HIV/AIDS

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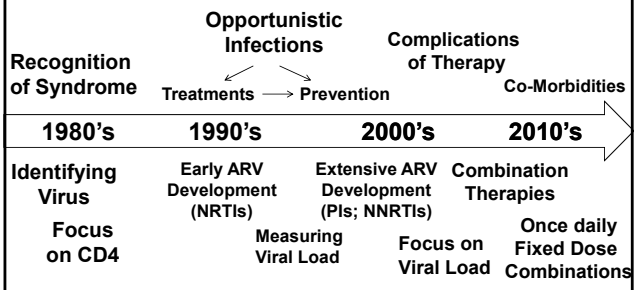
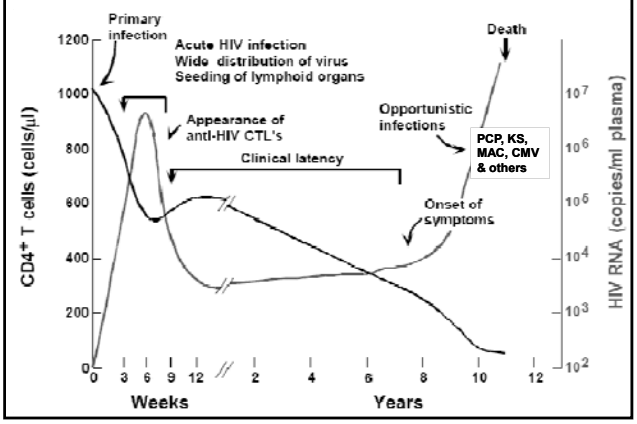
HIV through the Decades



"Typical" Course of Untreated HIV Infection



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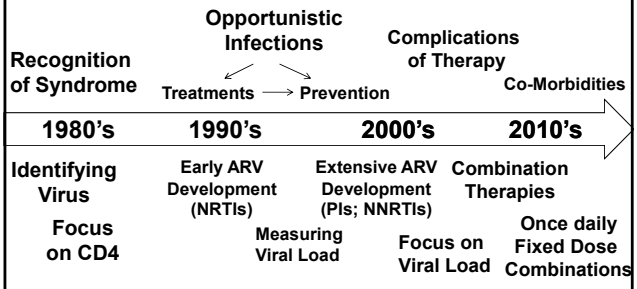
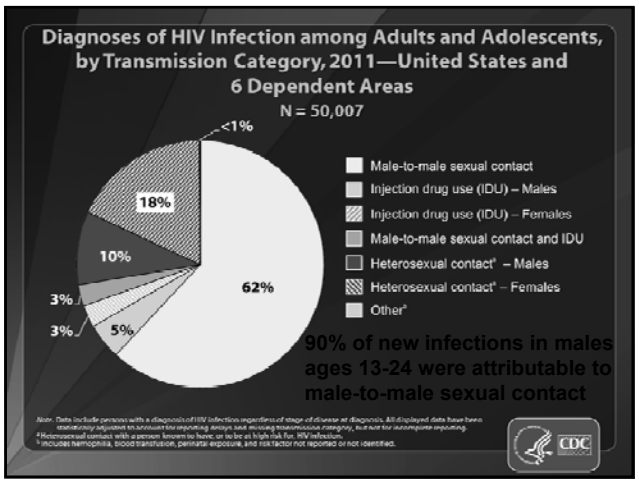
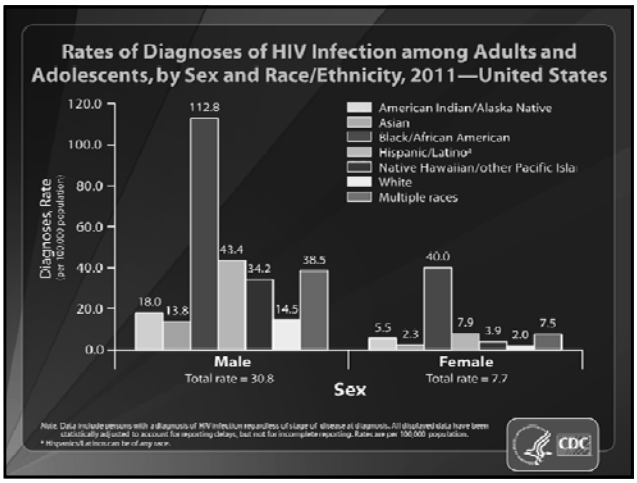
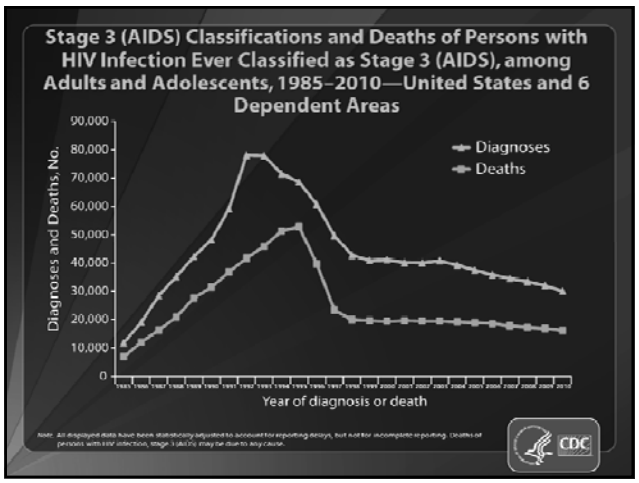


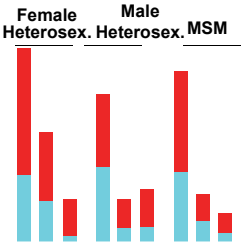






Contribution of AIDS & Non-AIDS Deaths to Loss in Life Expectancy by Transmission Risk Group

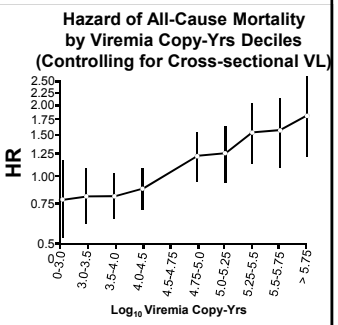
- Retrospective analysis of causes of death (n=47,780) from 16 European and North American cohort studies
- At 20 years of age, starting ART with higher CD4 resulted in less life expectancy lost
  - CD4 ≥ 350: lost < 2 years
  - CD4 <200: lost > 12 years
- There is a persistent contribution of non-AIDS deaths to the shortened life expectancy



May M, et al. CROI 2013; Atlanta, GA. #568

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.

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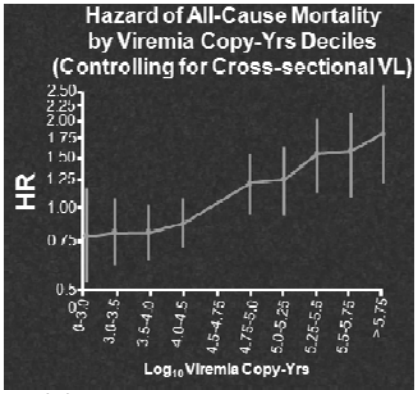


Mugavero M, et al. CROI 2014. Abstract 565. Reproduced with permission.

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 ≥ 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)

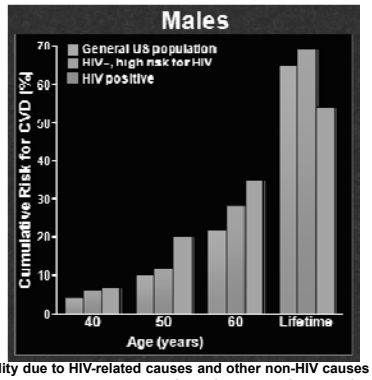
*serious non-AIDS–related events (CV or cancer) or all-cause death

Mussini C, et al. /Icona 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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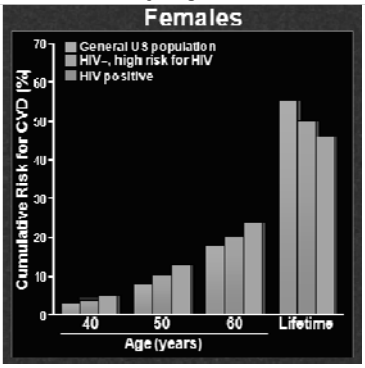

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Incidence of MI in HIV+ vs HIV- Subjects in Kaiser Cohort

- 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.

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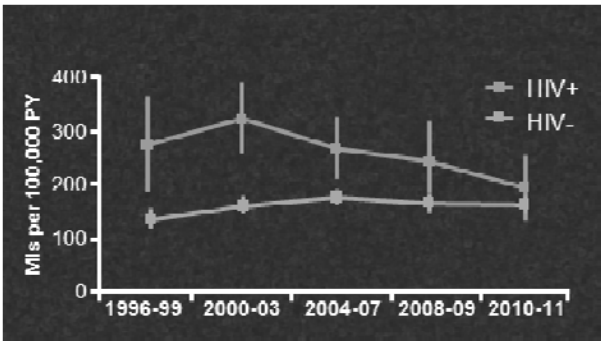

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Excess Burden of Cancer Among HIV-Infected Persons

- 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. 12st 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

Coghill 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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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: *Pregnancy* *Sexual (heterosexual, other)*	Any value	Treat	A-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 (ddI)
- 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.aidsetc.org 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.aidsetc.org May 2014

2014 DHHS Guidelines: Regimens for Treatment-Naïve Patients

Recommended	**• EFV • ATV/r, DRV/r (QD) • DTG, RAL, EVG/cobi } + TDF/FTC • DTG + ABC/3TC (1) [Recommendations for pregnant women differ; see (a)]**
For patients with VL<100,000	• EFV + ABC/3TC (1) • RPV + TDF/FTC (for patients with CD4 > 200) • ATV/r + ABC/3TC (1)
Alternative Regimens	• DRV/r + ABC/3TC (1) • LPV/r + (ABC/3TC or TDF/FTC) (1) • RAL + ABC/3TC (1)
Notes	• 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/perinatalgl.pdf **http://aidsinfo.nih.gov 27 May 2014**

Advances

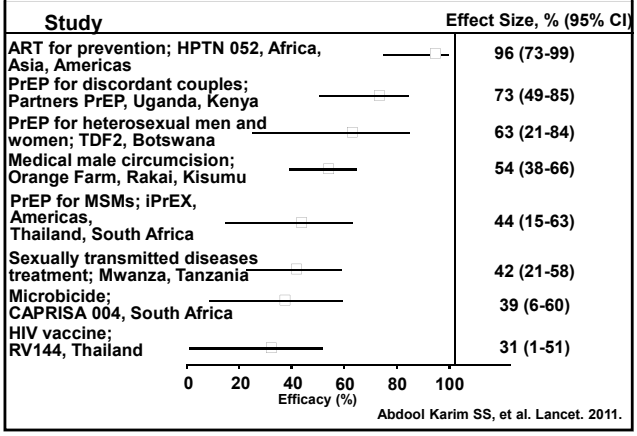
- **Comparative effectiveness (1)**
  - **ATV/r vs DRV/r vs RAL (with TDF/FTC)**
  - **RAL superior, mostly d/t tolerability**
- **New agents (2)**
  - **Long-acting, injectable agents**
  - **Phase IIb, equivalent to TDF/FTC/EFV**

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

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

Prevention

HIV Prevention



Abdool Karim SS, et al. Lancet. 2011.

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 (but 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, continuing, oral dose of TDF/FTC (Truvada), ≤30-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 oral/rectal STI testing	Assess pregnancy intent 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.