HIV/AIDS

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Professor of Internal Medicine
Department of Internal Medicine
The Ohio State University Wexner Medical Center

HIV through the Decades

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Identifying Virus</td>
<td>Early ARV Development (NRTIs)</td>
<td>Extensive ARV Development (PIs; NNRTIs)</td>
<td>Combination Therapies</td>
</tr>
<tr>
<td>Focus on CD4</td>
<td>Measuring Viral Load</td>
<td>Focus on Viral Load</td>
<td>Once daily Fixed Dose Combinations</td>
</tr>
</tbody>
</table>

“Typical” Course of Untreated HIV Infection

HIV through the Decades

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Recognition of Syndrome</td>
<td>Opportunistic Infections</td>
<td>Complications of Therapy</td>
<td>Co-Morbidities</td>
</tr>
<tr>
<td>Treatments</td>
<td>Prevention</td>
<td></td>
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</tr>
</tbody>
</table>

“Typical” Course of Untreated HIV Infection
90% of new infections in males ages 13-24 were attributable to male-to-male sexual contact.

<table>
<thead>
<tr>
<th>Year</th>
<th>CD4 &lt;200</th>
<th>CD4 200-349</th>
<th>CD4 ≥350</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS deaths</td>
<td>18.0</td>
<td>16.4</td>
<td>14.0</td>
</tr>
<tr>
<td>Non-AIDS deaths</td>
<td>5.5</td>
<td>2.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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

- Female Heterosexual, Male Heterosexual, Male MSM
- Non-AIDS deaths
- AIDS deaths

Note: Data are age- and sex-specific, calculated from a retrospective analysis of cause-of-death data. Analysis included men and women ages 15-64 years who died with an AIDS diagnosis in the United States during 1985-2010. Analysis excluded non-Hispanic white individuals, those with an AIDS diagnosis before 1985, those with an AIDS diagnosis on the day of death, and those with a death certificate delay of more than 1 year.
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

Hazard of All-Cause Mortality by Viremia Copy-Yrs Deciles (Controlling for Cross-sectional VL)


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

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


definition of terms

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.


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

<table>
<thead>
<tr>
<th>Component</th>
<th>HIV+</th>
<th>HIV-</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Mean Framingham score, 10-yr risk of MI, %</td>
<td>9.2</td>
<td>9.6</td>
<td>&lt; .001</td>
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<tr>
<td>Male, %</td>
<td>60.7</td>
<td>60.4</td>
<td>.42</td>
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<tr>
<td>Mean age, yrs</td>
<td>47.9</td>
<td>48.5</td>
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<td>30.0</td>
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<tr>
<td>HDL-C &lt; 40 mg/dL, %</td>
<td>38.4</td>
<td>28.2</td>
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</tr>
<tr>
<td>Hx of hypertension, %</td>
<td>28.5</td>
<td>26.2</td>
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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

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Expected # of Cancers</th>
<th>Excess or Deficit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL (1645)</td>
<td>203</td>
<td>87.7</td>
</tr>
<tr>
<td>KS (912)</td>
<td>2</td>
<td>99.8</td>
</tr>
<tr>
<td>Lung (837)</td>
<td>401</td>
<td>52.0</td>
</tr>
<tr>
<td>Anus (764)</td>
<td>20</td>
<td>97.4</td>
</tr>
<tr>
<td>Prostate (574)</td>
<td>969</td>
<td>-40.7</td>
</tr>
<tr>
<td>Liver (389)</td>
<td>106</td>
<td>72.7</td>
</tr>
<tr>
<td>Colorectal (357)</td>
<td>379</td>
<td>-5.8</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma (317)</td>
<td>29</td>
<td>90.0</td>
</tr>
<tr>
<td>Breast (177)</td>
<td>303</td>
<td>-41.6</td>
</tr>
</tbody>
</table>

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

| Adjusted Hazard Ratios for Cancer-Specific Mortality (HIV Infected vs Uninfected) |
|-----------------------------------------|---------------------------------|
| Oral cavity/pharynx                    | 1.50 (1.07-2.99)                |
| 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

HIV/AIDS

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Division of Infectious Diseases
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Treatment
## 2014 DHHS Guidelines: When to Start ART

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4 Cell Count (cells/mm³)</th>
<th>2014 DHHS Guidelines</th>
<th>Strength-Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness</td>
<td>Any value</td>
<td>Treat</td>
<td>A-I</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission prev:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Any value</td>
<td>Treat</td>
<td>A-I</td>
</tr>
<tr>
<td>Sexual (heterosexual, other)</td>
<td></td>
<td></td>
<td>(A-I, A-III)</td>
</tr>
</tbody>
</table>

### 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

### 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)

**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

**Current ARV Medications**

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### 2014 DHHS Guidelines: Regimens for Treatment-Naïve Patients

**Recommended**
- EFV
- ATV/r, DRV/r (QD)
- DTG, RAL, EVG/cobi
- 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/contentfiles/lvguidelines/perinatalgl.pdf)

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### 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/E芙


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### Prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART for prevention; HPTN 052, Africa, Asia, Americas</td>
<td>96 (73-99)</td>
</tr>
<tr>
<td>PrEP for discordant couples; Partners PrEP, Uganda, Kenya</td>
<td>73 (49-85)</td>
</tr>
<tr>
<td>PrEP for heterosexual men and women; TDF2, Botswana</td>
<td>63 (21-84)</td>
</tr>
<tr>
<td>Medical male circumcision; Orange Farm, Rakai, Kisumu</td>
<td>54 (38-66)</td>
</tr>
<tr>
<td>PrEP for MSMs; iPrEx, Americas, Thailand, South Africa</td>
<td>44 (15-63)</td>
</tr>
<tr>
<td>Sexually transmitted diseases treatment; Mwanza, Tanzania</td>
<td>42 (21-58)</td>
</tr>
<tr>
<td>Microbicide; CAPRISA 004, South Africa</td>
<td>39 (6-60)</td>
</tr>
<tr>
<td>HIV vaccine; RV144, Thailand</td>
<td>31 (1-51)</td>
</tr>
</tbody>
</table>

CDC PrEP Recommendations

<table>
<thead>
<tr>
<th>Branding/Advisory</th>
<th>Year</th>
<th>PrEP Provider</th>
<th>Notes</th>
</tr>
</thead>
</table>

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)

2. CROI 2013. Abstract 48LB.
3. CROI 2014. Abstract 144LB
4. CROI 2014. Abstract 75LB

Cure Research

- 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.