When to Start, What to Start – Focusing on the New Guidelines

ACTHIV: The American Conference for the Treatment of HIV

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At the conclusion of this presentation, you should be able to:

- Determine when to initiate antiretroviral treatment for HIV-infected individuals in your practice based on the new guidelines and the evidence supporting these recommendations
- Identify optimal antiretroviral regimens to start in individual HIV-infected patients utilizing the guidelines and other relevant factors

I do not intend to discuss any non-FDA-approved or investigational uses of any products/devices during this presentation.
You are a busy hospitalist at an academic medical center. As part of a routine testing initiative, all inpatients are tested for HIV infection. A 54 yo woman with a severe COPD exacerbation on your service is newly diagnosed with HIV as a result and you are asked by your intern to help break the news to her. The intern suspects “she has no idea that this is coming.”

PMH significant for COPD, 30 pack-year h/o smoking, mild right sided heart failure; never tested for HIV before

Meds include fluticasone/salmeterol MDI, daily aspirin

NKDA

SHx: Patient continues to smoke 15-20 cigs per day; lives with husband of 3 years; no EtOH or recreational drugs; declines further questioning on risk factors

PE most significant for obesity and end-expiratory wheezing B. lung fields
ARS Question
Undiagnosed rate varies by race/risk group

- 1,106,400 adults/adolescents living with HIV in US by end-2006
- Back-calculated undiagnosed infections by disease severity at diagnosis and deaths
- 21.0% (232,700, 95%CI 221,200-244,200) undiagnosed
  - Whites 18.8%; Hispanics/Latinos 21.6%; blacks 22.2%; Native Americans 25.8%; API 29.5%
  - IVDU lowest (14.5% male; 13.7% female)
  - Heterosexual risk male 26.7%; MSM 23.5%

Case (cont.)

The patient is surprisingly matter-of-fact about the news and resists questions about current sexual practices during prevention counseling. However, she has a number of questions related to her HIV disease and asks first if she is going to live a normal life span, when she would need to start HIV therapy and what should she start?
ARS Question
Balance now tipped on earlier treatment of HIV

WHY WAIT?
- Avoid drug-related toxicity
- Preserve future drug options
- Delay development of drug resistance

WHY NOT WAIT?
- Possibility of irreversible immune system depletion
- Increased possibility of progression to AIDS
- Current drugs less toxic
- Increased risk of HIV transmission
- Observational cohort data showing survival advantage
- Untreated HIV disease is associated with increased T cell activation/inflammation

HIV as chronic inflammatory condition – more CV disease, CA, hepatic, renal, “aging”
Even with “guideline” care, life expectancy in HIV less than noninfected

Estimated life lost 11.92 yrs (mean age seroconversion 33)

Risk-adjusted HIV negative

Guideline-based care, HIV positive

Increased rates of “non-AIDS” defining deaths in HAART era

- **D:A:D 1st** enrolled 1999 - ~33,000 patients
- **2192 deaths** - 13.8 deaths per 1000 person years
- **1/3 AIDS deaths** – rest shown

SMART study

- Given toxicities, one idea was to reduce total duration on therapy by going off and on
- Strategies for Management of Antiretroviral Therapy (SMART) Study

Eligibility: CD4 > 350 (N=5472)

Continuous Treatment

No Treatment until CD4 < 250, then treatment until >350, then stop

Baseline CD4: 596-599
CD4 nadir: 250-252
% < 400 copies/mL viral load: 71%
Mean follow-up: 14 months (2% LFU)

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count guided interruption of antiretroviral treatment. NEJM 2006
## SMART Study

<table>
<thead>
<tr>
<th>Event</th>
<th># Events</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of Disease/Death</td>
<td>164</td>
<td>2.5  (2.1, 2.9)</td>
</tr>
<tr>
<td>Death</td>
<td>84</td>
<td>1.9  (1.5, 2.3)</td>
</tr>
<tr>
<td>Serious HIV events</td>
<td>21</td>
<td>6.1  (4.4, 8.3)</td>
</tr>
<tr>
<td>Severe non-HIV Complications</td>
<td>114</td>
<td>1.5  (1.2, 1.8)</td>
</tr>
</tbody>
</table>

*(Cardiac/CVA/renal/hepatic)*

### Notes:
- **Increased risk for all clinical outcomes, including death, HIV and non-HIV events with interrupted therapy**
- **Favors off and on**
- **Favors continuous therapy**
Kitahata M. Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival; April 30, 2009

North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)
- Regional collaboration of 22 HIV research cohorts from US and Canada
- Active f/u between 1996-2000
- Outcome: All-cause mortality

Groups compared from same CD4 count level:
- Immediate treatment: Initiated ART within 1.5 yrs after 1st CD4 count >500 cells/mm³
- Deferred treatment: Did not initiate ART in this time frame
- Tried to simulate RCT with observational data
NA-ACCORD: Improved Survival in Group where ART was Started When CD4 Count ≥500

Relative Hazard of Death (deferred vs initiated) 1.6 (1.3, 1.9; p<0.001)
Treatment as prevention

- 415 serodiscordant couples in Rakai\(^1\) – 90 converted in 30 mo

- Viral load chief predictor of transmission (RR 2.45 per log \(\uparrow\))\(^2\)

- With starting ARVs earlier, increasing interest in treatment as form of prevention\(^4\)

Risk of transmission highest early in infection

Rakai study (Uganda) - serodiscordant couples

- Highest transmission risk early in infection\(^1\)
- Not on treatment:
  - Transmission rate, 8/1000 coital acts, during 1st 5 months
  - 1/1000 acts during asymptomatic infection
  - Increases to 4/1000 acts in late-stage infection

\(^1\)Wawer et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis 2005
ART and HIV transmission

- Partners in Prevention HIV/HSV Transmission study – 3408 serodiscordant African couples
- 349 (10%) initiated ART in 24 months
- 1 seroconversion in ART group occurred within 1st 18 days

<table>
<thead>
<tr>
<th>Linked HIV-1 infection</th>
<th>Person Years</th>
<th>Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART initiated</td>
<td>102</td>
<td>4558</td>
<td>2.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.84-2.72)</td>
</tr>
<tr>
<td>After ART initiation</td>
<td>1</td>
<td>273</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.09-2.04)</td>
</tr>
</tbody>
</table>

Unadjusted Relative Risk = 0.17 (95% CI 0.004, 0.94), p = 0.037
Adjusted* Relative Risk = 0.08 (95% CI 0.002, 0.57), p = 0.004

* For time on study and CD4 count

Universal HIV testing, immediate treatment, eliminate HIV

Only 20% of HIV+ pts in low or middle income countries know status

Model predicts reduction of HIV incidence & mortality to <1 case/1000 people in 10 yrs (prevalence to <1% within 50 yrs)

Rights, feasibility, costs


deo Cock AM et al. Can antiretroviral therapy eliminate HIV transmission?; Garnett GP et al. Treating our way out of the HIV pandemic: could we, would we, should we? Lancet; Jan 3 2009
When to Begin Treatment for asymptomatic patients - U.S. guidelines – NOVEMBER 30, 2009

HIV Infection

Asymptomatic

CD4+ T cells/mm$^3$

>350 Nov 2008 <350

Consider Treatment

RISKS BENEFITS

History of AIDS-defining illness or severe symptoms

Treat

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents; Available at: http://aidsinfo.nih.gov.
When to Begin Treatment for **asymptomatic** patients - U.S. guidelines – December 1, 2009

![Flowchart diagram]

**HIV Infection**

**Asymptomatic**

- CD4+ T cells/mm³
  - >500
  - Dec 1, 2009
  - <500
  - Treat
    - 55% of panel – strong recommendation; 45% - moderate
  - Consider Treatment
    - 50% of panel say treat
    - 50% of panel say optional

**h/o AIDS-defining illness, severe sx, pregnancy, HepB, HIVAN**

- Treat
- Acute OIs

**DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents; Available at: http://aidsinfo.nih.gov.**
ACTG 5164: Starting HAART immediately with OI treatment

- 282 pts with OI or AIDS-associated bacterial infxn (BI)
- RCT- starting ARV immediately (median 12d) vs deferred (median 45d)
- Immediate treatment group had ↓ rate of AIDS progression or death (14.2%) vs deferred (24.1%)
  - Most common OIs: PCP (63%), Cryptococcus (12%), BI (12%); TB excluded
- No differences in IRIS (10 immediate vs 13 deferred)
  - But 70% of patients with PCP received corticosteroids

What about global setting?
Randomized controlled trial of earlier versus deferred ART in Haiti: CIPRA HT 001

- Start ART at CD4+ <350/cu mm, compared to AIDS or CD4+ <200/cu mm
- 816 patients
- First line regimen: AZT, 3TC, EFV
- 23 deaths in deferred group, 6 in early treatment group (p<.001)
- 36 vs. 18 cases of TB in deferred vs early treatment group (p<.013)
- DSMB recommended immediate end of trial

New W.H.O. criteria for when to start,

- Start ARVs in all patients with CD4 < 350 irrespective of clinical symptoms (changed from CD4 <200)
- If clinical stage 1 or 2 disease, check CD4; if clinical stage 3 or 4, start ARVs regardless of CD4
- Start in TB (as soon as possible after initiating anti-TB therapy), HBV, pregnancy regardless of CD4
- Phase out d4T; First line (AZT or TFV) + (3TC or FTC) + (NVP or EFV)
- Challenged in current funding era

PEPFAR funding shifts

- PEPFAR initiated 2003 under GW Bush, now in 6th year
- Averted 1.2 million deaths and ↓ HIV mortality by 10.5% in PEPFAR focus countries; no major impacts on prevalence¹
- Unprecedented impact and funds (~$25 billion)
- New administration, era – Being folded into a new 6-year Global Health Initiative ($63 billion over 6 yrs) with focus on neglected tropical diseases, maternal-child²

At Front Lines, AIDS War Is Falling Apart – May 9, 2010

The New York Times
You check baseline HIV labs on patient, as well as administer routine immunizations, perform Pap smear, ask about domestic violence (in response to latter, pt states she has never experienced DV, but her husband is “in trouble” given her new diagnosis)

CD4 764 cells/mm³, HIV viral load 36,000 copies/ml, LFTs within normal limits, BUN 15; Creatinine 1.1, HLA-B5701 negative, baseline resistance panel shows no significant RT or Pr resistance
ARS Question
San Francisco opts for “universal treatment”

April 2, 2010

City Endorses New Policy for Treatment of H.I.V.

SF Department of Public Health recommends treating everyone with HIV infection upon diagnosis, regardless of CD4
DHHS panel split 50:50 with CD4 >500

**START**
- Untreated HIV may be associated with CVD, kidney disease, liver disease, malignancy, neurocognitive dysfunction
- Less robust CD4 responses if treatment started at older ages
- HAART now more convenient, potent, tolerated
- Early untreated HIV infection associated with sustained T-cell activation and high-level inflammation
- Side benefit on transmission

**WAIT**
- RCT data only available for <350 (350-500 all based on observational data already)
- Risks of short term or especially long-term toxicity unknown (NA-ACCORD mainly older regimens).
  - SMART – ART associated with bone loss; DAD – Some ARVs associated with CVD
- Nonadherence to lifelong therapy in asymptomatic patients
- Potential for drug resistance
- Cost
Pt declines to start HIV therapy, but states she will follow-up with your HIV consultant. Signs out AMA saying she has some “business to take care of” and returns 9 months later to HIV clinic for first appointment.

States HIV diagnosis has triggered life changes. Separated from husband who was not monogamous, stopped smoking, eats more healthy foods and states she is ready to start HIV therapy. Also wants to date again (specifically, her ex-husband’s best friend) and asks you about that possibility.

Repeat CD4 count 636 cells/mm$^3$; viral load 19,348 copies/mL, creatinine 1.2

What to start??
Many options. . . Fewer toxicities

Nucleoside and nucleotide RTIs
- Zidovudine, AZT (*Retrovir*)
- Abacavir, ABC (*Ziagen*)
- Lamivudine, 3TC (*Epivir*)
- Didanosine, ddI (*Videx*)
- Stavudine, d4T (*Zerit*)
- Tenofovir, TFV (*Viread*)
- Emtricitabine, FTC (*Emtriva*)
- **Combivir (AZT/3TC)**
- **Trizivir (AZT/3TC/ABC)**
- **Epzicom (3TC/ABC)**
- **Truvada (FTC/TFV)**

CCR5 receptor antagonist
- Maraviroc (*Selzentry*)

Integrase inhibitor
- Raltegravir (*Isentress*)

NNRTI’s:
- Delavirdine (DLV)
- Nevirapine, NVP (*Viramune*)
- Efavirenz, EFV (*Sustiva*)
- Etravirine* (*Intelence*)

Fusion inhibitors:
- Enfuvirtide, ENF or T20 (*Fuzeon*)

Protease inhibitors:
- Indinavir, IDV (*Crixivan*)
- Saquinavir, SQV (*Invirase, hgc*)
- Nelfinavir, NFV (*Viracept*)
- Amprenavir, APV (*Agenerase*)
- Atazanavir, ATZ (*Reyataz*)
- Kaletra (lopinavir/ritonavir)
- Darunavir (*Prezista*)*

Combination
- **Atripla (EFV/FTC/TFV)**

*Approved in past 3 years

red text – combination agents

Circled – most used/recommended ARVs in US (DHHS guidelines, 2009)
What to start – DHHS guidelines

<table>
<thead>
<tr>
<th>Preferred regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz + tenofovir + emtricitabine (Atripla®)</td>
</tr>
<tr>
<td>Raltegravir + tenofovir + emtricitabine</td>
</tr>
<tr>
<td>Ritonavir-atazanavir + tenofovir + emtricitabine</td>
</tr>
<tr>
<td>Ritonavir-darunavir + tenofovir + emtricitabine</td>
</tr>
</tbody>
</table>

**Alternative regimens:** NNRTIs (NVP or EFV) or other PIs (FPV/r, LPV/r, SQV/r) PLUS ABC/3TC* or AZT/3TC or TFV/FTC

**Acceptable or may be acceptable regimens:** EFV+ ddI + (3TC or FTC); Unboosted ATV with (ABC or AZT)/3TC; Maraviroc + AZT/3TC or Raltegravir + (ABC or AZT)/3TC or (DRV/r or SQV/r) + (ABC or AZT)/3TC

*Other major combination NRTI agent of ABC/3TC demoted to alternative
### What not to use – DHHS guidelines

<table>
<thead>
<tr>
<th>Monotherapy with NRTI or dual NRTI regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple NRTI regimens except ABC/ZDV/3TC or possibly TFV/ZDV/3TC</td>
</tr>
<tr>
<td>(ATV + IDV) or (d4T + ddI) - overlapping toxicities</td>
</tr>
<tr>
<td>2 NNRTI combinations</td>
</tr>
<tr>
<td>Etravirine + (unboosted PI) or (ATV/r or FPV/r or TPV/r)</td>
</tr>
<tr>
<td>FTC + 3TC (no benefit); d4T + AZT (antagonistic)</td>
</tr>
<tr>
<td>EFV in 1st trimester; NVP in women with CD4 &gt;250 or men CD4 &gt;400</td>
</tr>
<tr>
<td>Unboosted SQV or TPV or DRV</td>
</tr>
</tbody>
</table>
“Conditions where deferral of therapy might be considered”

- Significant barriers to adherence
- Comorbidities that complicate or prohibit ARVs (surgery that might interrupt or prohibitive drug-drug interactions)
- Poor prognosis 2° concomitant condition
  - Although AIDS condition with low CD4 may improve
- Long term nonprogressors and elite controllers
  - HAART may be theoretically beneficial, evidence lacking

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents; Available at: [http://aidsinfo.nih.gov](http://aidsinfo.nih.gov). December 1, 2009
ARS Question
Case (continued)

You start EFV/TFV/FTC and the patient returns 8 weeks later for a follow-up visit

She said she feels a little “weird” on the meds, but okay

Viral load undetectable, CD4 count 780

Pt then admits that her new male partner is HIV negative and they are not using condoms because they are in love

She has heard there is no need for condoms for prevention of transmission when she is on HIV therapy

NEXT TALK!!!!