HIV Management in 2015

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Plan for today

HIV management- current topics in 2015
-Diagnosis
-Management current guidelines 2015
-Recent 2015 data and new management guidelines on associated HIV topics

HIV Virology 101
Stages of HIV Infection
New – Simplified!

- 1. Early infection
- 2. Clinical latency
- 3. AIDS

Stages of HIV Infection

- Viral transmission
- Primary HIV infection: acute seroconversion syndrome or asymptomatic seroconversion
- Clinical latent period
- Early symptomatic HIV infection
- AIDS

Stages of HIV Infection

Summary

- Infection: Virus present
- AIDS = HIV Infection plus either
  - CD4 count less than 200 regardless of symptoms, or
  - AIDS-defining condition at any CD4 count
Stages of HIV Infection

- **Viral transmission**
- **Primary HIV infection**: acute seroconversion syndrome or asymptomatic seroconversion
- **Clinical latent period**
- **Early symptomatic HIV infection**
- **AIDS**
Viral Transmission

- Sex, blood, birth
- US
  - As %, MSM generally increasing, IVDU decreasing.
  - Now about 54% of new acquisitions are in MSMs
  - Women: Heterosexual acquisition
  - Minorities over-represented
  - Estimated at least 20% unaware of infection (200,000 of 1 million)

Transmission – Risk Factors

- Viral load
- Lack of circumcision
- Sexual partner number, practices
- STDs
- Genetic

Risk Factor – Viral Load

- Study: Ugandan serodiscordant couples, NEJM, 2000
  - 22% seroconversion over 2.5 years
  - VL higher in contacts of converters (90K vs 38K)
  - No transmission when VL less than 1500
- Two recent studies of serodiscordant couples showed:
  1. 92 to 96% reduction in transmission with ARV (Donnell et al Lancet 2010; HPTN 052 study)
  2. Study from Malawi: About 38% of transmissions were from source with acute infection (Lancet 2011)

Big conclusion: Treatment is prevention!

Risk Factor – Lack of Circumcision

- Data quite convincing that circumcision reduces transmission to the circumcised male
- Male to female transmission probably also reduced, but not so much

Risk Factor – Sexual Practices

- CDC rough estimates per sexual act without condom (with condom prob about 20-fold less)
  - Receptive penile/vag about 1 in 1000
  - Insertive penile/vag about 1 in 2000
  - Receptive anal about 1 in 200
  - Insertive anal about 1 in 1500
  - Receptive oral less than 1 in 10,000
  - Insertive oral less than 1 in 20,000

Nice CDC fact sheet at
http://www.cdc.gov/hiv/resources/factsheets/circumcision.htm

MMWR 1/21/05; http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5312a1.htm
Risk Factor – Sexual Practices

- MSM study (Buchbinder et al, JAIDS 2005)
  - Number of partners
  - Unprotected anal sex w/partner of ? HIV status
  - Use of nitrate inhalants

Stages of HIV Infection

- Viral transmission
- **Primary HIV infection: acute seroconversion syndrome or asymptomatic seroconversion**
- Clinical latent period
- Early symptomatic HIV infection
- AIDS

Primary HIV Infection

- **Primary HIV Infection**
  - Very infectious
    - Male-to-female likelihood of infection as high as 7-24%
  - Differential diagnosis
    - EBV (mono)
      - Note that heterophile may be falsely positive in acute HIV
    - CMV, toxoplasmosis, rubella, syphilis, hepatitis, disseminated GC
    - Withdrawal syndrome

Frequency of Common Symptoms in Acute HIV Infection

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>280</td>
<td>86</td>
</tr>
<tr>
<td>Malaise</td>
<td>154</td>
<td>74</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>146</td>
<td>70</td>
</tr>
<tr>
<td>Rash</td>
<td>146</td>
<td>70</td>
</tr>
<tr>
<td>Myalgia/myalgie</td>
<td>112</td>
<td>54</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57</td>
<td>22</td>
</tr>
<tr>
<td>Headache</td>
<td>46</td>
<td>22</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>Nightmares</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

Adapted from (No, HT, Stein, DC, Schuiteman, DH, J Infect Dis 1999; 180:1460.)
Primary HIV Infection
Summary

- Suspect in any mono-like illness, esp when only moderately mono-like
- Viral load very high; it is test of choice
- Patients very infectious

Stages of HIV Infection

- Viral transmission
- Primary HIV infection
- Clinical latent period
- *Early symptomatic HIV infection*
- AIDS

Examples of II conditions in early symptomatic HIV infection:

- Oral hairy leukoplakia
- Herpes zoster involving two episodes or more than one dermatome
- Peripheral neuropathy
- Respiratory angioedema
- Cervical dysplasia
- Cervical carcinoma in situ
- Constitutional complaints such as fever (38.5°C) or diarrhea for more than one month
- Idiopathic thrombocytopenic purpura
- Invasive inflammatory disease, especially if complicated by a tuberculosis alveolus

From Google Images 1/15/12

Medscape ©
http://www.medscape.com
Stages of HIV Infection

- Viral transmission
- Primary HIV infection
- Clinical latent period
- Early symptomatic HIV infection
- AIDS

AIDS-Defining Conditions

- Kaposi’s Sarcoma
- Lymphoma (burkitts, immunoablative, brain primary)
- Mycobacterial diseases disseminate or pulmonary TB
- PCP/PJP
- PML
- Salmonella septicemia
- Toxoplasmosis (brain)
- Invasive cervical cancer

HIV Epidemiology & Diagnosis

Summary

- HIV new infections still occurring at more than 40,000 per year in U.S.
- MSM (and substance abuse) main risk for males; heterosexual transmission for females; African-Americans disproportionately affected
- About 10,000 deaths per year in U.S., down from peak of 40,000 before 1995
- Testing
  - Antibody testing: Screen, Western Blot confirmation
  - Combined antibody/p24 antigen test
  - Viral load by PCR
  - CD4 count
- Staging of infection; AIDS case definition

Rationale for ART

- Effective ART w/ virologic suppression improves and preserves immune function in most patients, regardless of baseline CD4 count
  - Earlier ART initiation may result in better immunologic responses and clinical outcomes
    - Reduction in AIDS/ non-AIDS-associated morbidity and mortality
    - Reduction in HIV-associated inflammation/associated complications

Part 2
HIV Treatment

- When to start
- How to start
- The drugs
  - What we now actually use
  - Common side effects
- Genotype, phenotype testing
- How to monitor
- HIV in the elderly
- HIV as a primary care condition
- Pre- and post-exposure prophylaxis
Rationale for ART

**ART strongly indicated for all patients with low CD4 count or symptoms**

- ART can significantly reduce risk of HIV transmission
- Recommended ARV combinations are effective and well tolerated

Potential Benefits of Early Therapy

- Potential decrease in risk of many complications, including:
  - HIV-associated nephropathy
  - Liver disease progression from hepatitis B or C
  - Cardiovascular disease
  - Malignancies (AIDS defining and non-AIDS defining)
  - Neurocognitive decline
  - Blunted immunological response owing to ART initiation at older age
  - Persistent T-cell activation and inflammation

Potential Benefits of Early Therapy: Supporting Data

- CD4 count ≤350 cells/µL or history of AIDS-defining illness:
  - Randomized controlled trial (RCT) data show decreased morbidity and mortality with ART
- CD4 count 350-500 cells/µL:
  - RCT data as well as nonrandomized trials and cohort data support morbidity and perhaps mortality benefit of ART

When to Start ART

- Current recommendation: ART for all

Rating Scheme for Recommendations

- **Strength of recommendation:**
  - A: Strong
  - B: Moderate
  - C: Optional
- **Quality of evidence:**
  - I: ≥1 randomized controlled trials
  - II: ≥1 well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes
  - III: Expert opinion

Recommendations for Initiating ART: CD4 Count or Clinical Category

- Recommended for all CD4 counts:
  - CD4 count <350 cells/µL (AI)
  - CD4 count 350-500 cells/µL (AII)
  - CD4 count >500 cells/µL (BIII)
Rationale for Starting ART at CD4 500

The New England Journal of Medicine
August 27, 2015 vol. 373 no. 9
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection
The INSIGHT START Study Group*

“Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection” NEJM 8/27/15

BACKGROUND
• Data from randomized trials are lacking on the benefits and risks of initiating antiretroviral therapy in patients with asymptomatic human immunodeficiency virus (HIV) infection who have a CD4+ count of more than 350 cells per cubic millimeter.

METHODS
• We randomly assigned HIV-positive adults who had a CD4+ count of more than 500 cells per cubic millimeter to start antiretroviral therapy immediately (immediate-initiation group) or to defer it until the CD4+ count decreased to 350 cells per cubic millimeter or until the development of the acquired immunodeficiency syndrome (AIDS) or another condition that dictated the use of antiretroviral therapy (deferred-initiation group). The primary composite end point was any serious AIDS-related event, serious non–AIDS-related event, or death from any cause.

“Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection” NEJM 8/27/15

CONCLUSIONS
• The initiation of antiretroviral therapy in HIV-positive adults with a CD4+ count of more than 500 cells per cubic millimeter provided net benefits over starting such therapy in patients after the CD4+ count had declined to 350 cells per cubic millimeter.

Recommendations for Initiating ART

ART is recommended for treatment:
• “ART is recommended for all HIV-infected individuals to reduce the risk of disease progression.”
  - The strength of this recommendation varies on the basis of pretreatment CD4 count: stronger at lower CD4 levels (<350 cells/mm3 [A1]; CD4 count 350 to 500 cells/mm3 [AII]; CD4 count >500 cells/mm3 [BIII]).

Consider More-Rapid Initiation of ART

• Pregnancy
• AIDS-defining condition
• Acute opportunistic infection
• Lower CD4 count (eg, <200 cells/µL)
• Acute/recent infection
• Rapid decline in CD4
• Higher viral load (eg, >100,000 copies/mL)
• HIVAN
• HBV coinfection
• HCV coinfection

Potential Concerns about Early Therapy

• ARV-related toxicities
• Nonadherence to ART
• Drug resistance
• Cost
Recommendations for Initiating ART

ART is recommended for prevention:

• “ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV.”

- Strength/ evidence for this recommendation vary by transmission risks: (perinatal transmission (AI); heterosexual transmission (AI); other transmission risk groups (AIII)).

Consider Deferral of ART

• Clinical or personal factors may support deferral of ART
  – If CD4 count is low, deferral should be considered only in unusual situations, and with close follow-up
  – When there are significant barriers to adherence
  – If comorbidities complicate or prohibit ART
  – “Elite controllers” and long-term nonprogressors

How to start?

• One must use at least three active drugs. Studies on fewer so far have not been favorable.
• Before starting rx (indeed, as soon as HIV infection has been diagnosed) obtain genotype study. What’s that?

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)

PI
- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nevirapine (NVP)
- Saquinavir (SQV)
- Tipranavir (TPV)

Integrase Inhibitor (INSTI)
- Dolutegravir (DTG)
- Elvitegravir (EVG)
- Raltegravir (RA)

Fusion Inhibitor
- Enfuvirtide (ENF, T-20)

CCR5 Antagonist
- Maraviroc (MVC)

Pharmacokinetic (PK) booster
- Ritonavir (RTV)
- Cobicistat (COBI)
Drug Resistance Testing:
Recommendations

**Acute HIV infection, regardless of whether treatment is to be started**
To determine if resistant virus was transmitted; guide treatment decisions. If treatment is deferred, consider repeat testing at time of ART initiation. Genotype preferred.

**Chronic HIV infection, at entry into care**
Transmitted drug-resistant virus is common in some areas, is more likely to be detected earlier in the course of HIV infection. If treatment is deferred, consider repeat testing at time of ART initiation. Genotype preferred to phenotype. Consider integrase genotypic resistance assay if integrase inhibitor resistance is a concern.

Selecting Initial ART Regimen:
Factors to Consider

**Patient Characteristics**
- HIV RNA; CD4 count
- HIV resistance test results
- HLA-B*5701 status
- Patient preferences
- Anticipated adherence

**Comorbidities or Other Conditions**
- Cardiovascular disease, hyperlipidemia, renal disease, osteoporosis, psychiatric illness, others
- Pregnancy or pregnancy potential
- Coinfections: HCV, HBV, TB

**Regimen Characteristics**
- Genetic barrier to resistance
- Potential adverse effects
- Drug interactions with other medications
- Convenience (pills #, dosing frequency, fixed-dose combinations, food requirements)
- Cost

Adverse Effects: NRTIs
- All NRTIs:
  - Lactic acidosis and hepatic steatosis (highest incidence with d4T, then ddI and ZDV, lower with TDF, ABC, 3TC, and FTC)
  - Lipodystrophy (higher incidence with d4T)

Adverse Effects: NNRTIs
- All NNRTIs:
  - Rash, including Stevens-Johnson syndrome
  - Hepatotoxicity (especially NVP)
  - Drug-drug interactions

Adverse Effects: PIs
- All PIs:
  - Hyperlipidemia
  - Lipodystrophy
  - Hepatotoxicity
  - GI intolerance
  - Possibility of increased bleeding risk for hemophiliacs
  - Drug-drug interactions
Adverse Effects: Pharmacokinetic Boosters

- **Ritonavir**
  - GI intolerance
  - Hyperlipidemia, hyperglycemia
  - Hepatitis

- **Cobicistat**
  - GI intolerance
  - Increase in serum creatinine

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Substance abuse and HIV

- Dangerous intersect substance abuse/disinhibited behavior & HIV spread: Needle sharing, prostitution, awareness of HIV/Hep C status?
  - Higher rate needle sharing
- DeSouza et al Association of SES and the use of crack cocaine w/unprotected sex in a cohort of MSM in Brazil JAIDS 2002.
  - Significant association (AOR=1.91) unprotected anal sex crack cocaine use

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Higher risk behavior in treated ARV

- Tun et al Increase in sexual high risk behavior associated with immunologic response to HAART in IDU. CID 2004
  - Three fold increase in engaging in high risk sexual behavior after ART initiation
  - Continued risk reduction counseling is important in our ARV treated populations due to persistent misconceptions re transmission on therapy
**Drug interactions: ART & Methadone and Suboxone**

**Methadone:**
- Decreased plasma levels of methadone occur with concurrent administration: ritonavir, efavirenz and nevirapine: must adjust to avoid withdrawal

**Suboxone/ Naltrexone:**
- Monitor LFTS risk of hepatotoxicity especially on ARVS working through liver metabolism (NVP). ATZ can increase Bup and Bup can dec ATZ level

**Disulfuram:**
- Inhibits acetaldehyde dehydrogenase: LFTS

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**HIV ongoing management**

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**What happens long-term?**

- If we’re successful, our patients get older and older.
- They then face distinct challenges.
- Let’s take a look at HIV in the elderly.

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**HIV – The Old**

- Tend to have lower CD4 counts at presentation (Delay in diagnosis)
  - About 50% of those age 50-65 with AIDS dx within 12 mos, compared with about 30% of those age 25-45
- Less rise in CD4
- One-year survival after HIV dx
  - Age less than 30: 97%; 60-64: 81%; 65+: 71%.
- Cumulative no. of AIDS cases in those age 50+ up 7-fold between 1990 and 2005

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**HANA (HIV-Associated Non-AIDS Conditions)**

- Cardiac (Lipids, MI, thrombosis, stroke)
- Bone dis (osteoporosis, avascular necrosis)
- Cancers
- Pulm/ COPD
- Neuro incl periph neuropathy, dementia
- Liver fibrosis, cirrhosis, HCC
- Heme: Anemia, thrombocytopenia
- Decreased renal function incl ESRD

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**HANA – Data**

- VA Study presented CROI March 2011
  - After adjustment, approx 2-fold risk of MI (about same as DM); with decr GFR up almost 5-fold
  - 32% increase in fragility fractures (adjusted: 24%)
  - “VACS Index” with points based on age, CD4, HIV RNA, Hg, FIB-4, eGFR, hep C coinfection
    - Correlates with markers of inflammation (IL-6, CD14, D-dimer)
CVD Risk in HIV-Infected Patients is Beyond That Predicted by Traditional Risk Factors

A number of studies have shown an increased risk (1.3x - 2x) of heart disease in HIV+ patients remains even after controlling for known traditional CVD risk factors.

Cardiovascular Disease Mortality Among HIV-Infected Persons, New York City, 2001-2012

- In HIV individuals, CVD death increased 7%-31% of all deaths (p<0.001)
- Decreased in the general population: 47% to 30%; p<0.001
- HIV associated with a 54% increased rate of CVD death
- Both virologically suppressed HIV patients had higher CVD mortality rates than uninfected individuals until age 65.

"HIV care providers should emphasize preventive measures to reduce CVD risk such as smoking cessation, blood pressure control, and lipid management"

Statin Therapy Reduces Coronary Plaque Volume and Arrests Progression of CIMT in HIV Patients

- Rosuvastatin (10mg/day) vs. placebo, 52-week RCT
- No. of HIV+ pts, median age 46, on statin baseline w/ normal lipid profile, no statin use for ≥6 months
- CIMT: higher in pts with LDL≤130 mg/dL

Few more HIV Hot Topics

- Post-exposure scenarios
  - Health care worker sustains sharps injury from HIV-positive or HIV-unknown source; sexual assault victim; s/p high-risk exposure
  - CDC now recommends Truvada plus raltegravir for just about all cases
  - If details of source known, can be guided by what is known about the virus.
Postexposure px - Continued

- Sexual contact, eg rape victim
  - Very tough situation.
  - Needs individualized care.
  - We often end up giving rx even if statistics suggest low risk (eg if source positive single unprotected receptive vaginal intercourse probability of infection probably about 1:1,000)
- Splash, saliva, urine, etc: Negligible risk.

Results

<table>
<thead>
<tr>
<th>Use of post-exposure prophylaxis by arm:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate TVD: 13 subjects (5%); 15 prescriptions</td>
</tr>
<tr>
<td>Deferred TVD: 83 subjects (31%); 174 prescriptions</td>
</tr>
</tbody>
</table>

PROUD: Pragmatic Open-Label Randomized Trial of Pre-Exposure Prophylaxis

Group | Infections, n | Follow-up (PY) | Incidence/100 person-years (90% CI) |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
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<tr>
<td>Deferred</td>
</tr>
<tr>
<td>Overall</td>
</tr>
</tbody>
</table>

- **86% (90% CI: 58%-96%) Risk Reduction; P=0.0002**
- **Number needed to treat=13 (90% CI: 9-25)**

**Results**: Efficacy*

- 16 subjects infected
  - TVD (incidence: 6.6/100 PY)
  - Placebo (incidence: 6.0/100 PY)
- Mean follow-up=13 months
- Average 16 pills / month
- Number needed to treated: 18 for 1 year to prevent 1 HIV infection

86% (95% CI: 40-99, p<0.002)

Reduction in MSM at high risk of HIV infection who took on-demand PrEP

Adherence to PrEP Surrounding Recent Sexual Intercourse

<table>
<thead>
<tr>
<th>PrEP use, % (min-max)</th>
<th>TVD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct use*</td>
<td>45 (36-57)</td>
<td>40 (22-49)</td>
</tr>
<tr>
<td>Suboptimal use</td>
<td>27 (14-35)</td>
<td>31 (18-44)</td>
</tr>
<tr>
<td>No PrEP</td>
<td>27 (15-37)</td>
<td>29 (24-44)</td>
</tr>
</tbody>
</table>

*At least one pill before and one pill after sex

On demand PrEP was not used as indicated by the protocol for almost 60% of the 1,212 sexual events reported by the 319 participants

Part 2

HIV Treatment: Summary

- Genotype, phenotype testing
- When to start
- Treatment as prevention
- How to start
- The drugs
  - What we now actually use
  - Common side effects
- How to monitor
- HIV in the elderly
- Pre- and post-exposure prophylaxis

Websites to Access the Guidelines

- http://www.aidsetc.org
Hepatitis C HIV Coinfection data

Similar response rates in HCV/HIV co-infected patients compared to HCV mono-infected patients

SVR Rates for Approved Therapies in HCV GT 1 Patients Co-infected with HIV

LDV/SOF x 12 Weeks
SVR12 in HCV Mono-infected and HCV/HIV Co-infected


SOF+RBV 6 mo
PEG 12 mo
PEG+RBV 12 mo
BOC+PEG+RBV 6‐12 mo
TVR+PEG+RBV 6‐12 mo
SMV+PEG+RBV 6‐12 mo
SOF+PEG+RBV 3 mo
PHOTON‐1
LDV/SOF 3 mo
ION‐4, ERADICATE
OMV/PTV/RTV+DSV+RBV 3‐6 mo
TURQUOISE‐1
2015 AASLD/IDSA Guidance: "HIV/HCV co-infection should receive the same treatment as recommended for HCV mono-infected"