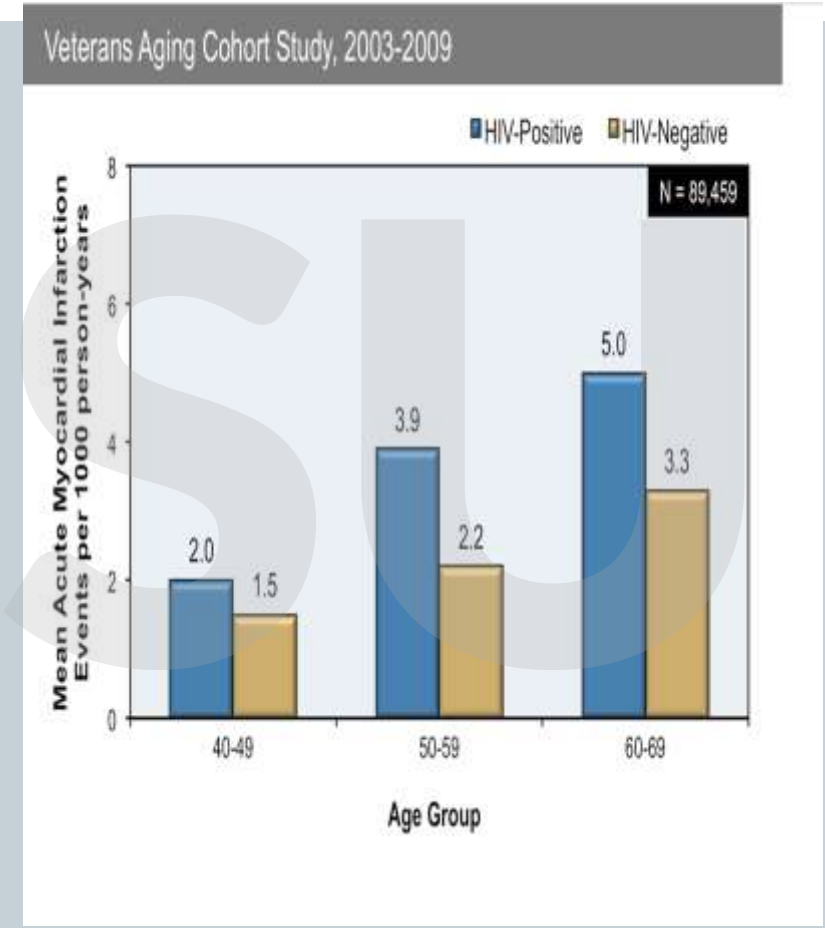
Mark Abramson has been HIV positive since 1988 and writes about his experiences in San Francisco.



Deeks, Gandhi, Chae, Lewandrowski, NEJM 2012

HIV + Persons are at risk for CVD

- 4th leading cause of death in HIV patient ins the D:A:D cohort
- High levels of markers of immune activation and inflammation → even with suppressed HIV
- Some ARVs found to be associated with increased risk for MI

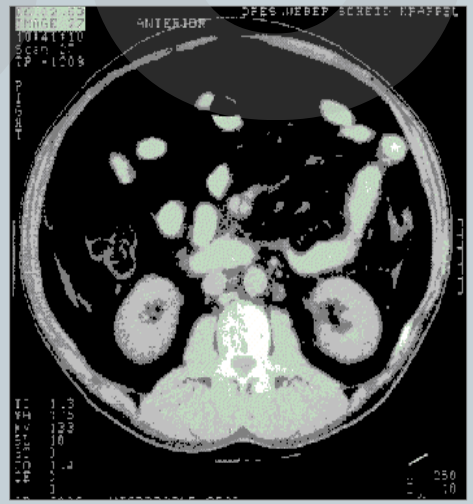


Triant, VA Curr HIV/ADIS Rep. 2013; 10;199-206. 2. Morgello, S et a. Arch Path Labs Med. 2002;126 182-190. 3. Subramanian S. et al. Jama, 2012. 308:379-386. 4. Post WS et al. Ann Internal Med 2014;160:458467. Deeks S. et al. Lancet 2013: 15250-1533. 6. Hunt PW. Curr HIV/AIDS Rep. 2012. 9:139-147. 7. Worms S. et al. J Infect Dis. 2010;201:318-330. 8. Drozd DR et. Al. JAIDS . 2017 Aug 15;75(5):586-576 . Source: Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med. 2013;173:614-22.

HIV + and Cardiovascular Disease

- Obesity is a much more common problem than wasting in the current therapeutic era
- Lipodystrophy with an increase in central adiposity and metabolic syndrome.

Lipodystrophy



Amorosa V, et al. 11th CROI. San Francisco, 2004. Abstract 879.
Seaberg EC et al, Multicenter AIDS Cohort Study AIDS. 2005;19(9):953.

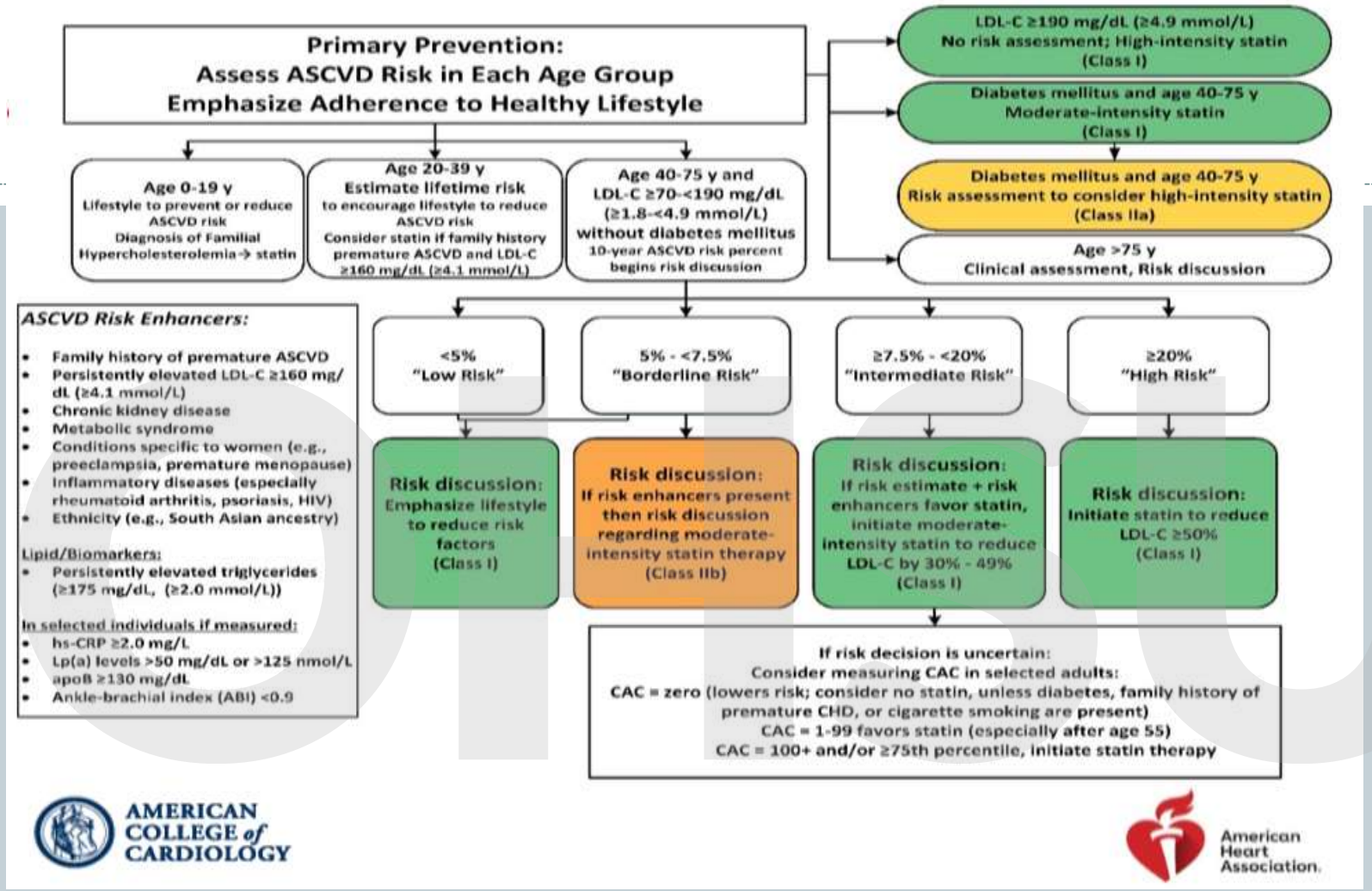
Impact of Antiretroviral Medication on Lipids

Class	Impact on Lipids
NRTIs	• Stavudine > Zidovudine > Abacavir: ⇧TG and ⇧LDL • Tenofovir alafenamide > Tenfovir DF: ⇧TG, ⇧LDL, ⇧HDL (no change TC:HDL ratio)
NNRTIs	• Efavirenz: ⇧TG, ⇧LDL, ⇧HDL
PIs	• All ritonavir- or cobicistat-boosted PIs: ⇧TG, ⇧LDL, ⇧HDL • Lopinavir-ritonavir = Fosamprenavir + Ritonavir: ⇧TG • Lopinavir-ritonavir > Darunavir + Ritonavir: ⇧TG • Atazanavir + Ritonavir: ⇧TG
ISTIs	• Elvitegravir-Cobicistat: ⇧TG, ⇧LDL, ⇧HDL
EIs	• NA

Abbreviations: NRTIs = nucleoside reverse transcriptase inhibitors; NNRTIs = nonnucleoside reverse transcriptase inhibitors; PIs = protease inhibitors; ISTIs = integrase strand transfer inhibitors; EIs = entry inhibitors

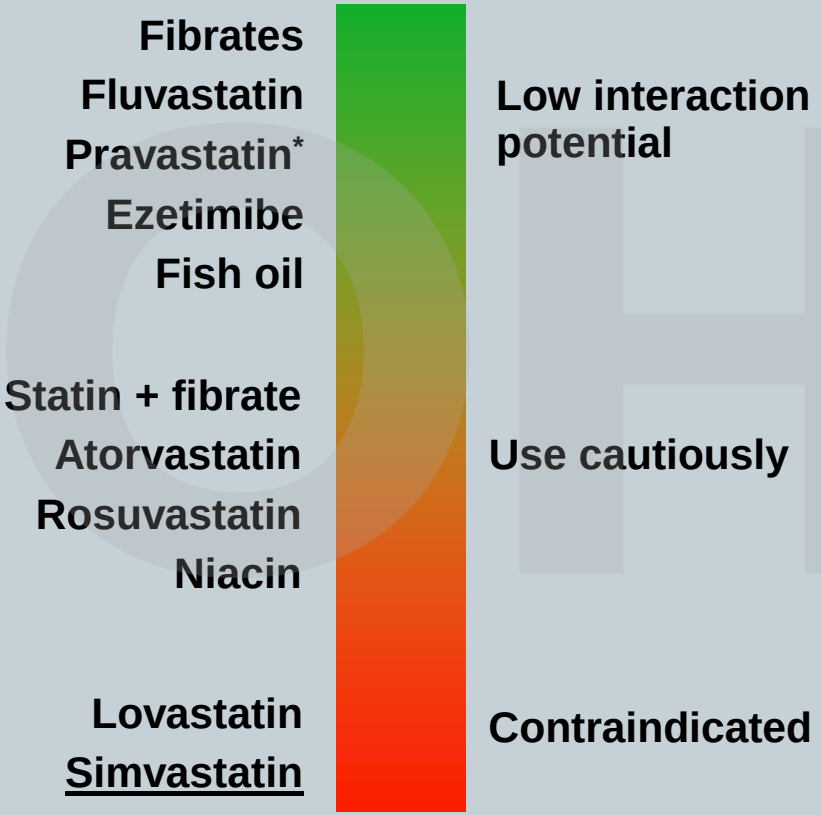
HIV & Cigarette Smoking

- HIV-infected patients are more likely to smoke and less likely to quit compared to general population
- Drug options include nicotine replacement (e.g., patch, gum, lozenge), bupropion, and varenicline, which can be used alone or in combination
- No important HIV drug interactions for commonly used smoking cessation drugs



In Adults 40 to 75 years of age without diabetes and 10 year risk for 7.5 % to 19 %, (intermediate risk), risk enhancing factors favor starting of a statin
Risk enhancing factors may favor statin therapy in patient wat 10 year risk of 5-7.5% (borderline risk)

HIV- and ART-induced dyslipidemia



*AUC □ with DRV

- HIV + can persistently low HDL cholesterol
- HIV have a poorer response to statin and fibrate therapies
- **Beware of Drug interactions !!!**

Aptivus [package insert]; 2005. Carr RA, et al. ICAAC 2000. Abstract 1644. Fitchenbaum CJ, et al. AIDS. 2002;16:569-577. Gerber JG, et al. CROI 2004. Abstract 603. Gerber J, et al. IAS 2003. Abstract 870. Hsue PH, et al. Antimicrob Agents Chemother. 2001;45:3445-3450. Lexiva [package insert]; 2007. Prezista [package insert]; 2006. Reyataz [package insert]; 2007.

General Approach to CV Risk in HIV Positive Patients

Obtain fasting lipid profile, prior to starting antiretrovirals and within 3 to 6 months of starting new regimen

↓

Count number of CHD risk factors and determine level of risk.
If ≥2 risk factors, perform a 10-year risk calculation

↓

Intervene for modifiable non-lipid risk factors, including diet and smoking

↓

If above the lipid threshold based on risk group despite vigorous lifestyle interventions, consider altering antiretroviral therapy or lipid-lowering drugs

↓

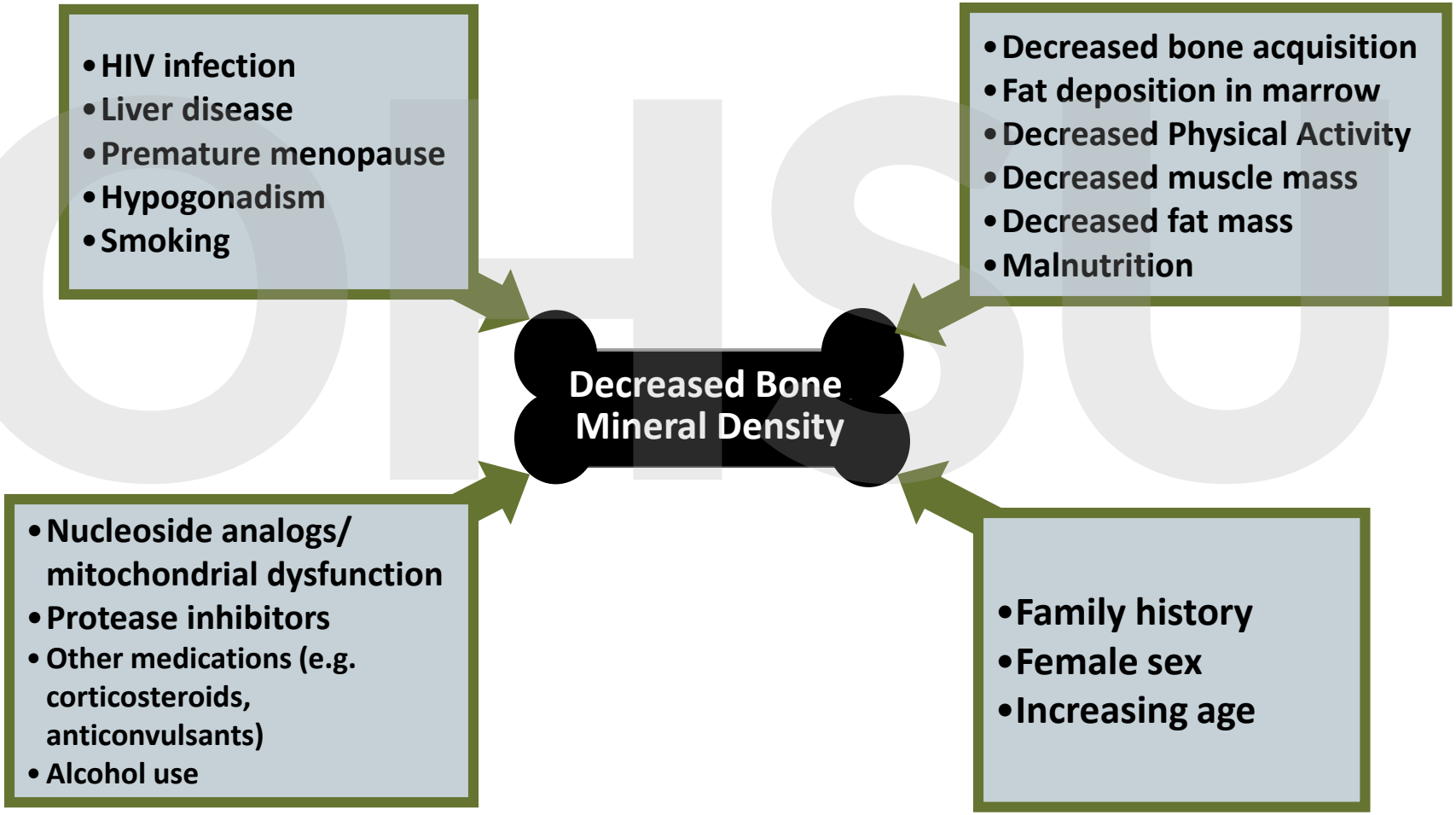
IF LIPID-LOWERING DRUGS ARE NECESSARY

Be Aware of Drug-Drug Interactions

Dubé MP et al. *Clin Infect Dis*. 2003;37:613-627.

IDSA = Infectious Diseases Society of America.

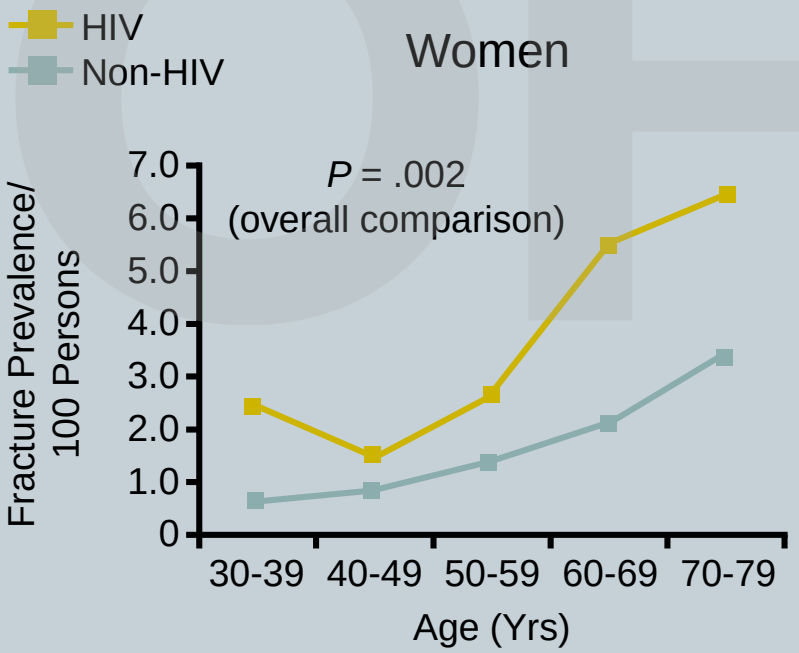
Bone Mineral Density in HIV Patients

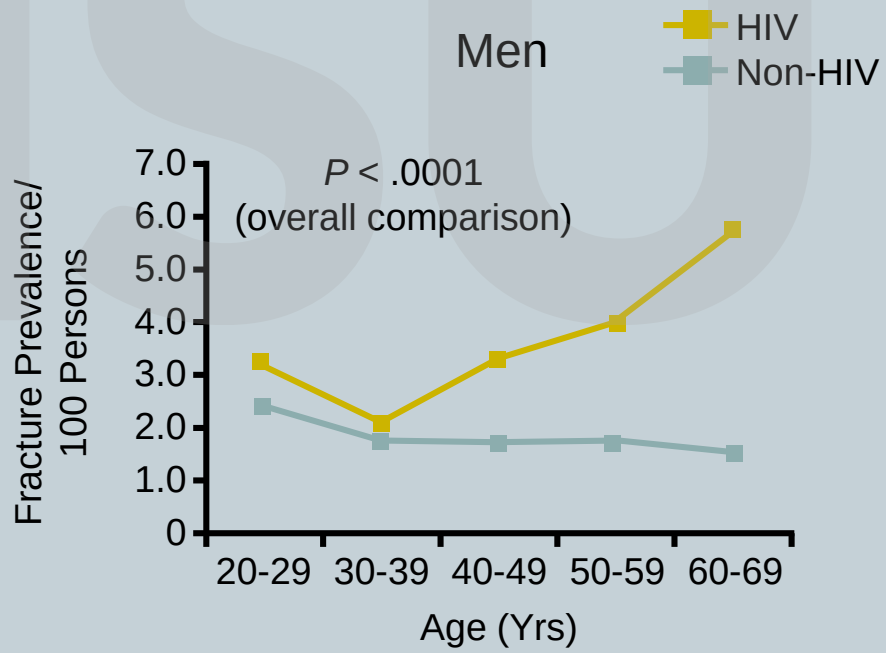


Glesby M et al. *CID* supplement September 2003.

HIV-Positive Pts Have Increased Risk of Bone Loss and Fractures

- HIV-positive patients had 6.4-fold increased risk of low BMD and 3.7-fold increased risk of osteoporosis
- 8525 HIV-infected pts compared with 2,208,792 uninfected pts in Partners HealthCare System, 1996-2008





1. Brown TT, et al. AIDS. 2006;20:2165-2174.
2. Triant V, et al. J Clin Endocrinol Metab. 2008;93:3499-3504.

HIV+ & Bone Health

Screening Recommendations

Age < 40

No screening needed

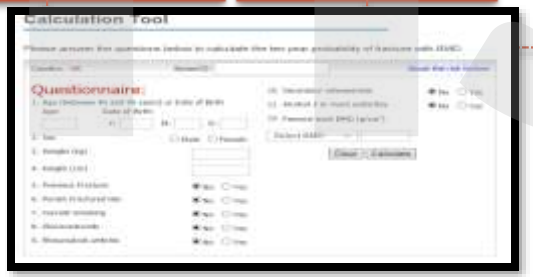
Age 40-50

Calculate FRAX

FRAX <10%

FRAX >10%, <20%

FRAX ≥20%



Ensure adequate Ca intake
Ensure adequate Vit D levels
Lifestyle advice

H/o fragility fx
Steroid (≥5mg X 3mos)
High risk of fall
Post-menopausal women
Men ≥50

BMD by DEXA (or FRAX if DEXA not available)

T score < -2.5
Or FRAX >20% or ≥3% at the hip
Or Hip or vertebral fracture

Exclude secondary causes of osteoporosis

Ensure adequate Ca intake
Ensure adequate Vit D levels +
Lifestyle advice

Consider Bisphosphonate therapy

Brown TT, et.al. Recommendations for evaluation and management of bone disease in HIV Clin Infect Dis, January 21, 2015

US National Osteoporosis Foundation (NOF) Guidelines for DXA Screening (2008)

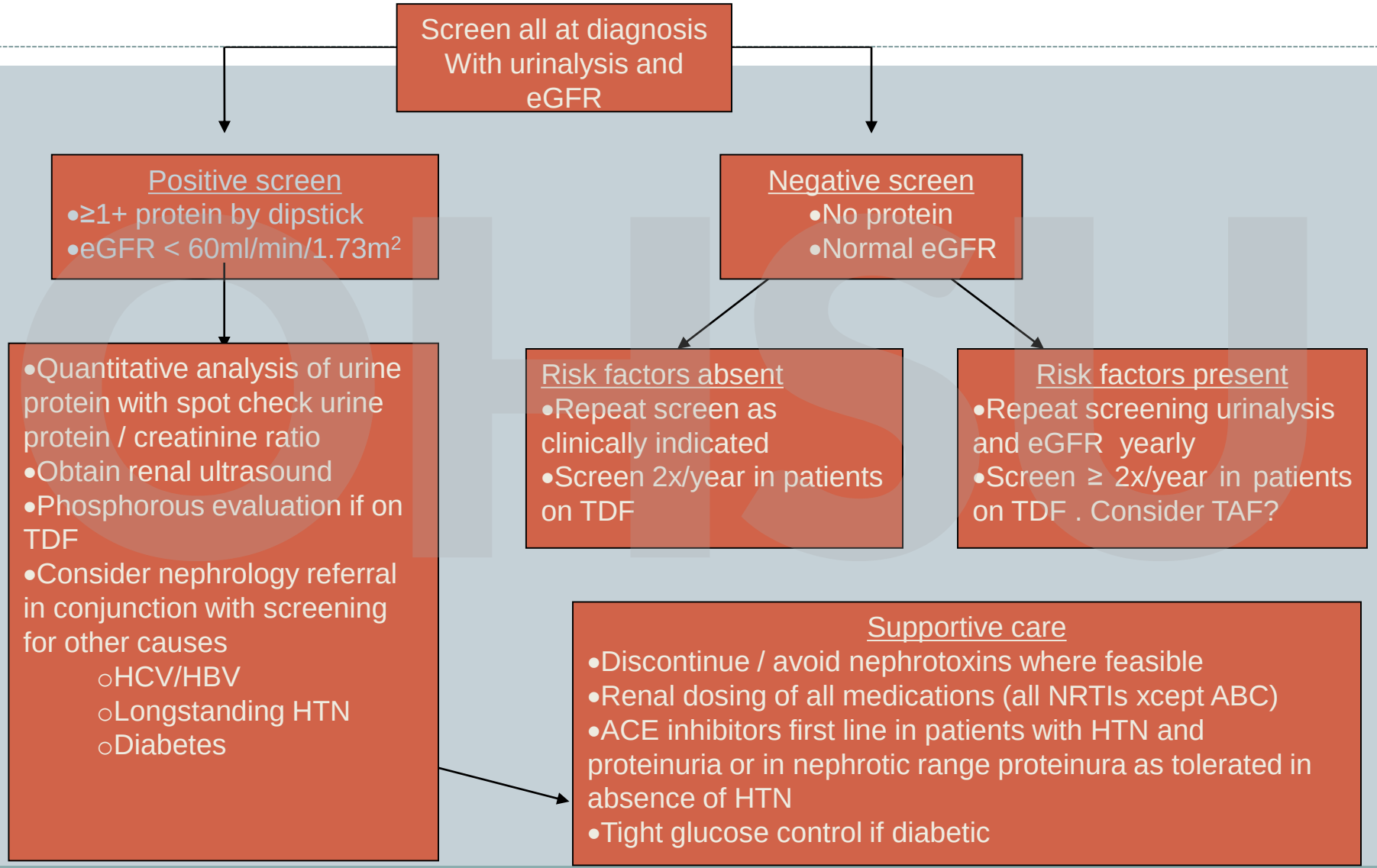
- Those with a history of fragility fracture
- Women ≥65 years, Men ≥70
- Postmenopausal women and men 50-70 years, if there is concern based on risk factor profile

Screening in HIV-infected Patients:

All post-menopausal women
Men ≥50 years

Slide Credit courtesy Todd Brown

Evaluation of Renal Disease in HIV



Adapted from Amy Bain; VANTHCS

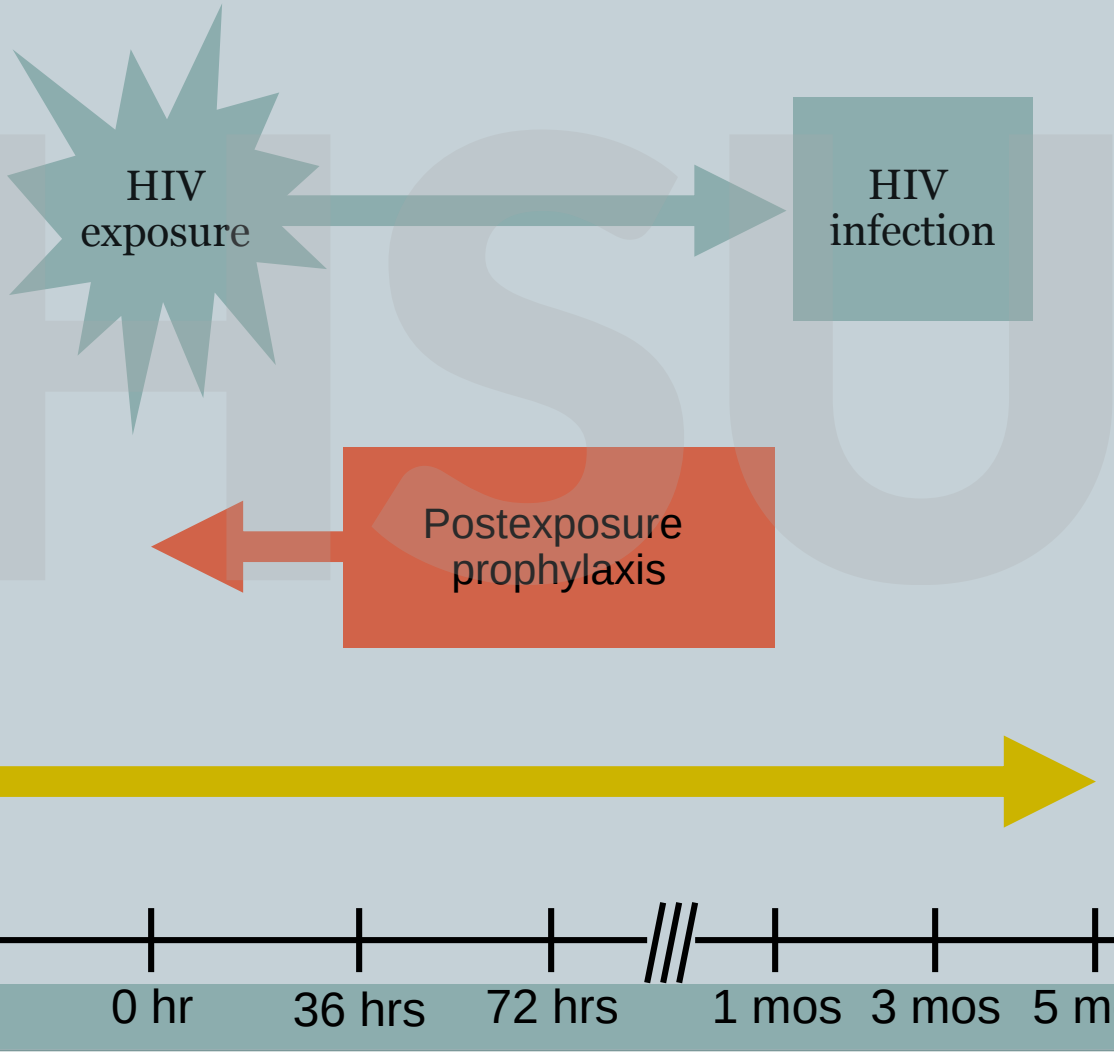
Drug Related Renal Disease in HIV
Tenofovir Nephrotoxicity (TDF vs TAF)

- Tenofovir nephrotoxicity: proximal tubular cell dysfunction that may be associated with AKI or chronic kidney disease
  - Fanconi was 60% of AKI with TDF use in one report. Most resolved with cessation, but a few incompletely
- Biopsy might be helpful: typically shows ATN without glomerular or interstitial changes
- TAF: pro-drug of tenofovir that concentrates in cells, converted to tenofovir (TFV) and is virologically as effective as TDF.
- TAF has more favorable effects on renal (CrCl > 30 cc/min) and bone markers.

Zimmermann. Clin Infect Dis 2006; 42:283-290

Pre- vs Post-exposure Prophylaxis

- After exposure to HIV, infection may become established
- Postexposure prophylaxis (initiated soon after exposure) reduces the chance of infection
- Pre-exposure prophylaxis begins treatment earlier (before exposure)
  - Malaria PPX, Birth control pill



What is PrEP?

- A prevention strategy in which a high-risk individual takes medication regularly to prevent infection
- Tenofovir-emtricitabine (*Truvada*) approved for HIV PrEP by the FDA in July 2012
- Added benefits: provides some protection against HSV and hepatitis B

Monitoring for Patients taking PrEP

Recommended Laboratory Testing and Frequency for Patients Taking PrEP				
Laboratory test	**Baseline**	**Every 3 months**	**At least every 6 months**	**Notes**
HIV screening assay	✓	✓		Consider need for HIV RNA PCR
HBV antibody panel and HCV antibody	✓			Offer HBV vaccination if not immune
Basic Metabolic Profile	✓		✓	Avoid PrEP if CrCl <60 mL/min
General STI screen	✓		✓	**Include oral/rectal * screen for MSM if risk**
Pregnancy test for women*	✓	✓		

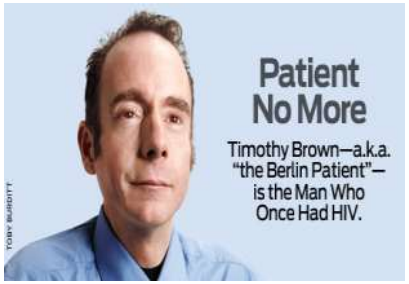
*The safety of PrEP in pregnancy has not been established

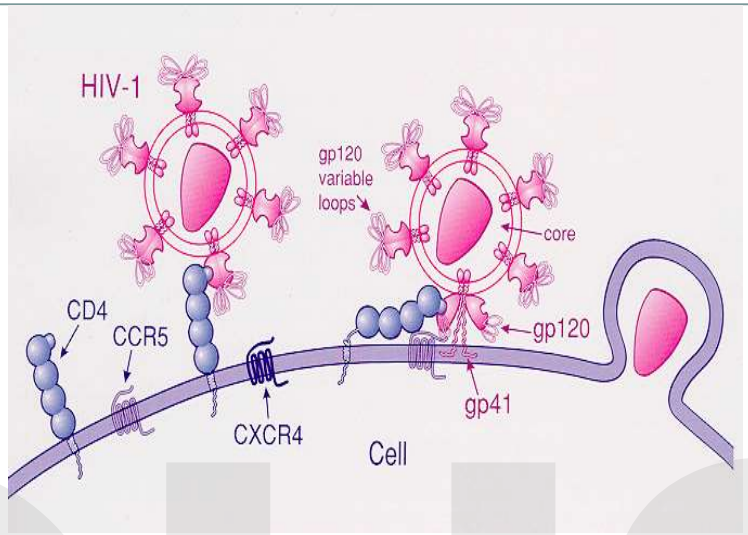
Source: US Public Health Service. Clinical practice guidelines for PrEP. May 2014.

Guidance for PrEP Use With HIV-Uninfected Sexually-Active Adults

	MSM	HRH
At Very High Risk of Acquiring HIV Infection	HIV+ partner STI history, high number of sex partners History of inconsistent or no condom use Commercial sex work	
		In high prevalence area or network
Clinically Eligible	Documented negative HIV test before prescribing PrEP No signs/symptoms of acute HIV infection Normal renal function, no contraindicated medications Documented hepatitis B virus infection/vaccination status	
Prescription	(Truvada®), daily # 90 day supply	
Other services	• Follow-up visits at least every 3 months to provide: HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment • At 3 months and every 6 months after, assess renal function • Every 6 months test for bacterial STIs	
	Do oral/rectal STI testing	Assess pregnancy intentions Every 3 months do pregnancy test Consider use for safer conception Consider continuing during pregnancy

***Main points only. See source documents:**
CDC. *MMWR*. 2011;60(3):65-68 and
CDC. *MMWR*.2012;61(31):586-590.





The New York Times

H.I.V. Is Reported Cured in a Second Patient, a Milestone in the Global AIDS Epidemic

Scientists have long tried to duplicate the procedure that led to the first long-term remission 12 years ago. With the so-called London patient, they seem to have succeeded.

- He underwent aggressive chemotherapy to clear the leukemia
- Received two bone marrow transplants from a CCR5-Δ32 individual.
- The new immune cells were not susceptible HIV, and the virus in currently HIV undetectable post-transplant.

HIV enters cells by binding to CD4 and a "corecepter" (often CCR5).

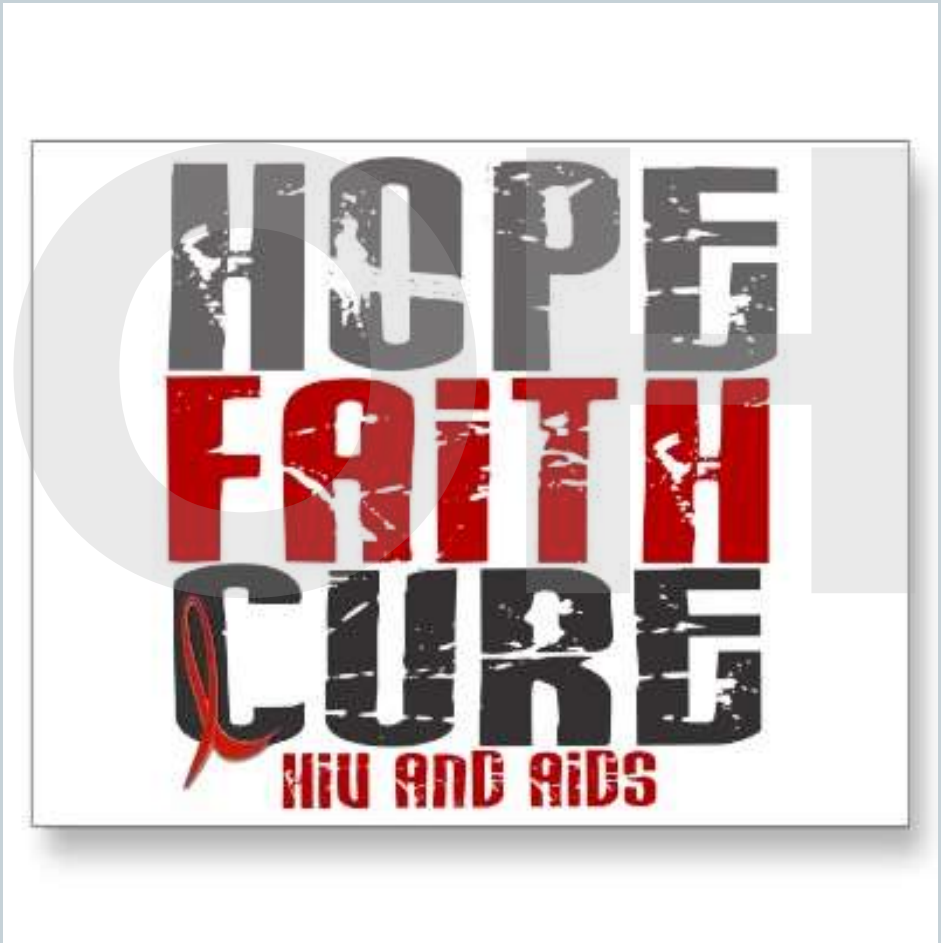
CCR5 is not functional in approximately 1% of Caucasians, which means they are highly resistant (but not completely immune) to infection with most strains of HIV.

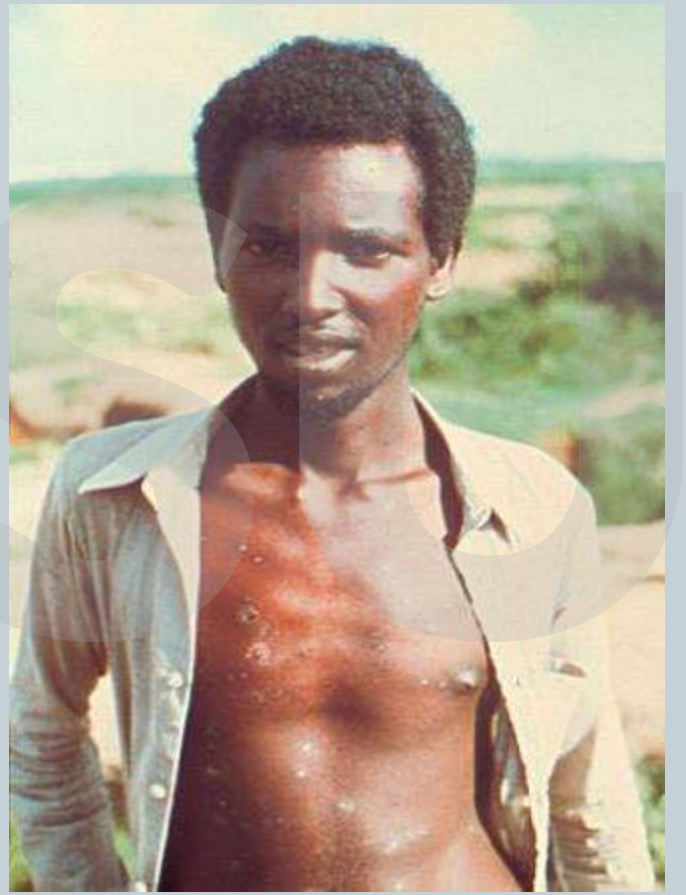
This mutation is called CCR5Δ32.

Reference:http://www.thefullwiki.org/Discovery_and_development_of_CCR5_receptor_antagonists

Conclusions: HIV management for the Non-specialist

- Remember that early diagnosis of HIV is important
- HIV accelerates Aging—be aware of Comorbidities
  - Cardiovascular, Renal and Bone Disease
- Poly pharmacy and drug-drug interactions
- More STR Options (HAART) – More Tolerable regiments
- Prevention- Pre Exposure Prophylaxis
- Don't forget Preventable screenings and Vaccines - & cancer screening.
- HIV Cure: Promising but not ready for Prime-Time





Ali Maalin

Thanks for Listening