Update on Antiretroviral Treatment for HIV Infection 2008

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Acknowledgements:
- CDC HIV Mortality Slides
- AETC NRC Antiretroviral Treatment Adults and Adolescents
Learning Objectives

- Participants should be able to summarize the indications for antiretroviral therapy for HIV infection according to 2008 guidelines.
- Participants should be aware of factors influencing choice of antiretroviral regimen for an individual patient.
- Participants should be able to list the goals of antiretroviral therapy for HIV infection.
- Participants should be able to discuss the potential benefits and risks of earlier initiation of HAART for HIV infection.
- Participants should be able to identify emerging issues in the treatment of HIV infected persons.
Outline

- Review Status of Global HIV Epidemic
- Impact of Antiretroviral Therapy on HIV morbidity/mortality
- 2008 HIV Treatment Guidelines
- Important considerations in ART
- Goals of ART for HIV Infection
- Emerging issues in HIV treatment
- Potential Benefits of earlier ART
## Global summary of the AIDS epidemic, December 2007

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Adults</th>
<th>Women</th>
<th>Children under 15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of people living with HIV in 2007</strong></td>
<td>33 million</td>
<td>30.8 million</td>
<td>15.5 million</td>
<td>2.0 million</td>
</tr>
<tr>
<td></td>
<td>[30 – 36 million]</td>
<td>[28.2 – 34.0 million]</td>
<td>[14.2 – 16.9 million]</td>
<td>[1.9 – 2.3 million]</td>
</tr>
<tr>
<td><strong>People newly infected with HIV in 2007</strong></td>
<td>2.7 million</td>
<td>2.3 million</td>
<td></td>
<td>370 000</td>
</tr>
<tr>
<td></td>
<td>[2.2 – 3.2 million]</td>
<td>[1.9 – 2.8 million]</td>
<td></td>
<td>[330 000 – 410 000]</td>
</tr>
<tr>
<td><strong>AIDS deaths in 2007</strong></td>
<td>2.0 million</td>
<td>1.8 million</td>
<td></td>
<td>270 000</td>
</tr>
<tr>
<td></td>
<td>[1.8 – 2.3 million]</td>
<td>[1.6 – 2.1 million]</td>
<td></td>
<td>[250 000 – 290 000]</td>
</tr>
</tbody>
</table>
Adults and children estimated to be living with HIV, 2007

- **North America**: 1.2 million (760,000 – 2.0 million)
- **Caribbean**: 230,000 (210,000 – 270,000)
- **Latin America**: 1.7 million (1.5 – 2.1 million)
- **Western & Central Europe & Central Asia**: 730,000 (580,000 – 1.0 million)
- **Eastern Europe & Central Asia**: 1.5 million (1.1 – 1.9 million)
- **Middle East & North Africa**: 380,000 (280,000 – 510,000)
- **Sub-Saharan Africa**: 22.0 million (20.5 – 23.6 million)
- **East Asia**: 740,000 (480,000 – 1.1 million)
- **South & South-East Asia**: 4.2 million (3.5 – 5.3 million)
- **Oceania**: 74,000 (66,000 – 93,000)

**Total**: 33 million (30 – 36 million)
## Estimated adult and child deaths from AIDS, 2007

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated Deaths</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western &amp; Central Europe</td>
<td>8000</td>
<td>[4800 – 17 000]</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>58 000</td>
<td>[41 000 – 88 000]</td>
</tr>
<tr>
<td>Middle East &amp; North Africa</td>
<td>27 000</td>
<td>[20 000 – 35 000]</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>1.5 million</td>
<td>[1.3 – 1.7 million]</td>
</tr>
<tr>
<td>North America</td>
<td>23 000</td>
<td>[9100 – 55 000]</td>
</tr>
<tr>
<td>Caribbean</td>
<td>14 000</td>
<td>[11 000 – 16 000]</td>
</tr>
<tr>
<td>Latin America</td>
<td>63 000</td>
<td>[49 000 – 98 000]</td>
</tr>
<tr>
<td>East Asia</td>
<td>40 000</td>
<td>[24 000 – 63 000]</td>
</tr>
<tr>
<td>South &amp; South-East Asia</td>
<td>340 000</td>
<td>[230 000 – 450 000]</td>
</tr>
<tr>
<td>Oceania</td>
<td>1000</td>
<td>[&lt;1000 – 1400]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2.0 million</strong></td>
<td><strong>(1.8 – 2.3 million)</strong></td>
</tr>
</tbody>
</table>
Estimated number of adults and children newly infected with HIV, 2007

- **North America**: 54,000 (9,600 – 130,000)
- **Caribbean**: 20,000 (16,000 – 25,000)
- **Latin America**: 140,000 (88,000 – 190,000)
- **Western & Central Europe**: 27,000 (14,000 – 49,000)
- **Eastern Europe & Central Asia**: 110,000 (67,000 – 180,000)
- **Middle East & North Africa**: 40,000 (20,000 – 66,000)
- **Sub-Saharan Africa**: 1.9 million (1.6 – 2.1 million)
- **East Asia**: 52,000 (29,000 – 84,000)
- **South & South-East Asia**: 330,000 (150,000 – 590,000)
- **Oceania**: 13,000 (12,000 – 15,000)

**Total**: 2.7 million (2.2 – 3.2 million)
Over 7400 new HIV infections a day in 2007

- More than 96% are in low and middle income countries
- About 1000 are in children under 15 years of age
- About 6300 are in adults aged 15 years and older of whom:
  - almost 50% are among women
  - about 45% are among young people (15-24)
Number of people receiving antiretroviral drugs in low- and middle income countries, 2002–2007

Source: Data provided by UNAIDS & WHO, 2008.
Estimated number of adult and child deaths due to AIDS globally, 1990–2007

This bar indicates the range.
Number and percentage of HIV-positive pregnant women receiving antiretroviral prophylaxis, 2004–2007

Source: UNAIDS, UNICEF & WHO, 2008; data provided by countries.

This bar indicates the range
Antiretroviral Therapy in High Income Countries

- 1986 AZT
- 1986–1995 Several NRTIS - DDI, DDC, 3TC, D4T, earlier Rx, use of dual NRTI regimens
- 1996 First generation Protease Inhibitors SQV, IND, RIT
- 1996 First generation NNRTIs Nev, Del, Effav
- 1996-1997 Rapid adoption of HAART with dramatic clinical impact
Trends in Annual Age-Adjusted* Rate of Death due to HIV Disease, United States, 1987–2005

Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.
*Standard: age distribution of 2000 US population
Trends in Annual Rates of Death due to the 9 Leading Causes among Men 25–44 Years Old, United States, 1987–2005

Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.
Impact of HAART on Mortality

- Agence Nationale de Recherches sur le Sida — Using pts from 2 french cohorts, calculated SMRs overall and for time with CD4>500 HIV-Infected Adults With a CD4 Cell Count Greater Than 500 Cells/mm3 on Long-Term Combination Antiretroviral Therapy Reach Same Mortality Rates as the General Population after 6 years of Rx – JAIDS Sept 2007 vol 46(1)

- “The average number of years remaining for an HIV+ person aged 20 yrs, on HAART is 49 yrs, about 2/3 that of the general population, lower for lower baseline CD4, IDU. - The Lancet 2008 Volume 372:293-99, Antiretroviral Cohort Collaboration NA and Eu
Outline

- Review Status of Global HIV Epidemic
- Impact of Antiretroviral Therapy on HIV morbidity/mortality
- 2008 HIV Treatment Guidelines
- Important considerations in ART
- Goals of ART for HIV Infection
- Potential Benefits of earlier ART
- Emerging issues in HIV treatment
Antiretroviral Treatment for HIV Infection- Guidelines

- IAS-USA Panel Recommendation Antiretroviral Treatment of Adult HIV Infection August 2008
- BHIVA 2005, updated 2006
- WHO Guidelines 2008
# Indications for Initiating ART: Chronic Infection

<table>
<thead>
<tr>
<th>Clinical Category and/or CD4 Count</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of AIDS-defining illness</td>
<td>Initiate ART</td>
</tr>
<tr>
<td>CD4 count of &lt;350 cells/µL</td>
<td></td>
</tr>
<tr>
<td>Pregnant women</td>
<td></td>
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<tr>
<td>HIV-associated nephropathy</td>
<td></td>
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<tr>
<td>Hepatitis B coinfection, when HBV treatment is indicated*</td>
<td></td>
</tr>
</tbody>
</table>

* Treatment with fully suppressive drugs active against both HIV and HBV is recommended.
Indications for Initiating ART: Chronic Infection (2)

<table>
<thead>
<tr>
<th>Clinical Category and/or CD4 Count</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count of &gt;350 cells/µL, asymptomatic, without conditions listed above</td>
<td>Optimal time to initiate ART is not well defined; consider individual patient characteristics and comorbidities</td>
</tr>
</tbody>
</table>
## 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 (ETV)
- Nevirapine (NVP)

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

### Fusion Inhibitor
- Enfuvirtide (ENF, T-20)

### CCR5 Antagonist
- Maraviroc (MVC)

### Integrase Inhibitor
- Raltegravir (RAL)
Initial Treatment: Choosing Regimens

- 3 main categories:
  - 1 NNRTI + 2 NRTIs
  - 1 PI + 2 NRTIs
  - 3 NRTIs

- Combination of NNRTI or PI + 2 NRTIs preferred
- Fusion inhibitor, CCR5 antagonist, integrase inhibitor not recommended in initial ART
- Few clinical end points to guide choices
- Advantages and disadvantages to each regimen
- Individualize treatment
Antiretroviral Therapy Considerations

- Results of drug resistance test
- Comorbidities (e.g., liver, psychiatric, or cardiovascular disease; tuberculosis)
- Adherence potential
- Dosing convenience (e.g., pill burden, dosing frequency)
- Potential adverse effects
- Potential drug interactions
- Pregnancy potential

- Gender and CD4 count, if considering NVP
- HLA B*5701 testing, if considering ABC
Antiretroviral Therapy

Considerations

- Patient readiness/commitment to therapy
- **Adherence**—95% adherence required to avoid development of resistant virus
- **Lifelong therapy** — *should not be interrupted unless serious toxicity or inability to take oral medications interruption usually results in immediate viral rebound, CD4 decline*
- **CD4 count, VL**
ARV Components in Initial Therapy: NNRTIs

**ADVANTAGES**
- Long half-lives
- Less metabolic toxicity (dyslipidemia, insulin resistance) than with some PIs
- PI options preserved for future use

**DISADVANTAGES**
- Low genetic barrier to resistance – single mutation
- Cross-resistance among most NNRTIs
- Rash; hepatotoxicity
- Potential drug interactions (CYP450)
ARV Components in Initial Therapy: PIs

**ADVANTAGES**
- Higher genetic barrier to resistance
- PI resistance uncommon with failure (boosted PI)
- NNRTI options preserved for future use

**DISADVANTAGES**
- Metabolic complications (fat maldistribution, dyslipidemia, insulin resistance)
- GI intolerance
- Potential for drug interactions (CYP450), especially with RTV
ARV Components in Initial Therapy: Dual-NRTI Pairs

**ADVANTAGES**
- Established backbone of combination therapy
- Minimal drug interactions

**DISADVANTAGES**
- Lactic acidosis and hepatic steatosis reported with most NRTIs (rare)
- Mitochondrial toxicity
Components of Initial ART: DHHS Categories

- **Preferred**
  - Clinical data show optimal efficacy and durability
  - Acceptable tolerability and ease of use

- **Alternative**
  - Clinical trial data show efficacy but also show disadvantages in ARV activity, durability, tolerability, or ease of use (compared with “preferred” components)
  - May be the best option in select individual patients

- **Other possible options**
  - Inferior efficacy or greater or more serious toxicities
# Initial Treatment: Preferred Components

**NNRTI Option**
- EFV*

**OR**

**PI Options**
- ATV + RTV
- FPV + RTV (BID)
- LPV/RTV (BID)

**NRTI Options**
- ABC + 3TC²
- TDF + FTC³

- * Avoid in pregnant women and women with significant pregnancy potential
- ¹ FTC can be used in place of 3TC and vice versa
- ² For patients who have tested negative for HLA-B*5701
- ³ TDF + FTC or 3TC is preferred in patients with HIV/HBV coinfection
**Initial Treatment: Alternative Components**

**NNRTI Option**
- NVP*

**PI Options**
- ATV¹
- FPV
- FPV + RTV (once daily)
- LPV/RTV (once daily)²
- SQV + RTV

* NVP should not be initiated in women with CD4 counts of >250 cells/µL or men with CD4 counts of >400 cells/µL
¹ ATV must be boosted with RTV if used with TDF
² May be insufficient if HIV RNA >100,000 copies/mL
Initial Treatment: Alternative Components (2)

NRTI Options (in order of preference)

- ZDV + 3TC¹
- ddI + (FTC or 3TC)

¹ FTC can be used in place of 3TC and vice versa
ARV Medications: Should Not Be Offered at Any Time

- ARV regimens not recommended
  - Inferior virologic efficacy, rapid development of resistance:
    - Monotherapy with NRTI*
    - Dual-NRTI therapy
    - 3-NRTI regimen (except ABC/3TC/ADV or possibly TDF + 3TC + ZDV, when other regimens are not desirable)

* For pregnant women, see Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States
**ARV Medications: Should Not Be Offered at Any Time (2)**

| Higher incidence of adverse events | ▪ ddI + d4T  
|                                  | ▪ ATV + IDV  
|                                  | ▪ 2-NNRTI combinations |
| Potential teratogenicity: avoid during pregnancy (especially 1st trimester) and in women with significant potential for pregnancy* | ▪ EFV |
| No potential benefit; similar resistance profile | ▪ 3TC + FTC |

* Women who are trying to conceive or who are not using effective and consistent contraception.
**ARV Medications: Should Not Be Offered at Any Time**

<table>
<thead>
<tr>
<th>Antagonistic effects</th>
<th>d4T + ZDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor bioavailability</td>
<td>SQV (unboosted)</td>
</tr>
</tbody>
</table>
Antiretroviral Therapy

Goals of Therapy

- Reduction HIV morbidity and mortality
- Improved quality of life
- Restoration/preservation of immune function
- Maximal + durable suppression viral load
- Possible Prevention of transmission - vertical transmission and to sex partners
Outline

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- Goals of ART for HIV Infection
- Emerging issues in HIV treatment
- Potential Benefits of earlier ART
Emerging Issues in HIV Treatment

- Antiretroviral treatment in pts with CD4 > 350
- Excess non opportunistic disease and malignancies in HIV+
- Cardiac Risk and Abacavir
Potential Benefits of Early Antiretroviral Therapy (CD4>350)

- Maintain higher CD4 count - prevent irreversible immune damage
- Decrease risk of HIV associated complications (TB, KS, NHL, peripheral neuropathy, HIV associated malignancies and cognitive impairment)
- Decrease risk non opportunistic conditions and non AIDS associated conditions (CV, renal and liver disease, infections, malignancies)
- Decrease transmission
Potential Risks of Early ARV Therapy (CD4>350)

- Inadequate time to learn about HIV, treatment and adherence
- Increase total time on ARVs, increase risk of treatment fatigue, drug resistance with failure
- ARV related side effects and toxicities
- Current therapy may be less effective/more toxic than future options
Benefits of Early ART (CD4>350)

- Maintain higher CD4 count - prevent irreversible immune damage -

✓ ATHENA (AIDS Therapy Evaluation Project Netherlands) Pts starting with CD4 > 350 significantly more likely to achieve CD4 > 800

✓ John Hopkins CC Pts starting ART CD4 < 350 significantly less likely to achieve CD4 >500
Benefits of Early ART (CD4>350)

- Decrease risk of HIV associated complications
- Decrease risk non opportunistic conditions and non AIDS associated conditions

- NA Accord- (22 research cohorts, part of the 'Intl Epid Databases to Evaluate AIDS Project', 8,374 pts, 24,994 person yrs follow up, data prospectively collected) Showed a 70% Survival benefit for pts initiating HAART CD4 351-500 vs CD4 < 350 – (RH 1.7, 1.4-2.1) Benefit seen across all subsets. Age, IDU, HCV associated with increased mortality

- SMART Substudy –Found a 5.7% difference in absolute risk of opportunistic disease and serious non-AIDS events with immediate versus deferred antiretroviral therapy (CD4 >350)
Benefits of Early Treatment

- *Decrease transmission*

✓ Abstract presented at Intl AIDS Conference 2008

Montaner — Prospective cohort of HIV+ and HIV- IVDU 1996-2004 —semi-annual plasma HIV level correlated with HIV incidence rates adjusted for risk behaviours, community HIV RNA level associated with time to seroconversion- *Conclusion* — *Treating an HIV infected community may decrease transmission*

✓ Serodiscordant couples- When VL<1000 c/ml on HAART very low risk of transmission
Potential Risks of Early ARV Therapy (CD4>350)

- *ARV related side effects and toxicities*

  ✓ HOPS Cohort (Prospective, dynamic cohort (>8000 patients)): Early Initiation of HAART Decreases Risk of Toxicities
Currently lack clinical trial evidence for earlier initiation of ART, so recommendation remains for CD4 > 350 consider on an individual basis.

Evidence is mounting in favour of earlier initiation of antiretroviral therapy.

START Trial - enrolling
Emerging Issues in HIV Treatment

- Antiretroviral treatment in pts with CD4> 350
- Excess non opportunistic disease and malignancies in HIV+
- Cardiac Risk and Abacavir
Comparison of Mortality, 2000-2005

- National Survey of causes of death in HIV+ pts in France
  - 78,000 pts followed at least 1 year
  - Compared deaths in 2000 (n=964) vs. 2005 (n=937)

- In 2005, increased deaths due to malignancies (38% respiratory tract), HCV, cardiovascular

- While AIDS-related deaths are declining, deaths due to CA, HCV, CV disease are increasing

Emerging Concerns
Non AIDS Malignancies

- Intl AIDS Conf Mexico 2008- 60% increase risk of non AIDS malignancies in HIV+ pts anal/lung/melanoma/liver
- Pre HAART < 10% deaths were from cancer, HAART 28% deaths cancer, ADM and non ADM,
- 4-14 fold inc incidence lung ca HIV+ - not associated with CD4, 10:1 M:F, smoking, usually advanced MST 3-8 mos
- D:A:D Cohort USA- Risk ADM nonADM increased with decreasing CD4<500, older age, smoking, HBV
“The most reasonable explanation for the 10–20-year gap in life expectancy so well documented by the ART-CC study is the previously unrealised clinical mischief of untreated HIV infection”

Lancet, Volume 372  Cooper
Emerging Issues in HIV Treatment

- Antiretroviral treatment in pts with CD4 > 350
- Excess non opportunistic disease and malignancies in HIV+
- Cardiac Risk and Abacavir
Abacavir and Cardiac Risk

- **SMART** — CD4 > 350 continuous(virology suppression) vs intermittent (drug conservation) — CVD Events in VS group (major clinical MI, silent MI, CVA, CAD Sx, CVD death) In pts with > 5 CRF, or ischaemic changes on EKG HR 3.1 ABC vs other NRTI

- Similar results NOT seen in GSK trials, HEAT

- Results significant enough that DHHS have “Updated” Guidelines – Use with caution in pts with increased CRF, or ischaemic disease
Websites to Access the Guidelines

- http://www.aidsetc.org
Case 1

- Mr and Mrs S - have been together several years. Mr. S recently diagnosed with HIV, current VL 45,000 c/ml, CD4 362, asymptomatic. Mrs S not infected. Refugees from Africa. Wanting to start a family.

- You are seeing Mr S in your office regarding management of his HIV.

- What are his options, what do you recommend?
Case 2

- 20 yo male from Ethiopia, newly diagnosed HIV+, baseline CD4 280, VL 5,000. Recent diagnosis of disseminated TB. Symptomatic with weight loss, diarrhea.
- What ART regimen would you recommend, and why? (What are the significant concerns with the different options NNRTI vs PI based)
Case 3

- You are meeting Ms. K for the first time. 36 yo F, advanced HIV, CD4 56, on methadone maintenance therapy. Several prior attempts at ART have been unsuccessful. She is wanting to try again. Medical hx significant for G3P2A1, HBV+

- What information do you need to choose ART?

- What medications should you avoid? What medications should be included? What might increase her likelihood of success?