Advances in Antiretroviral Treatment for HIV Infection

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Financial Relationships With Commercial Entities

Dr Gulick has no relevant financial affiliations to disclose. (Updated 09/04/15)

Learning Objectives

After attending this presentation, participants will be able to:

- Describe the latest data on strategies for treatment of HIV infection.
- Describe the latest data on new and investigational antiretroviral drugs
Unlabeled/Unapproved Uses

- Investigational antiretroviral agents

Antiretroviral Therapy: Questions

- When to start?
- What to start?
- When to change?
- What to change to?

When to Start?
START (Strategic Timing of Antiretroviral Treatment Study): Design

- HIV+, ART-naive, CD4+ >500 cells/mm³

**Immediate ART Group**
- Initiate ART immediately
- No. = 2,326

**Deferred ART Group**
- Defer ART until CD4+ <350 or AIDS
- No. = 2,359

Primary composite endpoint, target = 213
- Serious AIDS or death from AIDS
- Serious Non-AIDS Events and death not attributable to AIDS
  - CHF, ESRD, decompressed liver disease, & non-AIDS defining cancers

Stopped early by DSMB; average f/u 3 years

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**START: Primary Endpoint**

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Imm. ART</th>
<th>Def. ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AIDS</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Serious non-AIDS</td>
<td>29</td>
<td>47</td>
</tr>
<tr>
<td>Total*</td>
<td>42 (1.8%)</td>
<td>66 (2.8%)</td>
</tr>
</tbody>
</table>

HR 0.43 (0.30, 0.62; P<0.001)

Most common:
- AIDS events: TB, Lymphoma, Kaposi’s sarcoma, PCP, disseminated VZV
- Non-AIDS events: Non-AIDS cancers, CV disease

* One participant in each group had both a Serious AIDS and a Serious Non-AIDS Event

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**START: Other Analyses**

- No difference (all benefit)
  - age, sex, race, geography (low/middle vs. high income)
  - cigarette smoking, Framingham risk
  - baseline CD4, baseline VL
  - ↑ risk of clinical events with ↑ age, ↓ CD4, ↑ Framingham score
  - Toxicity: no differences
  - Conclusion: ART benefits all

- Implications (IAS 2015):
  - Chile, Thailand, UK all changed to recommend ART for ALL
  - WHO plans to change guidelines 12/15
HPTN 052: ART as Prevention

- 1,763 discordant couples (97% heterosexual) in Africa, Asia, Americas with HIV+ with CD4 350-550
- HIV+ partner randomized to start ART immediately or deferred until CD4 <250
- DSMB Interim analysis:
  - 49% of ART had HIV RNA <400
  - 40 incident cases of HIV
  - 29 linked genetically to partner
  - 96% reduction in transmission!

NEJM 2011;365:493

DSMB Interim analysis:
- 90% on ART had HIV RNA <400
- 40 incident cases of HIV
- 29 linked genetically to partner
- 96% reduction in transmission!

Eshleman IAS 2015 # MOAC0106LB

Update at IAS 2015: 8 additional linked events
(4 soon after ART started, 4 after virologic failure)
- No transmissions when index partner virologically suppressed

When to Start?: Guidelines

<table>
<thead>
<tr>
<th>AIDS/ symptoms</th>
<th>CD4 &lt;200</th>
<th>CD4 200-350</th>
<th>CD4 350-500</th>
<th>CD4 &gt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAS-USA 2014</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>EACS 2014 <a href="http://www.europeanaidsclinicalociety.org">www.europeanaidsclinicalociety.org</a></td>
<td>YES</td>
<td>YES</td>
<td>certain patients</td>
<td>certain patients</td>
</tr>
<tr>
<td>UK 2015 (draft)</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

What to Start?
Question

Which class of antiretroviral drugs is NOT currently a part of DHHS Guideline recommended initial regimens?

1. Nucleoside analogue reverse transcriptase inhibitors
2. NNRTI
3. Protease inhibitors
4. Integrase inhibitors

Newer ART Rx-Naïve Studies

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>N</th>
<th>Regimen</th>
<th>VL &lt;50 (96 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG 5257</td>
<td>605</td>
<td>2 NRTI + ATV/r</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>601</td>
<td>2 NRTI + DRV/r</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>603</td>
<td>2 NRTI + RAL</td>
<td>94%*</td>
</tr>
<tr>
<td>SINGLE Walmsley NEJM 20134 AIDS 2015 Aug 7 (epub)</td>
<td>414</td>
<td>ABC/3TC + DTG</td>
<td>80%*</td>
</tr>
<tr>
<td></td>
<td>419</td>
<td>TDF/FTC/EFV</td>
<td>72%</td>
</tr>
<tr>
<td>FLAMINGO Melia Lancet 2014/Glasgow 2014</td>
<td>242</td>
<td>2 NRTI + DTG</td>
<td>80%*</td>
</tr>
<tr>
<td></td>
<td>242</td>
<td>2 NRTI + DRV/r</td>
<td>68%</td>
</tr>
</tbody>
</table>
**Recommended Regimens**

(2 NRTI + 3rd drug)

- **PI-based**
  - tenofovir/emtricitabine + darunavir/r

- **INSTI-based**
  - abacavir/lamivudine/dolutegravir
  - tenofovir/emtricitabine + dolutegravir
  - tenofovir/emtricitabine/elvitegravir/cobicistat
  - tenofovir/emtricitabine + raltegravir

**Alternative Regimens**

(2 NRTI + 3rd drug)

- **NNRTI-based**
  - tenofovir/emtricitabine + efavirenz
  - tenofovir/emtricitabine + rilpivirine

- **PI-based**
  - tenofovir/emtricitabine + atazanavir/ritonavir (or cobicistat)
  - abacavir/lamivudine + darunavir/ritonavir (or cobicistat)
  - tenofovir/emtricitabine + darunavir/cobicistat

**Initial ART:**

No Longer Recommended For Initial Therapy

- **NRTI:** zidovudine (ZDV)
- **NNRTI:** nevirapine (NVP)
- **PI:**
  - unboosted atazanavir (ATV)
  - fosamprenavir (FPV/r)
  - saquinavir (SQV/r)
- **Other:** maraviroc (MVC)


New York, NY: September 21, 2015
**NRTI**

Need:
- Less long-term toxicity

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**Tenofovir alafenamide (TAF)**

- 2 Phase 3 studies: TAF vs. TDF with FTC/EVG/cobi
  - 1713 treatment naïve patients
  - 92% (TAF) vs. 90% (TDF) <50 at week 48
  - *San Lancet 2015;385:2606-15*
- 2 doses:
  - TAF 10 mg (with boosted PIs)
  - TAF 25 mg (with NNRTIs and IIs)
- Co-formulations
  - TAF/FTC/EVG/c (FDA target action date: 11/5/15)
  - TAF/FTC (FDA target action date: 4/7/16)
  - TAF/FTC/RPV (submitted to FDA 7/1/15)
  - TAF/FTC/DRV/c (in development)

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**NRTI-sparing and NRTI-lite**

- 2-drug regimens
  - PI/r + 3TC
    - GARDEL (LPV/r): Cahn *Lancet ID 2014;14:572*
  - PI/r + integrase inhibitor
    - NEAT-001 (DRV/r + RAL): Raffi *Lancet 2014;384:1942*
  - DTG + 3TC
    - PADDLE, ASPIRE (switch), A5353
    - DTG + RPV
    - SWORD (switch, phase 3)
NNRTI

Needs:
• Less toxic and better tolerated
• Fewer drug interactions
• Active against resistant viral strains

Doravirine (DOR; MK-1439)
• Investigational NNRTI
• Pre-clinical
  - Potent at low milligram dose
  - Metabolized by CYP3A4; not a CYP450 inhibitor or inducer
  - Active in vitro against viral strains with:
    • K103N
    • Y181C
    • G190A
    • E101K
    • E138K
    • K103N/Y181C

Study population: Treatment-naïve, VL>1000, CD4>100 (N=216)
Study regimen: TDF/FTC + DOR or EFV
Overall Results: VL <50 at week 24 74% (DOR) vs. 73% (EFV)

Patients with ≥1 CNS event: 27% (DOR) vs. 46% (EFV)
— Includes patients who discontinued due to non-treatment-related reasons but with last RNA <40 c/mL, or due to AE, or who lack data in week 24 window.
PI

• convenience

Integrase Inhibitors

Needs:
• long-acting

Cabotegravir (formerly GSK 744)

• Integrase inhibitor similar to DTG; similar resistance
• Potent in HIV+ individuals (10, 30, 60 mg oral)
  Margolis EACS 2013
• Nanotechnology formulation; SC + IM injections
• T ½ 21-50 days!
• Supports monthly or quarterly dosing
• Safety: ISR and nodules with SC dosing
• Pilot study with RPV-LA
LATTE-1: 2 NRTI + CAB or EFV → CAB + RPV

Primary Endpoint

Study population: Rx-naïve (N=243)

LATTE-2: CAB + RPV → IM dosing

New Mechanisms of Action

Question

Which new class of investigational drugs is farthest along in development?

1. Maturation inhibitor
2. CD4 attachment inhibitor
3. CXCR4 antagonist
4. RNase H inhibitor
**BMS-663068: Oral HIV Attachment Inhibitor**

- Prodrug of BMS-626529
- Inhibits CD4 binding by binding to gp120
- PK suggest QD or BID dosing without boosting
- ↓ baseline susceptibility in 12% of pts due to envelope polymorphism; screened by baseline IC50

*Nettles JID 2012;206:1002

**BMS-663068: Phase 2b**

- Randomized, partially blinded (to 068 dose)
- Rx-experienced pts (>1 wk on >1 ART) with IC50<100nM for 529 (N=251)
- Randomized to TDF + RAL + 1 of 4 doses of BMS 068 [400 or 800 bid or 600 or 1200 qd] or ATV/r
- Results:
  - 8d monotherapy: up to 1.5 log ↓ with 1200 mg qd
  - Wk 24 VL <50
  - BMS 068: no SAE or rx d/c

*Lalezari CROI 2014 #86
Brinson Glasgow 2014 #O432A/B

**BMS-955176 (Maturation Inhibitor)**

- Study population: Rx-naive, VL≥5000, CD4≥200 (N=28)
- Median change in HIV-c RNA at Day 29:
  - +0.66 to -2.18 log10 c/mL (BMS-955176 arms)
  - +0.22 log10 c/mL (2 NRTI + ATV) arm

*Hwang IAS 2015 #TUAB0106LB*
ART Controversies: Conclusions

• When to start? At any CD4 and “when the patient is ready.”
• What to start? Many excellent options and new comparative data; individualization is key.
• Virologic failure: Drugs with new mechanisms of action (CD4 attachment and maturation inhibitors)
• Further research is necessary.

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