Clinical Manifestations and Treatment of HIV

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Director, UCLA Center for Clinical AIDS Research and Education (CARE Center)
The Natural History of HIV Infection

Clinical Manifestations of HIV

- Early signs and symptoms
- Oral manifestations
- Malignancies
- Opportunistic Infections
- Neuro-psychiatric illnesses
- Women and HIV

= Not in today’s presentation,
Signs and Symptoms
CDC Stage of HIV Disease

- Stage I: Acute HIV infection
- Stage II: Asymptomatic HIV
- Stage III: Early Symptomatic HIV
- Stage IV: Late Symptomatic HIV
  - A: Constitutional Disease
  - B: Neurological Disease
  - C: Secondary Infections
    - C1: AIDS defining
    - C2: Other infections
  - D: Secondary Cancers
  - E: Other Conditions
# Acute Retroviral Syndrome

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>96%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>74%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>70%</td>
</tr>
<tr>
<td>Rash</td>
<td>70%</td>
</tr>
<tr>
<td>Myalgia/Arthraligia</td>
<td>54%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32%</td>
</tr>
<tr>
<td>Headaches</td>
<td>32%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>27%</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>14%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>13%</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>12%</td>
</tr>
</tbody>
</table>
Clinical Findings Associated with Early HIV Disease

- Generalized lymphadenopathy
- Oral thrush
- Hairy leukoplakia
- Herpes-zoster virus infection
- Dermatitis/seborrhea
- Recurrent vaginitis
Symptomatic HIV Infection in Children: CDC Class P-2A

Nonspecific Findings

- Fever
- Failure to thrive
- Weight loss of more than 10% of baseline
- Hepatomegaly
- Splenomegaly
- Generalized lymphadenopathy
- Parotitis*
- Persistent or recurrent diarrhea

* More common in children than in adults.
Symptomatic HIV Infection in Children: CDC Class P-2B

Progressive Neurologic Disease

- Loss of developmental milestones or intellectual ability
- Impaired brain growth
- Progressive symmetric motor deficits (2 or more of the following)
  - Paresis
  - Abnormal tone
  - Pathologic reflexes
  - Ataxia
  - Gait disturbance
Oral Manifestations of HIV
<table>
<thead>
<tr>
<th>Stage</th>
<th>Adults and Adolescents (&gt;15 yo)</th>
<th>Children &lt; 15 yo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No disease</td>
<td>No disease</td>
</tr>
<tr>
<td>2</td>
<td>Angular cheilitis</td>
<td>Angular Cheilitis</td>
</tr>
<tr>
<td></td>
<td>Recurrent oral ulceration</td>
<td>Linear gingival erythema, extensive warts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent oral ulcerations, parotid enlarge</td>
</tr>
<tr>
<td>3</td>
<td>Persistent oral candidiasis</td>
<td>Persistent oral candidiasis (after 8ws)</td>
</tr>
<tr>
<td></td>
<td>Oral hairy leukoplakia</td>
<td>Oral hairy leukoplakia</td>
</tr>
<tr>
<td></td>
<td>Acute necrotizing ulcerative stomatitis, gingivitis, periodontitis</td>
<td>Acute necrotizing ulcerative gingivitis or periodontitis</td>
</tr>
<tr>
<td>4</td>
<td>Chronic (&gt;1 mo) orolabial HSV</td>
<td>Chronic (&gt;1 mo) orolabial HSV</td>
</tr>
<tr>
<td></td>
<td>Kaposi’s sarcoma</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
</tbody>
</table>

HIV-related Oral Lesions

- **Infections**
  - Fungal, Viral, Bacterial

- **Neoplasms**
  - Kaposi’s Sarcoma, Non-Hodgkin’s Lymphoma

- **Other**
  - Aphthous-like Ulcers, Lichenoid or Drug Reactions, Salivary Gland Disease
### Oral Candidiasis

#### Clinical Types

<table>
<thead>
<tr>
<th>Erythematous Cheilitis</th>
<th>Pseudomembranous</th>
<th>Angular</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Erythematous Cheilitis" /></td>
<td><img src="image2.png" alt="Pseudomembranous" /></td>
<td><img src="image3.png" alt="Angular" /></td>
</tr>
</tbody>
</table>
Hairy Leukoplakia

• Treatment and Management:
  – Generally does not require treatment
  – Antiviral treatment and topical podophyllum resin have been used to treat -- the result is temporary
  – May wax and wane without treatment
Oral Ulcers

- Herpes simplex infection
- Cytomegalovirus infection
- Aphthous ulcers
- Histoplasmosis
- HPV lesions
- Lymphoma
- Necrotizing ulcerative gingivitis (NUG)
- Necrotizing ulcerative periodontitis (NUP)
- Necrotizing stomatitis (NS)
Aphthous Lesions
Clinical Types

Minor (Lip)
Minor (Tongue)
Major
Oral Aphthous Lesions
Treatment Options

• **Topical Therapy**
  - Topical Corticosteroids

• **Intralesional**
  - Triamcinolone: 40 mg /ml (0.5 ml-1.0 ml injected bid)

• **Systemic Therapy**
  - Prednisone: 0.5-1.0 mg/kg qd x 7-10d, then taper
  - Thalidomide: 200 mg PO qd
Lesions Caused By Human Papilloma Virus (HPV)

- Appearance: exophytic, papillary, oral mucosal lesions
- Several different types of HPV have been reported to cause lesions
- May be multiple
- Often difficult to treat due to a high risk of recurrence
Kaposi’s Sarcoma

- **Appearance**: Oral lesions appear as reddish purple, raised or flat
- **Size**: Ranges from small to extensive
- **Behavior**: Behavior is unpredictable
- **Definitive diagnosis**: Biopsy and histologic examination
- **No curative therapy**: Antiretroviral therapy, radiation treatment, chemotherapy and sclerosing agents have been used to control oral lesions
Cancers in HIV

Shiels M S et al. J Natl Cancer Inst 2011;103:753-762
Categorizing Cancers in PWHA

- **AIDS Defining Cancer** (decreasing)
  - KS
  - NHL (BL, CNS, DLCBL)
  - Cervical Cancer (added in 1993)

- **Non AIDS defining Cancers** (increasing)
  - Anal Cancer
  - Lung Cancer
  - Hodgkin Lymphoma
  - Liver Cancer

- **Elevated risk but rare**
  - Merkel Carcinoma
  - Leiomyosarcoma
  - Salivary gland LEC

- **Unchanged risk**
  - Breast
  - Colorectal
  - Prostate
  - Follicular lymphoma
## Cancers in HIV Disease

<table>
<thead>
<tr>
<th><strong>AIDS-Defining</strong></th>
<th><strong>Virus</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi’s Sarcoma</td>
<td>HHV-8</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma (systemic and CNS)</td>
<td>EBV, HHV-8</td>
</tr>
<tr>
<td>Invasive Cervical Carcinoma</td>
<td>HPV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Non-AIDS Defining</strong></th>
<th><strong>Virus</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal Cancer</td>
<td>HPV</td>
</tr>
<tr>
<td>Hodgkin’s Disease</td>
<td>EBV</td>
</tr>
<tr>
<td>Leiomyosarcoma (pediatric)</td>
<td>EBV</td>
</tr>
<tr>
<td>Squamous Carcinoma (oral)</td>
<td>HPV</td>
</tr>
<tr>
<td>Merkel cell Carcinoma</td>
<td>MCV</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>HBV, HCV</td>
</tr>
</tbody>
</table>
Breakdown of causes of death: France 2005

- AIDS
- Cancer
- Hepatitis C
- CVD
- Suicide
- Non-AIDS infection
- Accident
- Hepatitis B
- Liver disease
- OD / drug abuse
- Neurologic
- Renal
- Pulmonary
- Digestive
- Iatrogenic
- Metabolic
- Psychiatric
- Other
- Unknown

N = 937 deaths

Hessamfar-Bonarek Int. J. Epid 2010;39:135-146
Lewden JAIDS 2008, 48:590-9
Non-AIDS Defining Cancers
NADC
## Non AIDS-defining Cancers

### Emerging Epidemiologic Features

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Proportion of Cancers in HIV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NADC</td>
<td>31%</td>
<td>58%</td>
</tr>
<tr>
<td><strong>Standardized Incidence Ratio HIV:non-HIV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>2.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Larynx</td>
<td>1.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Anus</td>
<td>10</td>
<td>9.1</td>
</tr>
<tr>
<td>Liver</td>
<td>0</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Factors Contributing to the Increase in Cancer cases in HIV

- 4-fold increase in HIV/AIDS Population
- Greater and earlier start to smoking in HIV
- Rising proportion of HIV pts > 50 yo
- Cancer incidence increases with age
- Increase in some CA incidence rate among HIV
  - Lung (3X), anal (29X), liver (3X), HL (11X)
  - Suggests may be additional risk from HIV
NADC Incidence and Mortality

- Retrospective survey of Kaiser Permanente, N. and S. California; 22,081 HIV+, 230,069 HIV- matched by age, sex, clinic and initial yr of F/U
- 5-yr survival for incident prostate, anal, lung, colorectal cancers or Hodgkin lymphoma. All cause mortality rates and mortality hazard ratios
- Earlier mean age at dx in HIV+ for anal, lung and colorectal, but not for prostate or HL
- HIV+ dx at higher stage for lung and HL
- HIV+ reduced survival for HL, lung and prostate, but not for anal and colorectal

NADC Mortality HIV+ vs HIV-

Hodgkin Lymphoma
HR 3.0 (1.3-10.8)

Lung
1.7 (1.3-2.2)

Prostate
2.2 (1.2-4.3)

Anal
1.7 (0.6-5.4)

Colorectal
1.6 (0.8-3.1)

Pathogenesis of Cancer in HIV

- Many are virally-induced cancers, but not all
- Immune activation, inflammation and decreased immune surveillance
- HIV may activate cellular genes or proto-oncogenes or inhibit tumor suppressor genes
- HIV induces genetic instability (e.g. 6 fold higher number of MA in HIV lung CA over non-HIV)¹
- Increase susceptibility to effects of carcinogens
- Endothelial abnormalities may allow for cancer development
- Population differences based on genetics and exposure to carcinogens

Lymphomas
Pathology of AIDS-Related Non-Hodgkin’s Lymphoma

- Small noncleaved-cell lymphoma
  - Burkitt’s lymphoma and Burkitt-like lymphoma
- Immunoblastic lymphoma (primary CNS)
- Diffuse large-cell lymphoma (90% CD20+)
  - Large noncleaved-cell lymphoma
  - CD30+ anaplastic large B-cell lymphoma
- Plasmablastic lymphoma
- Advanced stage (>75% III or IV)
- Extranodal involvement
  - Central nervous system, liver, bone marrow, gastrointestinal

AIDS-related Lymphoma Experience Suggests Cancer Treatment Outcome Can be Equivalent to General Population

Little et al Blood. 2003; 101: 4653-4659
Sparano et al. Blood, 2010;115:3008-16
Cancer Screening in HIV
ACS, NCI and USPSTF Cancer Screening Guidelines

- **Cervical CA** – begin within 3 yrs of 1st intercourse or 21 yo and q 1-2 yrs. If 30-70 and 3 normal Paps q3 yrs
- **Prostate CA** – discuss with MD at 50. DRE yearly and individualized PSA testing
- **Breast CA** – clinical breast exam q 3 yr 20-30, yearly at 40, yearly mammogram start age 50
- **Colon CA** – flex sig q 5yrs or colon q 10 yrs and FOBT yearly
- **Others** – periodic health exams after age 20, with health counseling and oral, skin, lymph nodes, testes, ovaries and thyroid exam
- **Other tests** based on family history, other known cancer risk exposures or known risk factors
HIV Patient Screening

• Routine screening for HIV patients seems to be done LESS frequently than age-appropriate SOC screening for breast (67% vs 79%) and colon (56% vs 77.8%) and prostate biopsies
  – Reinhold JP. Am J Gastroenterol 2005;100:1805-12

• Concerns about higher false positive rate in HIV (eg, NLST found reduction in lung cancer mortality (20%) in older cigarette smokers with CT) but also high false positive rates, which may be true in HIV as well
Why is anogenital cancer important?

- Cervical cancer is the most common cancer in women worldwide and anal cancer is as common in MSM (75/100,000) as cervical cancer in unscreened populations of women (50-150/100,000 person-yr)
- Anal cancer particularly common in HIV+ MSM
- Anal cancer occurs in women as well
- Anal cancer is one of several cancers whose incidence in the HAART era is increasing, not decreasing
Screening for cervical and anal dysplasia

- No USA national or international guideline for anal screening other than NYS DOH anal Pap screening guidelines.
- Many HIV groups recommend yearly cervical and anal PAP, with colposcopy and/or HRA and biopsy of any suspicious lesions and q 6m F/U for those with abnormalities noted.
- Many cervical cancer screen and treat program now operating in resource-limited settings.

Goldie SJ et al. JAMA 1999;282:1822-9
Cancer Prevention

- Smoking Cessation – Highest priority
  - Varenicline not hepatic met and no ART drug interaction expected
- Hepatitis B and HPV vaccination
- Treat active Hepatitis C
- Yearly cervical and anal Paps – Gyn and HRA
- Advise sun screen and avoid overexposure
- Maintain high index of suspicion for cancer
- Complete family history for malignancies
- Breast, prostate and colon screening as per guidelines for general population
- CT Lung and liver ultrasound controversial
- Treat all HIV patients with HAART
Summary

- As HIV population ages with persistent immune abnormalities, cancers will increase in number.
- The risk of NADC is high with lung, anal, liver and HL accounting for most of this increase. The risk of colon, breast and prostate cancers not elevated in HIV. HL occurs at older age, but may reflect lack of younger age peak, as all cases in HIV are EBV+
- As a minimum, we should conduct age/gender appropriate screening for cancer. Counsel patients on ways to reduce cancer risks.
- Only through prospective clinical trials research can prevention strategies and new treatments be effectively evaluated.
Thank You

• For information on AMC clinical trials see: http://www.aidsccancer.org

• For information on NCI programs in HIV cancer see: http://www.cancer.gov/cancertopics/types/AIDS

• To refer for AMC clinical trials in LA, call UCLA CARE Center 310-557-1891 ask for Maricela Gonzalez or page/email Dr. Mitsuyasu, 310-825-6301.
Use of Antiretroviral Therapy
Overview

- Benefits and limitations of HAART
- When to start
- What to start with
- Simplified drug regimens and treatment adherence
- When to change therapy
- Second line therapies
Benefits of ART

- Prevention of mother to child transmission
- Post exposure prophylaxis (PEP)
- Secondary prevention of HIV transmission
- Primary prevention (PrEP)
- Clinical management of patients with HIV
  - Reduces HIV replication
  - Increase or maintain CD4 numbers
  - Maintain “less fit” mutated HIV
Current antiretroviral targets

- **Fusion Inhibitor**
  - Enfuvirtide

- **Reverse transcriptase Inhibitors**
  - ZDV, ddl, ddC, d4T, 3TC, ABC, TDF, FTC

- **Entry Inhibitors**
  - CCR5, MRV

- **Viral protease Inhibitors**
  - SQV, RTV, IDV, NFV, APV, LPV, FOS, ATZ, TPV, DRV

- **Integrase Inhibitors**
  - Raltegravir, Elvitegravir

- **Proviruses**
  - DNA

- **RNA**
  - RT
  - Proteins
Antiretroviral Drugs 2013

**Reverse Transcriptase Inhibitors (13)**

Nucleoside analogues
- zidovudine (AZT, ZDV)
- didanosine (ddI)
- zalcitabine (ddC)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)

Nucleotide analogue
- tenofovir (TFV)

Non-nucleoside analogues
- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETV)
- rilpivirine (RPV)

**Protease Inhibitors (10)**

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- amprenavir (APV)
- lopinavir/r (LPV/r)
- fosamprenavir (FPV)
- atazanavir (ATV)
- tipranavir (TPV)
- darunavir (DRV)
- dolutegravir (DTG)

**Integrase Inhibitor (2)**
- raltegravir (RAL)
- elvitegravir (ELV)

**Fusion Inhibitor**
- fuzeon (T20)

**Entry Inhibitor (CCR5)**
- maraviroc (MVC)
Overview

- Benefits and limitations of HAART
- **When to start**
- What to start with
- Simplified drug regimens and treatment adherence
- **When to change therapy**
- Second line therapies
Case

- 47 yo Black Male
- Diagnosed on routine insurance examination
- PMHx remarkable for HTN, diet controlled
- No AIDS associated diseases or symptoms
- No medications
- Understands treatment issues and wants to begin therapy if you think it is appropriate
- Has insurance that can pay for his meds
If his viral load is 30,000 c/ml, at which CD4 count would you recommend starting therapy?

1. Would treat at any CD4 count
2. 750 cells / ul
3. 500 cells / ul
4. 350 cells / ul
5. 250 cells / ul
6. < 200 cells / ul
7. < 50 cells / ul
8. Would not recommend ART
When to Start Therapy: Balance Tipping in Favor of Earlier Initiation

- Drug toxicity
- Preservation of limited Rx options
- Cost

- Potency, durability, simplicity and safety of current regimens
- Improved formulations and PK
- New classes of drugs
- Excess morbidity/mortality at higher CD4

Delayed CD4 Earlier
Reasons to Start Early

- The Biology
- Association of Inflammation and Disease
- Better Tolerated/Easier to Take Medications
- Randomized Controlled Trial Data
- Cohort Data
- Irreversible Damage
- Public Health
HIV Infected Cells

Uninfected Resting CD4+ Lymphocytes

Uninfected Activated CD4+ Lymphocytes

Latently Infected CD4+ Lymphocytes

HIV virions

Antiretroviral Rx

Uninfected Activated CD4+ Lymphocytes

Uninfected Resting CD4+ Lymphocytes

M Saag, UAB
Opportunistic Infections Occur at Higher CD4+ Cell Count Strata

Podlekareva et al. J Infect Dis 2006;194:633
When to start?:
ART Cohort Collaboration

- Modeled data
- 10,855 patients included, with >61,000 person-years of F/U (median 2.7 yrs)
- 934 progressed to AIDS or died
- IDUs excluded from model

### Delayed Initiation of ART and Increased Risk of Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>CD4+ count 351-500 cells/ml</th>
<th>CD4+ count &gt;500 cells/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk</td>
<td>P</td>
</tr>
<tr>
<td>ART deferral</td>
<td>1.6 (1.2-2.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.9 (1.7-2.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Older age (10yr)</td>
<td>1.9 (1.7-2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline CD4+ (100 cell increment)</td>
<td>0.7 (0.6-1.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline HIV RNA (log 10 increment)</td>
<td>1.1 (1.0-1.3)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Kitahata et al, New Eng J Med 2009;360:1815 (adapted)
**Cumulative Mortality Estimates**

Calculated Using Extended Kaplan-Meier Survival Estimates

- **CD4 > 500 & Defer HAART**
  - \((N=6,539)\)

- **CD4 > 500 & Initiate HAART**
  - \((N=2,616)\)

Most New Infections Transmitted by Persons who Do Not Know Their Status

- 25% Unaware of Infection
- 75% Aware of Infection

account for...

- 54% New Infections
- 46% of New Infections

Source: G. Marks et al. AIDS 2006
HPTN 052

1763 HIV discordant couples (HIV+ partner CD4 350-550)

886 immediate HAART

877 delayed HAART (CD4 250)

All receiving HIV prevention services

1 transmission* & 3 cases of extrapulmonary TB

27 transmissions* & 17 cases of extrapulmonary TB

*96% reduction in HIV transmission to HIV-negative partner median follow-up 2 years

Reasons to Start Early

• The Biology
• Association of Inflammation and Disease
• Better Tolerated Medications Today
• Randomized Controlled Trial Data
• Cohort Data
• Public Health
• Common Sense!
Relative Time on Treatment...

CD4 650/ul
40 years on Rx

CD4 500/ul
35 years on Rx

5 years

HARM?
So ....what is the harm?

- Destruction of Lymphoid Tissue
- Inflammation
- Increased Cardiovascular Events
- Increased incidence of certain malignancies
- Accelerated ‘Aging’
- Accelerated Cognitive Decline
Conclusions

- Balance of data support starting Rx in ~ all individuals regardless of CD4+ T cell counts
  - Understanding of HIV pathogenesis
  - Cohort data
  - Public health implications
  - No randomized clinical trial data for higher CD4 counts > 500 yet (START study is enrolling)

- Waiting until RCT data could well lead to harm that likely will not be reversible
When to Start Treatment

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4 Count (cells/mm³)</th>
<th>HIV RNA (copies/mL)</th>
<th>2/13/13 DHHS Guidelines</th>
<th>2012 IAS-USA Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness or severe symptoms</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt;500</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td></td>
<td>&gt;500</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>HIV-associated nephropathy</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>HIV/HBV coinfection when HBV treatment is indicated</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
</tbody>
</table>

*Unless elite controller (HIV RNA <50 copies/mL) or has stable CD4 cell count and low-level viremia in absence of therapy.

The IAS-USA guidelines also recommends initiating antiretroviral therapy in HIV-infected patients with active hepatitis C virus infection, active or high risk for cardiovascular disease, and symptomatic primary HIV infection.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>CD4 &lt; 350</th>
<th>CD4 350-500</th>
<th>CD4 &gt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>British HIVA</td>
<td>treat</td>
<td>Consider unless: HBV or HCV, High CV risk, HIVAN, pregnant-then treat</td>
<td>Unknown</td>
</tr>
<tr>
<td><a href="http://www.bhiva.org">www.bhiva.org</a></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>September, 2012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European ACS</td>
<td>treat</td>
<td>Consider unless: HCV, HIVAN, HBV needing Tx; CD4 decline &gt;50-100/yr, pregnant – Treat</td>
<td>Unknown</td>
</tr>
<tr>
<td><a href="http://www.eacs.eu/guide">www.eacs.eu/guide</a></td>
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<td>November, 2012</td>
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<tr>
<td>IAS-USA:</td>
<td>treat</td>
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<td><a href="http://www.iasusa.org">www.iasusa.org</a></td>
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<td>July, 2012</td>
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<td>DHHS:</td>
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<td><a href="http://www.aidsinfo.nih.gov">www.aidsinfo.nih.gov</a></td>
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When to Start Therapy: Balance Tipping in Favor of Earlier Initiation

• Drug toxicity
• Preservation of limited Rx options
• Cost

• Potency, durability, simplicity and safety of current regimens
• Improved formulations and PK
• Enhanced adherence
• Diminished emergence of resistance
• New classes of drugs
• Excess morbidity/mortality at higher CD4 < 350

Everyone?
Overview

- Changing epidemiology of AIDS in the United States
- Benefits and limitations of HAART
- When to start
- **What to start with**
  - Simplified drug regimens and treatment adherence
  - Second line therapy
Factors to consider in choosing first-line therapy

- Patient’s willingness to commit to therapy
- Baseline resistance
- Efficacy data
- Tolerability
- Convenience
- Comorbid conditions
- Consequences of failure (resistance)
- Since the introduction of potent ARV therapy preferred regimens all include NRTIs + third drug
DHHS Guidelines for Adolescents/Adults: What to Start

| Preferred Regimens | • EFV/TDF/FTC  
|                    | • ATV/r + TDF/FTC  
|                    | • DRV/r (once daily) + TDF/FTC  
|                    | • RAL + TDF/FTC  
|                    | [Pregnant Women Only: LPV/r (twice daily) + ZDV/3TC] |

| Alternative Regimens | • EFV + ABC/3TC  
|                      | • RPV + (TDF or ABC)/(FTC or 3TC)  
|                      | • ATV/r or DRV/r + ABC/3TC  
|                      | • FPV/r or LPV/r (qd or bid) ABC/3TC or TDF/FTC  
|                      | • RAL + ABC/3TC  
|                      | • EVG/COBI/TDF/FTC (9/18/12) |

| Acceptable Regimens | • EFV or RPV + ZDV/3TC  
|                     | • NVP + TDF/FTC or ZDV/3TC or ABC/3TC  
|                     | • ATV + (ABC or ZDV)/3TC  
|                     | • ATV/r, DRV/r, LPV/r, FPV/r, RAL + ZDV/3TC  
|                     | • MVC + ZDV or ABC/3TC  
|                     | • SQV/r + TDF/FTC or ABC/3TC or ZDV/3TC (with caution) |

Boosted-Protease Inhibitors

KLEAN\textsuperscript{1} (ITT-E, TLOVR) 48 weeks

ARTEMIS\textsuperscript{2} (ITT, TLOVR) 96 weeks

CASTLE\textsuperscript{3} (ITT, NC=F) 96 weeks

ATV/r vs. EFV

Primary Endpoint

Pooled* ECHO and THRIVE W48 analysis: VL <50 copies/mL over 48 weeks (ITT-TLOVR)

- Each of the trials reached their primary objective of non-inferiority of RPV to EFV in confirmed virologic response†

CI = confidence interval; *Pooled analyses were preplanned
†Difference (95% CI) in response rates estimated by logistic regression adjusted for stratification factors: 1.6 (–2.2, 5.3)

Cohen JAIDS 2012
STARTMRK: RAL vs. EFV

ITT, NC=F

Number of Contributing Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Patients</th>
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<tbody>
<tr>
<td>Raltegravir 400 mg BID</td>
<td>281 278 279 280 281 281 277 280 281 281 277 281 279</td>
</tr>
<tr>
<td>Efavirenz 770 mg QHS</td>
<td>282 282 282 281 282 282 281 281 282 282 282 279</td>
</tr>
</tbody>
</table>

CD4 Change: RAL +374 vs. EFV +312

Elvitegravir/Cobicistat/FTC/TDF (Quad) vs. EFV/FTC/TDF (Study 236-102)

Primary Endpoint: Proportion with HIV-1 RNA < 50 copies/mL at Week 48
• FDA snapshot analysis (ITT), 12% non-inferiority margin

Treatment-Naïve
Any CD4 count
• Randomized 1:1
• Stratification by HIV-1 RNA (>100,000 c/mL)

n=350
Quad QD
EFV/FTC/TDF QHS
Placebo

n=350
EFV/FTC/TDF QHS
Quad Placebo QD

Week 48
Week 192

Study 236-102: Primary Endpoint: HIV-1 RNA < 50 copies/mL

Virologic Success: 88% (Quad) vs. 84% (EFV/FTC/TDF)

Virologic Non-Suppression: 7% (Quad) vs. 7% (EFV/FTC/TDF)

No W48 Data: 5% (Quad) vs. 9% (EFV/FTC/TDF)

CD4+ change: Quad +239 vs. EFV +206 c/mm³ (p=0.009)

+3.6%, 95% CI 3.6 (-1.6% to +8.8%)

Elvitegravir/Cobicistat/FTC/TDF (Quad) vs. ATV/r + FTC/TDF (Study 236-103)

Multicenter, international, randomized, blinded 192-week study

ART-naïve subjects
HIV RNA >5,000 c/mL
eGFR ≥ 70ml/min
(N = 708)

Stratification by
HIV RNA (> or ≤100,000 c/mL)

Quad QD

ATV/r + FTC/TDF Placebo QD

ATV/r + FTC/TDF QD

Quad Placebo QD

Baseline: HIV RNA >100,000 c/mL 40-43%
CD4 Count 364-375 cells/mm³

Primary Endpoint: Proportion with HIV-1 RNA < 50 c/mL at Week 48
– FDA snapshot analysis, 12% non-inferiority margin

DeJesus E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 627.
Study 236-103: HIV-1 RNA < 50 c/mL Through Week 48

Percent with HIV RNA < 50 c/mL (ITT, M=F)

**DeJesus E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 627.**
## Comparisons of First Line Regimens

<table>
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<tr>
<th>Anchor Drug</th>
<th>Anchor Drug</th>
<th>Result</th>
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<tr>
<td>Efavirenz</td>
<td>Lopinavir/r</td>
<td>Superior</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>ATV/r</td>
<td>Tied</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>RAL</td>
<td>Tied</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rilpivirine</td>
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<tr>
<td>Efavirenz</td>
<td>Maraviroc</td>
<td>Superior</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Elvitegravir/cobisistat</td>
<td>Tied</td>
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</table>
A5202: Study Design

HIV-1 RNA ≥1000 c/mL
Any CD4+ count ≥ 16 years of age

ART naïve
1857 enrolled
Randomized 1:1:1:1

Stratified by screening HIV-1 RNA (< or ≥ 100,000 c/mL)

Enrolled 2005-2007
Followed through Sept 2009, 96 wks after last pt enrolled

Randomized 1:1:1:1

- TDF/FTC QD
  - ABC/3TC Placebo QD
  - EFV QD
- ABC/3TC QD
  - TDF/FTC Placebo QD
  - EFV QD
- TDF/FTC QD
  - ABC/3TC Placebo QD
  - ATV/r QD
- ABC/3TC QD
  - TDF/FTC Placebo QD
  - ATV/r QD
A5202: Time to Virologic Failure in Patients with HIV RNA >100,000 c/mL

**Probability of No Virologic Failure**

- **TDF-FTC (26 events)**
- **ABC-3TC (57 events)**

P<0.001, log-rank test
Hazard ratio, 2.33 (95% CI, 1.46-3.72)

<table>
<thead>
<tr>
<th>Weeks since Randomization</th>
<th>ABC-3TC</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No. at Risk</td>
</tr>
<tr>
<td>12</td>
<td>363</td>
</tr>
<tr>
<td>24</td>
<td>313</td>
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<tr>
<td>36</td>
<td>267</td>
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<tr>
<td>96</td>
<td>49</td>
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<tr>
<td>108</td>
<td>20</td>
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</table>

<table>
<thead>
<tr>
<th>weeks since Randomization</th>
<th>TDF-FTC</th>
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<tbody>
<tr>
<td>12</td>
<td>361</td>
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<tr>
<td>24</td>
<td>321</td>
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<tr>
<td>36</td>
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<td>84</td>
<td>104</td>
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<td>96</td>
<td>65</td>
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<tr>
<td>108</td>
<td>23</td>
</tr>
</tbody>
</table>

ABC/3TC vs. TDF/FTC
Low Viral Load Stratum

Concerns regarding NRTIs

• For individuals with higher viral loads (e.g. >100,000 c/ml) TDF/FTC superior to ABC/3TC
• Conflicting results regarding relationship between ABC and CV events
• TDF-associated with greater decline in bone mineral density
• TDF-associated with variable decline in renal function
• Given rise to preferred regimens of TDF/FTC with ABC/3TC as alternative
What Not to Use

Guidelines: IAS-USA\textsuperscript{1}, WHO\textsuperscript{2}, DHHS\textsuperscript{3}

- Any mono- or dual-therapy combo
- AZT + 3TC + ABV + FTC (first line)
- Nelfinavir (first line)
- ddl + TDF
- ddl + d4T
- AZT + d4T
- ATZ + IDV
- SQV or DRV or TPV unboosted
- RIT (full dose therapy)
- EFV in pregnancy
- Nevirapine in naïve women CD4>250 or men >400
- Etravirine with unboosted PI or with ATZ/r, FOS/r, TPV/r

\textsuperscript{1}Thompson, et al. \textit{JAMA} 2010;304:32; \textsuperscript{2}Available at: www.UNAIDS.org;
\textsuperscript{3}Available at: \url{http://aidsinfo.nih.gov/Default.aspx}. Revision March 27, 2012.
Side Effects and Toxicities
Patients Don’t Like Surprises: Short-Term Side Effects to Discuss Before Starting Therapy

- **NNRTIs**
  - Efavirenz: neuropsychiatric side effects, rash
  - Nevirapine: hepatotoxicity, rash

- **PIs**
  - Gastrointestinal toxicity
  - Atazanavir: jaundice and scleral icterus

- **NRTIs**
  - Zidovudine: nausea, anemia, fatigue
  - Didanosine: gastrointestinal toxicity, neuropathy, pancreatitis
  - Stavudine: neuropathy, pancreatitis
HAART: Long-Term Complications

Dyslipidemia/CHD

Hepatotoxicity

Abnormalities of Body Composition
Overview

- Changing epidemiology of AIDS in the United States
- Benefits and limitations of HAART
- When to start
- What to start with
- **Simplified drug regimens and treatment adherence**
- When to change therapy
- Second line therapies
The Move Toward Simpler 3-Drug Regimens

1996

- Didanosine + stavudine + saquinavir
  - 24 pills/dose, 5 doses
  - Saquinavir: 6 q8h with fatty food
  - Didanosine: 2 bid ½ hour ac or 2 hours pc
  - Stavudine: 1 pill bid

2006

- Emtricitabine/tenofovir DF + efavirenz (Atripla)
  - 1 pills qd
  - No food restrictions
One pill, once a day ART

- EFV + TDF + FTC (Atripla)
- RPV + TDF + FTC (Complera)
- EVG + TDF + FTC + COBI (Stribild)
- NVP + d4T + 3TC (not available in west)
Overview

• Changing epidemiology of AIDS in United States
• Benefits and limitations of HAART
• When to start
• What to start with
• Simplified drug regimens and treatment adherence

• **When to change therapy**
• Second line therapies
When to Change Therapy?

Virologic failure
- <0.5-0.75 log reduction in HIV RNA by 4 weeks or <1.0 log reduction by 8 weeks
- Failure to suppress HIV RNA BLD by 3 months
- Repeated detection of HIV RNA after suppression BLD

Immunologic failure
- Persistently declining CD4 cell counts

Clinical failure
- Clinical deterioration or disease progression
Why Do Treatment Fail Patients?

- Poor adherence
- Baseline resistance or cross-resistance
- Use of less potent antiretroviral regimens
- Sequential mono- or dual-therapy
- Drug levels and drug interactions
- Tissue reservoir penetration
- Other, unknown reasons
Long-Term Risk of Developing Drug Resistance

- Risk of developing antiretroviral drug resistance from UK CHIC Study (n=4306)
  - Longitudinal cohort from 6 clinics in London
  - Started antiretroviral therapy with 2 NRTIs plus a third agent
- Overall risk of treatment failure
  - 38% over 6 years
- Risk of accumulating resistance mutations to any drug
  - 27% overall

Overview

- Changing Epidemiology of AIDS in the United States
- Benefits and limitations of HAART
- When to start
- What to start with
- Simplified drug regimens and treatment adherence
- When to change therapy
- Second line therapies
Strategic Therapy Considerations for the Treatment-Experienced Patient

- HIV drug resistance testing
  - Optimize available treatment options
- Pharmacokinetic enhancement
  - PK-boosting regimens (ritonavir or cobicistat)
- Availability of new drugs (and drug classes)
  - Combine as many new drugs as possible
  - Utilize new agents with favorable resistance profiles
- Maintenance of reduced viral fitness (less critical now)
  - Example: adding lamivudine/emtricitabine or abacavir to maintain M184V mutation
Treatment Goals and Challenges

Treatment Experienced Patient

• All patients
  – Zero tolerance for virologic failure ( > 2 VL detectable)
  – At least 2 fully active agents
    • Do we always need 3 fully active agents
      – A boosted PI plus TDF/FTC enough if no TDF resistance
    • There is a balance between complexity of the second regimen with including 3 fully active agents
  – High bar for safety in treatment experienced patients
Drug Resistance Testing: Caveats

- Resistance tests are most accurate in assessing resistance to the current regimen.
- Absence of resistance to a previously used drug does not rule out archived resistant virus that might emerge after re-initiation of that drug.
- Reduced potency should be expected from recycled drugs.
New Paradigm in Therapy

- Complete suppression of plasma HIV-1 RNA should be the goal in all patients with HIV given the availability of new drugs.
- Maximize virus suppression while minimizing drug toxicity.
- For those who do not tolerate new agents, goal should be to maintain CD4 count as high as possible.
- Second line therapy should be chosen on the basis of resistance testing, treatment history, tolerability.
“Long-term strategic anti-HIV therapy is similar to a chess game against a vastly superior opponent, in which the objective is to avoid checkmate and remain on the board after 20 years”

DD Richman, Science 1993
Clinical Manifestations and Treatment of HIV

Questions

Ronald Mitsuyasu, MD
Professor of Medicine
Director, UCLA Center for Clinical AIDS Research
University of California, Los Angeles