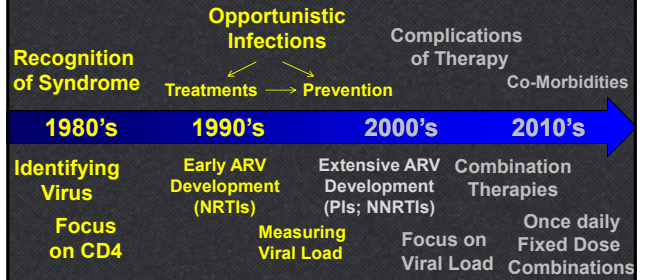


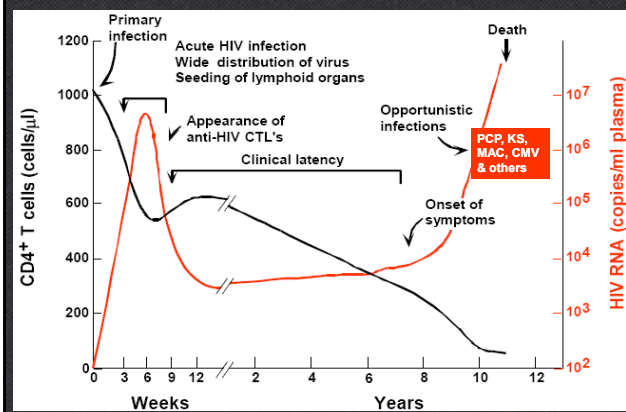
HIV/AIDS

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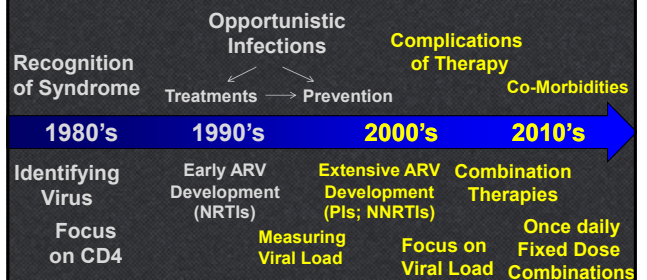
HIV through the Decades

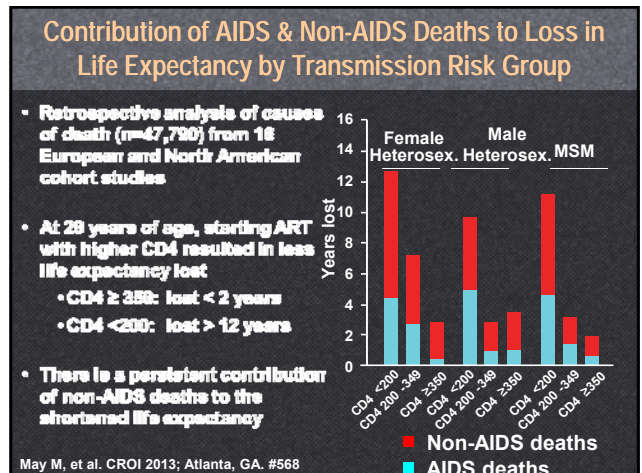
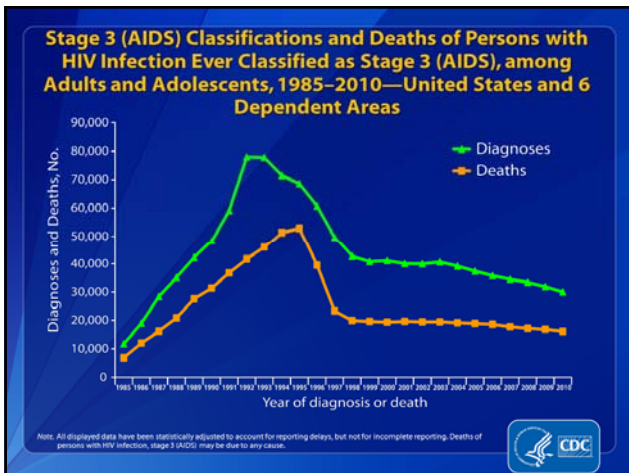
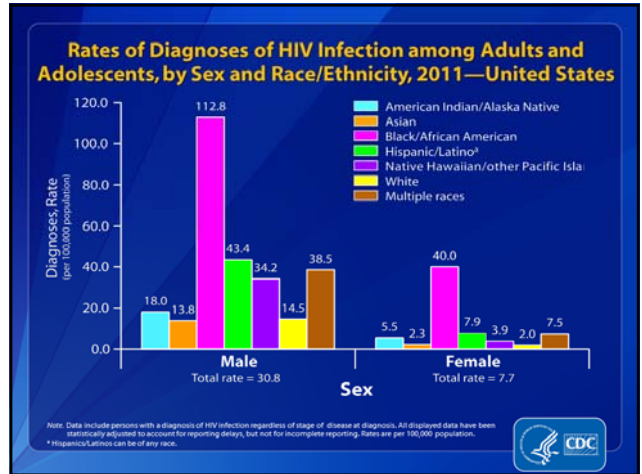
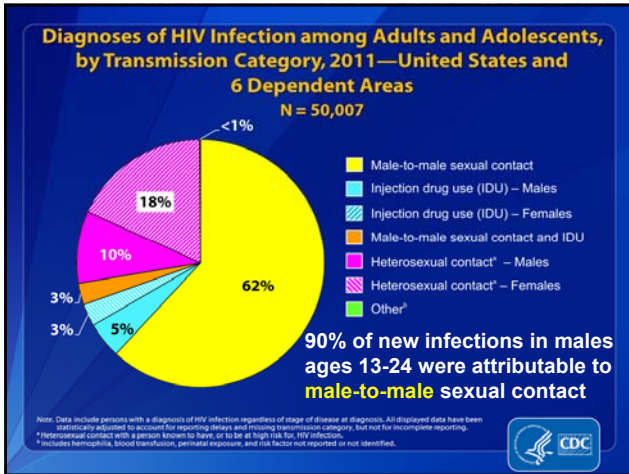


"Typical" Course of Untreated HIV Infection



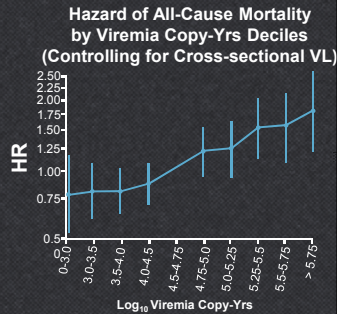
HIV through the Decades





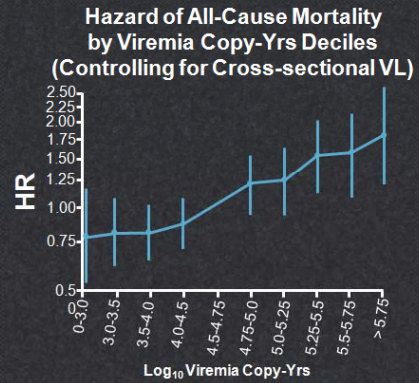
Cumulative Viral Load Predicts Mortality in ART-Treated Patients

- Estimated cumulative VL (viremia copy-yrs) assessed in 33,563 pts at 17 sites of ART Cohort Collaboration
- After adjusting for age, sex, risk group, BL and time-related VL, and cohort, viremia copy-yrs stratum predicted
 - All-cause mortality
 - AIDS-related mortality



Mugavero M, et al. CROI 2014. Abstract 565. Reproduced with permission.

Cumulative Viral Load Predicts Mortality in ART-Treated Patients



Mugavero M, et al. CROI 2014. Abstract 565. Reproduced with permission.

Normalization of CD4/CD8 Ratio and Non-AIDS Events

- 3,236 pts on ART with virologic suppression
 - 7,305 PYFU
 - 458 pts reached CD4/CD8 \geq 1
 - Median time to normalization: 10.1 yrs
 - Younger pts, those starting ART in recent yrs, and those with higher CD4+ counts more likely to normalize
- Current CD4/CD8 ratio predicted incidence of clinical progression
- Remained predictive after adjusting for current CD4+ cell count

Time	Probability of CD4/CD8 Normalization (95% CI)
1 yr	4.4 (3.7-5.2)
2 yrs	11.5 (10.2-13.0)
5 yrs	29.4 (26.7-32.4)

Current CD4/CD8 Ratio	Incidence of Clinical Progression* (95% CI)
< 0.30	4.8 (3.9-5.9)
0.30-0.45	2.4 (1.9-3.1)
> 0.45	2.0 (1.7-2.3)

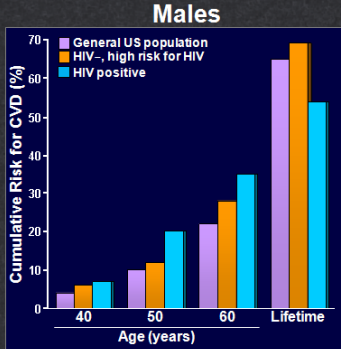
*serious non-AIDS-related events (CV or cancer) or all-cause death

Mussini C, et al. IIcona Study Group. CROI 2014. Abstract 753.

Common Co-morbid Conditions in HIV-infected Persons

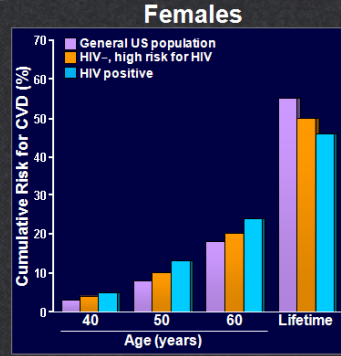
- Cardiovascular diseases
- Metabolic complications
 - lipids/diabetes
- Bone disorders
- Renal
- Liver
- Malignancies

Projecting CVD Risk in HIV: Cumulative Risk by Age and Over a Lifetime



Competing mortality due to HIV-related causes and other non-HIV causes within the HIV-infected population results in lower overall CVD lifetime risk for HIV-infected persons. Losina E, et al. 20th CROI. Atlanta, 2013. Abstract 747.

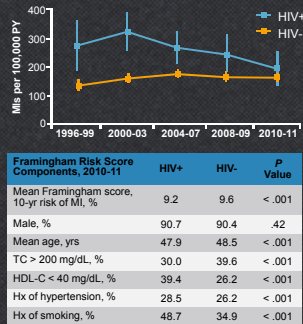
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Incidence of MI in HIV+ vs HIV- Subjects in Kaiser Cohort

- Retrospective analysis of Kaiser cohort EMRs during 1996-2011 for inpatient MI diagnosis
- HIV-/HIV+ pts matched 10:1
- MI rates in HIV+ and HIV- converged over time
 - 40% increased risk of MI in HIV+ pts overall, but difference no longer observed in most recent yrs



Framingham Risk Score Components, 2010-11	HIV+	HIV-	P Value
Mean Framingham score, 10-yr risk of MI, %	9.2	9.6	< .001
Male, %	90.7	90.4	.42
Mean age, yrs	47.9	48.5	< .001
TC > 200 mg/dL, %	30.0	39.6	< .001
HDL-C < 40 mg/dL, %	39.4	26.2	< .001
Hx of hypertension, %	28.5	26.2	< .001
Hx of smoking, %	48.7	34.9	< .001

Klein D, et al. CROI 2014. Abstract 737. Reproduced with permission.

Incidence of MI in HIV+ vs HIV- Subjects in Kaiser Cohort



Klein D, et al. CROI 2014. Abstract 737. Reproduced with permission.

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Klein D. et al. CROI 2014. Abstract 737. Reproduced with permission.

Excess Burden of Cancer Among HIV-Infected Persons

- Estimated cancer rates in HIV - HIV/AIDS Cancer Match Study

- Expected cancer rates for general population from SEER program (Surveillance, Epidemiology, and End Results)

- Excess = excess/total
- Deficit = deficit/expected

50.4 % excess cancers in HIV-infected - most occurred among males (51.5%) - largest excess among ages 40-49

Estimated Total & Excess Cancer among HIV-infected Persons in the U.S. (2010)

Type of Cancer (Total Number)	Expected # of Cancers	Excess or Deficit (%)
NHL (1645)	203	87.7
KS (912)	2	99.8
Lung (837)	401	52.0
Anus (764)	20	97.4
Prostate (574)	969	-40.7
Liver (389)	106	72.7
Colorectal (357)	379	-5.8
Hodgkin's lymphoma (317)	29	90.0
♀Breast (177)	303	-41.6

Robbins et al. 12th CROI Boston 2014 #707

HIV and Cancer-Specific Mortality in the U.S. (1996-2010)

- Retrospective analysis from 5 US Cancer registries (HIV/AIDS Cancer Match Study) - Cancer specific mortality by HIV status
- HIV-infected cancer patients experienced higher cancer-specific mortality

Adjusted Hazard Ratios for Cancer-Specific Mortality (HIV Infected vs Uninfected)

	HR (95% CI)
Oral cavity/pharynx	1.50 (1.07-2.09)
Larynx	1.92 (1.23-2.98)
Pancreas	1.63 (1.26-2.10)
Colon and rectum	1.69 (1.36-2.11)
Lung	1.28 (1.17-1.40)
Melanoma	1.76 (1.10-2.79)
Breast	2.71 (2.10-3.50)
Prostate	1.83 (1.16-2.87)

Liver, anal, cervical cancers had suggested elevations

Cohill et al 21st CROI. Boston 2014 #99

HIV and the Older Patient

- In the U.S., approximately 30% of HIV-infected persons are ≥50 years of age
- Aging-related comorbidities may complicate management of HIV
- HIV may increase risk of comorbidities and may accelerate the aging process
- Limited data on effects of ARVs in older persons (eg, adverse effects, drug-drug interactions)

HIV and the Older Patient: HIV Risk, Diagnosis, and Prevention

- Reduced mucosal and immunologic defenses and changes in risk behaviors may lead to increased risk of HIV acquisition and transmission
- HIV screening rates in older persons are low
- Older persons may have more advanced HIV at presentation and ART initiation
 - Screen for HIV per CDC recommendations
 - Sexual history, risk-reduction counseling, screening for STIs (as indicated) are important to general health care for HIV-infected and HIV-uninfected older persons

Recommendations for HIV Testing

- HIV screening is recommended for patients in all health-care settings
 - Patient should be notified that testing will take place unless patient declines (opt-out testing)
- Persons at high risk for HIV should be screened at least annually
- HIV screening should be included in the routine panel of prenatal screening for pregnant women
- Neither separate written consent nor prevention counseling should be required

MMWR 2006;55(R14):1-17.

HIV/AIDS

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The Ohio State University Wexner Medical Center

Treatment

2014 DHHS Guidelines: When to Start ART

Clinical Category	CD4 Cell Count (cells/mm ³)	2014 DHHS Guidelines	Strength-Quality
AIDS-defining illness	Any value	Treat	A-I
Asymptomatic	<350	Treat	A-I
	350 to 500	Treat	A-II
	>500	Treat	B-III
Transmission prev:			
<i>Pregnancy</i>	Any value	Treat	A-I
<i>Sexual (heterosexual, other)</i>			(A-I, A-III)

<http://aidsinfo.nih.gov> 27 May 2014

Goals of Treatment

- Decrease in morbidity/mortality
 - Improvement in quality of life
- Virologic suppression
 - VL < 400 at 24wks
 - VL < 50 (ND) at 48wks
 - Anything else = virologic failure
- Immunologic recovery (reconstitution)
 - Increase in CD4+ number and/or percentage
 - Anything else = immunologic failure
 - Especially decline in CD4+ to < 200
- Surveillance for side effects

<http://aidsinfo.nih.gov/>

Current ARV Medications

NRTI

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

NNRTI

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

Protease Inhibitor (PI)

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

* EVG currently available only in coformulation with cobicistat (COBI)/ TDF/FTC

www.aidsinfo.nih.gov May 2014

Current ARV Medications

Integrase Inhibitor (II)

- Dolutegravir (DTG)
- Elvitegravir* (EVG)
- Raltegravir (RAL)

Fusion Inhibitor

- Enfuvirtide (ENF, T-20)

CCR5 Antagonist

- Maraviroc (MVC)

* EVG currently available only in coformulation with cobicistat (COBI)/ TDF/FTC

www.aidsinfo.nih.gov May 2014

2014 DHHS Guidelines: Regimens for Treatment-Naïve Patients

Recommended	<ul style="list-style-type: none"> • EFV • ATV/r, DRV/r (QD) • DTG, RAL, EVG/cobi • DTG + ABC/3TC (1) <p>[Recommendations for pregnant women differ; see (a)]</p>	} + TDF/FTC
For patients with VL < 100,000	<ul style="list-style-type: none"> • EFV + ABC/3TC (1) • RPV + TDF/FTC (for patients with CD4 > 200) • ATV/r + ABC/3TC (1) 	
Alternative Regimens	<ul style="list-style-type: none"> • DRV/r + ABC/3TC (1) • LPV/r + (ABC/3TC or TDF/FTC) (1) • RAL + ABC/3TC (1) 	
Notes	<ul style="list-style-type: none"> • 1 – only in patients who are HLA-B*5701 negative • 2 – 3TC and FTC may be used interchangeably throughout 	

(a) <http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinataltgl.pdf> <http://aidsinfo.nih.gov> 27 May 2014

Advances

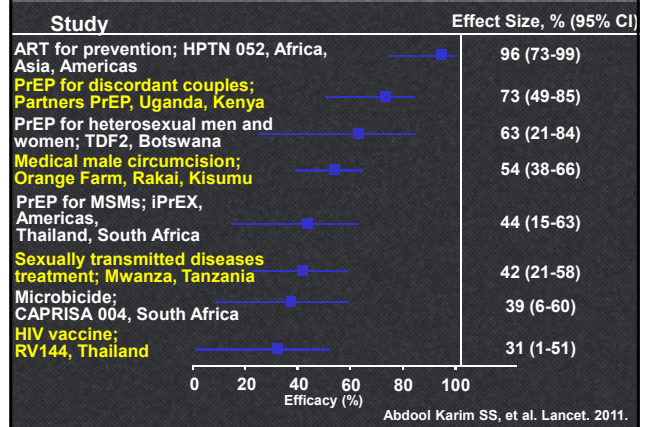
- **Comparative effectiveness (1)**
 - ATV/r vs DRV/r vs RAL (with TDF/FTC)
 - RAL superior, mostly d/t tolerability
- **New agents (2)**
 - Long-acting, injectable agents
 - Phase IIb, equivalent to TDF/FTC/EFV

1. Landovitz R, et al. CROI 2014. Abstract 85.

2. Margolis D, et al. CROI 2014. Abstract 91LB.

Prevention

HIV Prevention



CDC PrEP Recommendations

Table 1: Summary of Guidance for PrEP Use

	Men Who Have Sex with Men	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection	HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work	HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work In high-prevalence area or network	HIV-positive injecting partner Sharing injection equipment Recent drug treatment (not currently injecting)
Clinically eligible	Documented negative HIV test result before prescribing PrEP No signs/symptoms of acute HIV infection Normal renal function; no contraindicated medications Documented hepatitis B virus infection and vaccination status		
Prescription	Daily, containing, oral doses of TDF/FTC (Truvada), ≤90-day supply		
Other services	Follow-up visits at least every 3 months to provide the following: HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment At 3 months and every 6 months thereafter, assess renal function Every 6 months, test for bacterial STIs		
	Do rectal STI testing	Assess pregnancy status Pregnancy test every 3 months	Access to clean needles/syringes and drug treatment services

STI: sexually transmitted infection

<http://www.cdc.gov/hiv/pdf/PrEPProviderSupplement2014.pdf> <http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf>

Cure Research

Promising Studies

- Adults “cured” of HIV
 - Patient with AML, s/p BMT
 - Remains ND off ART (1)
 - Others s/p BMT → relapse of HIV (2)
- Infants “cured” of HIV
 - One in Mississippi, ND off ART (3)
 - One new infant, ND on ART (4)

1. *N Engl J Med.* 2009;360:692-8

2. CROI 2014. Abstract 144LB

3. CROI 2013. Abstract 48LB.

4. CROI 2014. Abstract 75LB

Promising Studies

- Failure of PrEP
 - Possibility of reduced seeding of reservoir (1)
- Gene “editing”
 - Removal of co-receptor from CD4 cells by use of a Zn-finger endonuclease (2)

1. CROI 2014. Abstract 397LB.

2. *N Engl J Med.* 2014; 370(10):901-910.