HIV Treatment Basics

Babafemi Taiwo, MBBS
Gene Stollerman Professor of Medicine
Chief, Division of Infectious Diseases
Northwestern University, Chicago
Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Describe the rationale for HIV treatment in all PLWH
• Describe the principles of ART initiation including laboratory evaluation and drug classes
• Understand emerging concepts such as rapid ART initiation and two-drug ART

Faculty Disclosures
Please consult your program book or the Conference App.

• Dr. Taiwo has served as a paid consultant to ViiV Healthcare, GlaxoSmithKline, Gilead, and Janssen and received research funding through Northwestern University from ViiV, GlaxoSmithKline, Janssen and Pfizer.

Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.
This was then..1985

• "I knew it was a possibility but I never thought it would happen," said Patrick McCalister, a 24-year-old AIDS victim. "I'm going to die; I know that."

GOALS OF ART

• Viral suppression with a convenient, well tolerated, safe regimen

• Prevention and management of co-morbidities

• Prevention of viral transmission
Rocky Road → New Horizon

Viral Suppression Rates of Initial Regimens


SD, standard deviation.
START: Immediate vs Deferred ART

- START: International, randomized phase IV study involving 215 sites in 35 countries
  - Study stopped by DSMB following results of interim analysis
    - Overall HR: 0.43 ($P < .001$)
    - HR for serious AIDS-related events: 0.28 ($P < .001$)
    - HR for non-AIDS–related events: 0.61 ($P = .04$)

Which of the following is true about Rapid ART?

A. Approximately half of ART initiations in the U.S. meet the definition of Rapid ART
B. In a recent observational study, about 90% of persons who initiated Rapid ART were virally suppressed a year later
C. Guidelines recommend Rapid ART in ALL persons initiating treatment
D. Rapid ART is too risky and should not be considered
Treat All and Consider Rapid ART

- RAPID Program at Ward 86 UCSF started in 2013

- **Provided Services**
  - Same or next day appointment
  - Same day ART after insurance, educational and support help.
  - 3-5 day starter pack, prescriptions
  - Check up phone call, return within 2 weeks

Rapid ART

- **Median time**
  - HIV diagnosis to ART start = 7 days
  - RAPID intake to ART start = 0 days
  - HIV diagnosis to viral suppression <200 = 60 days

- VL < 200 copies/ml = 91.6%, a median of 1.09 years after ART start.
Recommendations on Same-Day ART Initiation

• DHHS guidelines - October 2018.[1]
  – *Same-day initiation of ART may be feasible and could potentially improve clinical outcomes...this approach remains investigational.*
• IAS-USA guidelines - July 2018.[2]
  – *ART should be initiated as soon as possible after diagnosis, including immediately after diagnosis, unless patient is not ready to commit to starting therapy.*

**Take-Home Message: Do not delay treatment!**

ACTHIV 2019: A State-of-the-Science Conference for Frontline Health Professionals

HIV in a Nutshell

First line ART regimens target HIV enzymes:

- **Reverse Transcriptase (3)**
- **Integrase (4)**
- **Protease (6)**

**Key to Terms**
- **HIV capsid**: HIV's core that contains HIV RNA
- **HIV envelope**: Outer surface of HIV
- **HIV enzymes**: Proteins that carry out steps in the HIV life cycle
- **HIV glycoproteins**: Protein “spikes” embedded in the HIV envelope
- **HIV RNA**: HIV's genetic material

Source: AIDS Info

Source: Wiring Diagram
One ARV agent has a cellular target:

CCR5 inhibitor

Which of these ARV agents has been in the DHHS guidelines since they were first written?

A. Lamivudine
B. Tenofovir
C. Lopinavir
D. Efavirenz
E. Raltegravir
First DHHS Guidelines (1998)

**Recommended Antiretroviral Agents for Treatment of Established HIV Infection**

<table>
<thead>
<tr>
<th>Preferred</th>
<th>One choice each from column A and column B.</th>
</tr>
</thead>
</table>
| **Column A** | Indinavir (AI)  
Nelfinavir (AII)  
Ritonavir (AI)  
Saquinavir – SGC* (AII)  
Ritonavir + Saquinavir SGC or HGC** (BII)  
Efavirenz (AII) |
| **Column B** | ZDV +ddI (AI)  
d4T + ddI (AII)  
ZDV + ddC (AI)  
ZDV + 3TC* (AII)  
d4T + 3TC† (AII) |

Guidelines still recommend use of 3 drugs when starting ART in most people.

DHHS https://aidsinfo.nih.gov/contentfiles/adultandadolescentgl12011998012.pdf

Current regimens **STILL** with THREE drugs

**Column A (ONE AGENT)**
- Integrase Inhibitor
- Boosted PI
- Non-nucleoside reverse transcriptase inhibitor

**Column B (TWO AGENTS)**
- Nucleos(t)ide reverse transcriptase inhibitors
Era of Integrase Inhibitors

- Clinical trials favoring INSTI over boosted PI

<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>FLAMINGO</th>
<th>WAVES</th>
<th>ARIA</th>
<th>DAWNING</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>83%</td>
<td>87%</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>ATV/3TC</td>
<td>90%</td>
<td>82%</td>
<td>71%</td>
<td>69%</td>
</tr>
<tr>
<td>ATV/3TC/EFV</td>
<td>82%</td>
<td>81%</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>ATV/3TC/EFV</td>
<td>83%</td>
<td>82%</td>
<td>71%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Virologically suppressed patients (%)

bPI: drug interactions and comorbidities
NNRTIs: lower resistance barrier

Can two-drug dual-site regimens provide similar efficacy but better long-term safety, cost and drug interaction profile?
Selecting initial ART from myriad of options

- Hepatitis B positive (must include TAF/TDF) or use entecavir
- HLA B5701 status (negative to use ABC)
- Co-morbidities, e.g. TDF (renal/bone), boosted PI (dyslipidemia, CVD, drug interactions), abacavir (? CVD)
- Can booster be avoided?
- Patient preference e.g. single tablet regimen, food requirements
- Cost/insurance

DHHS or IAS recommended initial regimens for most PLWH include all the following except

- Bictegravir/TAF/FTC
- Dolutegravir/abacavir/lamivudine
- Dolutegravir plus lamivudine
- Raltegravir plus TAF/FTC
- Dolutegravir plus TDF/FTC
Recommended Regimens for First-line ART

<table>
<thead>
<tr>
<th>DHHS*[1]</th>
<th>IAS-USA†[2]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended initial regimens for most people with HIV:</strong></td>
<td><strong>Generally recommended initial regimens:</strong></td>
</tr>
<tr>
<td>▪ BIC/TAF/FTC</td>
<td>▪ BIC/TAF/FTC</td>
</tr>
<tr>
<td>▪ DTG/ABC/3TC, if HLA-B*5701 negative</td>
<td>▪ DTG/ABC/3TC, if HLA-B*5701 negative</td>
</tr>
<tr>
<td>▪ DTG + (TAF or TDF)/FTC</td>
<td>▪ DTG + TAF/FTC</td>
</tr>
<tr>
<td>▪ RAL + (TAF or TDF)/FTC</td>
<td></td>
</tr>
</tbody>
</table>

Bold text identifies single-tablet regimens.

* DHHS does not recommend DTG for pregnant individuals within 12 wks post conception, women of childbearing potential planning to become pregnant, or sexually active women of childbearing potential not using effective contraception.

† IAS-USA recommends documenting negative pregnancy test in women of childbearing age before initiating DTG and counseling on potential risk of NTDs.

Baseline: History and Physical

- History
  - General medical/surgical
  - Psychosocial
  - Mental health (e.g., PHQ-9 depression scale)
  - Substance use
  - Sexual
- Review of systems
- Physical examination

DHHS Guidelines: CD4 Cell Count Testing

- Entry into care
  - Stratifies for risk of opportunistic conditions
- On ART
  - Every 3-6 months if HIV RNA not controlled
- If on ART >2 years with consistent viral suppression
  - 300-500 cells/mm³: monitor every 12 months
  - >500 cells/mm³: monitoring optional
- Resume more frequent CD4 monitoring
  - Virologic rebound, new HIV-associated clinical symptoms, develop conditions or initiate therapy that may lead to reduction in CD4 count
DHHS Guidelines:
HIV RNA Viral Load and ART Resistance Testing

<table>
<thead>
<tr>
<th>At Entry Into Care</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA</td>
<td>√</td>
</tr>
<tr>
<td>Drug resistance testing</td>
<td>√</td>
</tr>
<tr>
<td>Recommended for all persons with an HIV RNA &gt;1000 copies/mL, regardless of treatment initiation Consider if HIV RNA 500 to 1000 copies/mL Genotypic assay is preferred</td>
<td></td>
</tr>
</tbody>
</table>

Resistance Testing- Genotype

- Reverse transcriptase (RT) ✓
- Protease (PR) ✓
- Integrase – ✓ “IF IT IS A CONCERN”
- Co-receptor tropism- NOT NEEDED FOR INITIAL THERAPY
Select the **false statement** about resistance testing prior to ART initiation

A. Genotypic testing is better than phenotypic testing  
B. Guidelines recommend testing reverse transcriptase, protease, and integrase genes in all patients  
C. Resistance testing remains valuable even in persons who have infected for a long time  
D. Treatment can be started before seeing the resistance results in most persons

---

**Should We Be Testing for Baseline Integrate Resistance in Patients Newly Diagnosed With Human Immunodeficiency Virus?**

- Assumed base integrate resistance = 0.1%  
- Initiate DTG – based regimen  
- Integrate resistance if not suppressed at week 12  
- If resistant, switch to DRV/r based regimen

- IR testing = worse clinical outcomes and increased costs by $200/person/year.  
- Prevalence of transmitted INSTI-R virus did not affect results.  
- No IR testing preferred unless DTG suppression of INSTI-R virus was <20% or 96-week DRV/r suppression was >92%.

Koullias et al. CID 2017
Transmitted Drug Resistance in the U.S. 2013-2016

- Any transmitted drug resistance- 19%
- NNRTI-11.9%
- NRTI-6.8% (M184V- 0.68%)
- Protease- 4.3%
- Integrase-0.8%

- Transmitted resistance to 2 drug classes-2.4%
- Transmitted resistance to 3 drug classes-0.3%

McClung et al. CDC. CROI 2019

DHHS Guidelines: Recommended Laboratory Tests for Initial Visit

<table>
<thead>
<tr>
<th>Test</th>
<th>Entry Into Care</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum NA, K, HCO₃, Cl, BUN, creatinine, glucose (preferable fasting)*</td>
<td>√</td>
<td>Every 6 to 12 months</td>
</tr>
<tr>
<td>Liver function (ALT, AST)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (total and direct)</td>
<td>√</td>
<td>Every 6 to 12 months</td>
</tr>
<tr>
<td>CBC with differential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>√</td>
<td>If normal, annually</td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other Baseline Tests

- HLA-B*5701 if abacavir to be used
- Screen for chronic HBV (HBsAg) or HBV immunity (HBsAb)
- Screen for chronic HCV (HCV IgG and confirmatory HCV RNA)
- Latent TB screening
- *Toxoplasma gondii* serology (IgG)

Adherence

- Necessary for treatment success
- Poor adherence increases the risk of treatment failure and resistance
- Clinician may not be able to predict which patient will be adherent
- If patient says they are non-adherent, believe them. If they say they are adherent, .... it depends
- Consequences of poor adherence depend on the regimen
  - Boosted PIs favored
  - ? Dolutegravir/Bictegravir
- Be proactive about adherence
  - Patient education
  - Pill box and reminders
Low-level viremia = 50-200 copies/mL

Is this non-suppressible viremia from viral replication or is it from cellular proliferation with proviral expression?
Nonsuppressible viremia on ART from large cell clones carrying intact proviruses.

10 Median VL of 97.5 cpm after median of 10 year on ART

9 No evolution on SGS and no resistance

1 Evolution with resistance

6/9 proviral and plasma sequences matched

Conclusion: Avoid Complacency

- BMJ- “HIV/AIDS: complacency risks reversing progress on ending epidemic, conference hears”

- Jamaica Observer: “Dangerous complacency' looms over world AIDS meeting”

- Lancet: “Response to HIV/AIDS epidemic at risk of 'dangerous complacency' as urgent change in approach is needed”
Acknowledgments

• Chicago AIDS Clinical Trials Unit
• Volunteer PLWH