HIV: Approach to the Treatment-Naïve Patient

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Approach to the Treatment-Naïve Patient

• Case-based presentation, reviewing:
  – Who gets treated
  – Who gets what

• Frequent incorporation of questions to encourage dialogue
Case Presentation

• 36-year-old man newly diagnosed with HIV
  – Last negative test 10 years ago
  – Works full-time as health professional
  – No medical problems; PE normal
  – CD4+ cell count: 590 cells/mm³
  – HIV-1 RNA: 21,000 copies/mL
  – No drug resistance
• He wonders whether he needs antiretroviral therapy; he will do whatever you recommend
Question

Should antiretroviral therapy be started?

1. No – clinical benefits not proven at this high CD4 level (590 cells/mm³)
2. Yes – on balance, all patients with HIV should be treated
3. Maybe – some patients like this should be treated, but some shouldn’t; I first need to get to know him better
Question

What would you do for yourself if you were in his situation?

1. Monitor
2. Treat
3. I first need to get to know myself better

“Word! You need professional help.”
Question

What is the primary reason clinicians have deferred treatment?

1. Acute side effects (rash, GI, CNS, etc)
2. Long-term toxicity (hyperlipidemia, lipoatrophy and fat accumulation, etc.)
3. Risk of resistance without nearly-perfect adherence
4. Randomized studies show no benefit to immediate therapy at CD4 counts above 350 cells/mm³
5. Cost of treatment
Historical Reasons for Deferring Antiretroviral Therapy

Body shape changes

High pill burden

High cost

Metabolic abnormalities/↑CV risk

Resistance
HIV Treatment Guidelines: 2008 and 2009 Compared

• 2008:
  – “The optimal time to initiate therapy in asymptomatic patients with CD4 count >350 cells/mm3 is not well defined.”

• 2009:
  – “Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm3.”
  – “For patients with CD4 counts >500 cells/mm3, 50% of Panel members favor starting antiretroviral therapy; the other 50% of members view treatment as optional in this setting.”

What data led to this change?

http://aidsinfo.nih.gov/Guidelines
# IAS-USA: When to Start ART

<table>
<thead>
<tr>
<th>Specific conditions</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic HIV disease</td>
<td>ART recommended regardless of CD4 cell count</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>High HIV-1 RNA Level (&gt;100,000 copies/mL)</td>
<td></td>
</tr>
<tr>
<td>Rapid CD4 count decline (&gt;100 cells/mm³ per year)</td>
<td></td>
</tr>
<tr>
<td>Active hepatitis B or C* virus co-infection</td>
<td></td>
</tr>
<tr>
<td>Active or high risk for cardiovascular disease*</td>
<td></td>
</tr>
<tr>
<td>HIV-associated nephropathy</td>
<td></td>
</tr>
<tr>
<td>Symptomatic primary HIV infection*</td>
<td></td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td></td>
</tr>
<tr>
<td>Risk for secondary HIV transmission is high*</td>
<td></td>
</tr>
</tbody>
</table>

| CD4 cell count ≤500 cells/mm³                    | ART recommended                                      |
| CD4 cell count >500 cells/mm³                    | ART should be considered§                            |

*Thompson MA, et al. JAMA 2010;304:321-333*
SMART: Outcome Superior if Patients with High CD4 Randomized to Treatment

Likelihood of AIDS, serious non-AIDS event, or death in receiving continuous (blue) or intermittent (red) therapy. All had CD4 > 350 at baseline.

JID 2008197:1133–1144.
A Major Reason to Treat Earlier: Risk of Non-AIDS Diseases and Death

• In HIV+ versus HIV uninfected, higher rates of:
  – CV disease
  – Liver disease (esp with viral co-infection)
  – Renal disease
  – Malignancies

• Lower CD4+ cell count and/or higher HIV RNA increase the risk of all of these conditions
Recent Studies Showing Non-AIDS Associations with Lower CD4+ Count

- **Renal**
  - Excess of chronic kidney disease: Highest risk <350 cells/mm³; higher between 350-500 vs >500 cells/mm³

- **Bone**
  - HOPS cohort: CD4 counts <200 cells/mm³ significantly higher fracture rates vs CD4 counts >350 cells/mm³ (HR: 1.60; 95% CI 1.11 – 2.31)

- **Neurologic**
  - CHARTER Cohort: Higher risk of HIV-associated neurocognitive disorders with lower CD4 nadir (up to 350 cells/mm³)

- **CVD**
  - Harvard/Partners cohort: CD4 counts <200 cells/mm³ the most important HIV-related predictor of increased MI risk

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1Ganesan A et al. 17th CROI; San Francisco, CA; February 16-19, 2010; Abstract 738.  
2Dao C et al. 17th CROI; San Francisco, CA; February 16-19, 2010; Abstract 128.  
3Ellis R et al. 17th CROI; San Francisco, CA; February 16-19, 2010; Abstract 429.  
4Triant VA, et al. 18th IAC; Vienna, Austria; July 18-23, 2010; Abstract WEPE0130.
NA-ACCORD: Survival Benefit if ART Started at CD4 > 500

Relative risk for death for deferral of ART until CD4 < 500: **1.94**

## Number Needed to Treat (NNT): Prevention of First Myocardial Infarction

<table>
<thead>
<tr>
<th>Intervention</th>
<th>5-year NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>40-70</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>80-160</td>
</tr>
<tr>
<td>Aspirin</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

### NNT to Prevent AIDS/Death for ART before CD4 < 350: 34

Treatment Reduces the Risk of HIV Transmission

2,993 couples were followed for a median of 512 days

<table>
<thead>
<tr>
<th>ARV Status</th>
<th>CY Observation</th>
<th>No. Linked Infections</th>
<th>Infection Rate (C-Y)</th>
<th>Infection Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not on ARV</td>
<td>5,062</td>
<td>171</td>
<td>3.4/100</td>
<td>---</td>
</tr>
<tr>
<td>On ARV</td>
<td>547</td>
<td>4</td>
<td>0.7/100</td>
<td>0.21 (0.08, 0.59)</td>
</tr>
<tr>
<td>On ARV – conservative*</td>
<td>547</td>
<td>6</td>
<td>1.0/100</td>
<td>0.32 (0.14, 0.73)</td>
</tr>
</tbody>
</table>

*Includes 2 partners who seroconverted in the same 3-month interval when the HIV-infected partner initiated ARVs

- Sexual risk behaviors lower in those on ART (19% vs 25%, P<0.05)
- Both ART and change in behavior independently reduced HIV transmission

Sullivan P, et al. 16th CROI; Montreal, Canada; February 8-11, 2009. Abst. 52bLB.
Question

What % of patients currently in care on treatment have an HIV-1 RNA < 50 copies/mL?

1. 20 or lower%
2. 40%
3. 60%
4. 80 or higher%
Treatment Success is Steadily Increasing

- N= 5422 receiving therapy in British Columbia
- Also noted: >12-fold reduction in new cases of drug resistance

START Study: Study Design

2009-10: Enrolled 900 patients in feasibility pilot

Immediate Treatment

Defer Treatment until CD4+ cell count < 350 cells/mm³

Data collection at Months 1, 4, and every 4 months thereafter; duration undetermined

Treatment-naive patients with CD4+ cell count > 500 cells/mm³

(N = 4000)

Study endpoints: fatal AIDS or non-fatal serious AIDS events (cardiovascular, liver, renal, and cancer), and non-AIDS–related deaths; duration 6 years
Question

I would refer asymptomatic patients with CD4+ cell counts > 500 cells/mm³ to the START study.

1. Yes – there is still sufficient uncertainty
2. No – available data are already abundant to persuade me that all should start therapy
3. No – some patients need to start, some should wait
When to Start with High CD4: Ready When You Are

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4+</th>
<th>My View</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness or severe</td>
<td>Any value</td>
<td>Treat!!</td>
</tr>
<tr>
<td>symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt;200/µL</td>
<td>Treat!</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>200-500/µL</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt; 500/µL</td>
<td>Treat if Patient is Ready!</td>
</tr>
</tbody>
</table>

But … Are Resources Available?

- In the USA, currently 4500 patients on waiting lists for state-provided ART
- Increased HIV testing and treatment could yield 46,000 new cases and cost $2.7 billion over the next 5 years
- Where treatment limited, starting at lower CD4 thresholds is the best way to allocate resources

Case Outcome

• After one year of monitoring and stable lab values, patient elected to start therapy
  – New relationship with HIV-uninfected partner was a motivating factor
• Chose TDF/FTC/EFV – one pill daily
• Current CD4 normal, HIV RNA < assay
Case Presentation

• 41-year-old woman, extensive psych history
  – Meds: mirtazapine, fluoxetine, lorazepam
• Diagnosed with AIDS Dec 2007 – 3 month hospitalization with PCP
  – CD4 7, HIV RNA 515,000; no resistance
• Since discharge, multiple different regimens tried over 6 month period – all stopped rapidly due to side effects, poor compliance
• Now with severe watery diarrhea, ongoing weight loss → admitted for further evaluation and treatment
Case Presentation

• How would you approach this case from the antiretroviral therapy perspective?

1. Work-up for possible OIs first; avoid ART until on Rx is started due to risk of the immune reconstitution inflammatory syndrome
2. Start ART while working up for possible OIs
3. Something else
Do We Have an Irrational Fear of IRIS?
ACTG 5164: Study Design

Opportunistic Infection Treatment Starts

Immediate Arm Start ART

Deferred Arm Start ART

Recommended Start window

Study day

-14 0 2 28 42 84 224

Enrollment

48 wks

48 wks

“Early” ART Reduces Risk of AIDS Progression or Death

CAMELIA: Early vs. Late ART in Active TB

- Randomized, prospective study comparing early (2 weeks) vs. late (8 weeks) ART for patients with newly diagnosed TB starting TB therapy (n= 661)
- Results
  - Early ART strategy significantly improved survival (59 vs 90 deaths)
  - More IRIS in early ART arm (110 vs 48), but most cases minor
  - Virologic suppression in >95% at 150 weeks
- Results of study confirm benefits of early ART in patients with acute OIs

Blanc F, et al. 18th IAC; Vienna, July 18-23, 2010; Abst. THLBB106.
ART Started in the ICU Associated with Improved Survival

Timing of ART and Cryptococcal Meningitis: Zimbabwe

- Immediate vs. delayed (10 weeks) ART in cryptococcal Meningitis (N=54)
  - Tx: Fluconazole 800 mg daily and d4T/3TC/NVP
  - No use of amphotericin or LPs to manage raised intracranial pressure
- 2 yr Mortality: 87% immediate vs. 37% delayed (P=0.002)
  - Most deaths in immediate ART group occurred within the first month, possibly due to IRIS

Makadzange AT et al., Clin Infect Dis 2010 Jun 1; 50:1532.
How Common is IRIS? Results from Prospective Studies

• A5164
  – Early ART: 8/141 (6%)
  – Delayed ART: 12/141 (9%)
  – No deaths
• A5202
  – 52/1848 (3%)
  – Onset 1-298 days after starting ART
  – No deaths
• SAPIT
  – 53 of 429 patients (12%)
  – No deaths

• South Africa
  – 423 ART-naïve patients
  – 44 (10%) cases of IRIS
  – Median onset 48 days
  – Most cases mild; two deaths

• Predictors in most studies
  – Lower CD4
  – Higher HIV RNA
  – Prior diagnosis of AIDS

Case Presentation

• Summary: 41-year-old woman, extensive psych history
  – CD4 7, HIV RNA 515,000; no resistance; HLA-B*5701 negative
  – Now with severe watery diarrhea, ongoing weight loss → admitted for further evaluation and treatment
  – You decide to start ART now as w/u continues

• What NRTI pair would you use?
  1. ABC/3TC
  2. TDF/FTC
  3. ZDV/3TC
HIV Treatment 2010: What to Start

<table>
<thead>
<tr>
<th>Dual NRTI</th>
<th>Key 3(^{rd}) Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
<td>EFV, ATV/r, DRV/r, RAL</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>LPV/r, FPV/r, MVC</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td></td>
</tr>
</tbody>
</table>

Comparison to 2009 DHHS Guidelines:
- “Recommended” therapies are the same as “Preferred” regimens
- In addition to “Alternative” therapies listed, 2009 DHHS Guidelines “Alternative” and “Acceptable” regimens include ZDV/3TC, ddi + 3TC, NVP, unboosted ATV, and SQV/r

TDF/FTC vs ABC/3TC with High HIV RNA

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

log rank test p-value: 0.0003
HR (95%CI) 2.33 (1.46, 3.72)

# Studies Comparing ABC/3TC to TDF/FTC

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Size</strong></td>
<td>1858 (797 HIV RNA &gt; 100,000 c/mL)</td>
<td>688</td>
<td>385</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>Double-Blind</td>
<td>Double-Blind</td>
<td>None</td>
</tr>
<tr>
<td><strong>3rd Drug</strong></td>
<td>EFV or ATV/RTV</td>
<td>LPV/RTV QD</td>
<td>EFV</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Time to Virologic Failure</td>
<td>&lt;50 c/mL at 48 wks</td>
<td>Change in eGFR at wk 48 by MDRD</td>
</tr>
<tr>
<td><strong>HLA-B*5701 Testing</strong></td>
<td>Permitted, not required</td>
<td>No</td>
<td>Required, only negative pts enrolled</td>
</tr>
<tr>
<td><strong>Key Results</strong></td>
<td>For those with HIV RNA &gt;100,000 c/mL, study stopped early due to higher rate of virologic failure with ABC/3TC; no difference in low VL stratum</td>
<td>ABC/3TC non-inferior</td>
<td>No difference in eGFR; proportion &lt;50 c/mL favored TDF/FTC (71% vs. 59%; difference 11.6%, 95% CI 2.2-21.1); total hip and lumbar spine BMD decline more with TDF/FTC</td>
</tr>
</tbody>
</table>

A5224s: Percent Change in Lumbar Spine BMD

McComsey G, et al. 17th CROI; 2010; San Francisco, CA. #106LB.
NRTI Summary

- **Most patients**: TDF/FTC
  - Caution with renal disease, low bone density
- **Other patients**: ABC/3TC
  - Pre-treatment HLA-B*5701 testing *required*
  - Caution with multiple cardiac risk factors
  - Caution with HIV RNA > 100K
- **Some others (pregnancy)**: ZDV/3TC
  - Caution with anemia, leukopenia
  - Long-term use causes lipoatrophy
Case Presentation

• **Summary:** 41-year-old woman, extensive psych history
  – CD4 7, HIV RNA 515,000; no resistance; HLA-B*5701 negative
  – Now with severe watery diarrhea
  – You decide to start ART now as w/u continues

• **In addition to TDF/FTC, what key 3rd drug would you use?**
  1. Efavirenz
  2. Nevirapine
  3. Atazanavir/r
  4. Darunavir/r
  5. Lopinavir/
  6. Raltegravir
Many “3rd Drug” Potential Choices, Though Not All Preferred Equally

- **NNRTI**
  - Efavirenz
  - Nevirapine

- **Ritonavir-boosted PIs**
  - Atazanavir
  - Darunavir
  - Fosamprenavir
  - Lopinavir
  - Saquinavir

- **Integrase inhibitor**
  - Raltegravir

- **CCR5 antagonist**
  - Maraviroc
ACTG 5202: ATV/r and EFV Similar in Virologic Efficacy

- Similar time to virologic failure with ATV/r vs EFV when combined with either ABC/3TC or TDF/FTC in overall population analysis
  - With ABC/3TC, HR: 1.13 (95% CI: 0.82-1.56)
  - With TDF/FTC, HR: 1.01 (95% CI: 0.70-1.46)

Other Important Comparative Studies of First-Line Therapy

- Boosted PIs
  - CASTLE: ATV/r non-inferior to LPV/r, better tolerated
  - ARTEMIS: DRV/r non-inferior to LPV/r, better tolerated; possibly better efficacy at high HIV RNA
- Integrase inhibitor
  - STARTMRK: RAL non-inferior to EFV, better tolerated

Current “3rd Drug” Preferred Choices

- NNRTI
  - Efavirenz
  - Nevirapine

- Ritonavir-boosted PIs
  - Atazanavir
  - Darunavir
  - Fosamprenavir
  - Lopinavir
  - Saquinavir

- Integrase inhibitor
  - Raltegravir

Compared in ACTG 5257 – enrolling now
Convergence of First-Line Regimens: Can Anything Challenge This?

In 2007, 95% started either TDF/FTC/EFV (85%) or TDF/FTC + ATV/r (10%).

The TDF/FTC/EFV Era: Potentially Destabilizing Forces

• Once-daily raltegravir
• Investigational options for coformulation
  – Elvitegravir/cobicistat
  – Rilpivirine (TMC-278)
  – S/GSK1349572
• NRTI-sparing strategies
• Generic lamuvidine (2011) and efavirenz (2013-14)
Rilpivirine (TMC-278)

- RPV: Investigational NNRTI promising in phase II study
- Phase III, double blind study comparing TDF/FTC + EFV vs RPV (n=1368)
- Virologic results favored EFV in high HIV RNA stratum; tolerability and safety favored RPV; overall response non-inferior

Cohen C, et al. 18th IAC; Vienna, July 18-23, 2010; Abst. THLBB206.
**Question**

- When rilpivirine gets approved – and assuming there’s a “B-Tripla” soon after – will it be used over TDF/FTC/EFV?

1. In all patients
2. Only in those with HIV RNA < 100,000
3. In those who have HIV RNA < 100,000 and are not good EFV candidates
4. Other
Question

Will two-drug regimens that do not use NRTIs be as effective as our current standard of care?

1. Yes
2. Yes – but only if one is a boosted PI with its high barrier to resistance
3. No – NRTIs are critical
# Ongoing or Planned NRTI-Sparing Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV/RTV + TDF/FTC vs DRV/RTV (QD) + RAL (BID)</td>
<td>800</td>
<td>PI + INSTI</td>
</tr>
<tr>
<td>(start 3Q/09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL + DRV/RTV</td>
<td>111</td>
<td>PI + INSTI</td>
</tr>
<tr>
<td>RAL + LPV/RTV vs RAL + TDF/FTC</td>
<td>44</td>
<td>PI + INSTI</td>
</tr>
<tr>
<td>RAL + LPV/RTV vs EFV/TDF/FTC</td>
<td>50</td>
<td>PI + INSTI</td>
</tr>
<tr>
<td>RAL + LPV/RTV (naive and exp. pts)</td>
<td>30</td>
<td>PI + INSTI</td>
</tr>
<tr>
<td>RAL QD 800 mg + unboosted ATV 400 mg QD</td>
<td>15</td>
<td>PI + INSTI</td>
</tr>
<tr>
<td>Maraviroc + ATV/RTV vs TDF/FTC + ATV/RTV</td>
<td>88</td>
<td>CCR5 + PI</td>
</tr>
<tr>
<td>Vicriviroc + ATV/RTV vs TDF/FTC + ATV/RTV</td>
<td>200</td>
<td>CCR5 + PI</td>
</tr>
<tr>
<td>ATV BID + RAL BID vs TDF/FTC + ATV/RTV</td>
<td>90</td>
<td>PI + INSTI</td>
</tr>
</tbody>
</table>
NRTI-Sparing Studies: The Score so Far

- **LPV/r + RAL**: Lipids worse, BID regimen, more pills, more expensive
- **ATV + RAL**: More AEs, EKG changes, more resistance, BID, more expensive
- **ATV/r + MVC**: More hyperbilirubinemia, needs pre-Rx tropism test
- **ATV/r + VCV**: Not as effective virologically, needs pre-Rx tropism test
The TDF/FTC/EFV Era: Potentially Destabilizing Forces

- Once-daily raltegravir
- Investigational options for coformulation
  - Elvitegravir/cobicistat
  - Rilpivirine (TMC-278)
  - S/GSK1349572
- NRTI-sparing strategies
- Generic (in USA) lamuvidine (2011) and efavirenz (2013-14)
Case Outcome

• Patient started on TDF/FTC, RAL
  – Rationale: Avoidance of drug-drug interactions, CNS toxicity of EFV, and anything that may worsen diarrhea

• Extensive w/u for cause of diarrhea negative – diagnosis “HIV enteropathy”

• Two years later: Diarrhea resolved, CD4 314, HIV RNA < assay
Starting Therapy: Final Words

• Who to treat
  – Symptomatic HIV disease or CD4 < 200: Treat sooner rather than later, especially with active OI
  – Asymptomatic, CD4 200-500: Treat, with urgency greater at < 350
  – Asymptomatic, CD4 > 500: Treat if patient is willing

• What to use
  – Two NRTIs: TDF/FTC (or ABC/3TC)
  – Third drug: EFV, ritonavir-boosted ATV or DRV, or RAL
  – Little data so far supporting novel strategies