Advances in Treatment of HIV/AIDS

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Disclosure Information

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Continuing Medical Education committee members and those involved in the planning of this CME Event have no financial relationships to disclose.

Eric S. Daar, M.D.

I have the following financial relationships to disclose:

- Consultant for: Bristol Myers Squibb, Gilead, Janssen, Merck, ViiV
- Speaker’s Bureau for: None
- Grant/Research support: Abbott, Gilead, Merck, ViiV
- Stockholder in: None
- Honoraria from: None
- Employee of: None

and

I will not discuss off label use and/or investigational use in my presentation.
Overview

• Epidemiology
• Testing
• Treatment
• Prevention
• Future issues
AIDS Diagnoses and Deaths of Adults and Adolescents with AIDS, 1985–2009—United States and 6 U.S. Dependent Areas

Note. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting. Deaths of persons with an AIDS diagnosis may be due to any cause.
Life Expectancy of HIV-Infected Patients

- Life expectancy of Athena cohort to general population (n=4,174)
- Expected life years remaining at age 25
  - 53.1 (44.9-59.5) for general population
  - 52.7 for asymptomatic HIV+ patients

Infected and Unaware

CDC and Prevention National HIV Surveillance System\(^1\)

- Females (n=279,200)
- Males (n=869,000)

Diagnosed

- 85%
- 81%

Transmission Risk\(^2\)

- \(~25\%\) Unaware of Infection
- \(~75\%\) Aware of Infection

People Living with HIV

- Accounting for:

New Sexual Infections

- \(~54\%\) New Infections
- \(~46\%\) New Infections

n=1,148,200 HIV-infected persons, 18% of whom are unaware of their infection.

2. Marks et al. AIDS 2006; 20:1447
Revised CDC Recommendations for HIV Testing in Healthcare Settings

• Routine voluntary testing for patients ages 13 to 64 years in healthcare settings
  – Not based on patient risk
• Opt-out testing
• No separate consent for HIV
• Pretest counseling not required
• Repeat HIV testing left to discretion of provider
  – Based on patient risk

Rapid Home HIV Testing
(Approved July 2012)
HIV Cascade

![Bar chart showing engagement in HIV care.](image)

On November 29, 2011, this report was posted as an MMWR Early Release on the MMWR website (http://www.cdc.gov/mmwr).
When to Start?
Why not treat everyone?

• Not ready to commit to treatment
• Short-term and long-term toxicity
• Need for life long therapy
• Risk of virologic failure, resistance and cross-resistance
• Limited evidence for earlier therapy being associated with better outcomes than delayed therapy
Physical Manifestations of Fat Redistribution Syndromes
Case for Earlier Therapy

- Recent cohort studies (4 for 350-500 cells/uL and 1 for >500 cells/uL)
- HIV replication associated with non-AIDS-defining diseases (e.g. cardiovascular, renal, liver, malignancy) and irreversible damage
- Evidence that ARVs may reduce risk of transmission
- ARV more effective, convenient, better tolerated than in the past

CIPRAHT001: Randomized Trial of When to Start ART in Haiti

Randomized clinical endpoint study of when to start therapy

- Early Treatment (Immediate ZDV/3TC + EFV)
- Standard Treatment (Delay until CD4+ <200 or AIDS)

Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Early (n=408)</th>
<th>Standard (n=408)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Male (%)</td>
<td>41%</td>
<td>44%</td>
</tr>
<tr>
<td>Median CD4+ (cells/mm³)</td>
<td>280</td>
<td>282</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>21.4</td>
<td>21.0</td>
</tr>
</tbody>
</table>

### CIPRAHT001: Clinical Endpoints

**May 2009: DSMB review stopped study due to excess deaths in Defer Treatment arm**

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Early</th>
<th>Standard</th>
<th>Hazards Ratio (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>6</td>
<td>23</td>
<td>4.0 (.0011)</td>
</tr>
<tr>
<td>Incident Tuberculosis</td>
<td>18</td>
<td>36</td>
<td>2.0 (.0125)</td>
</tr>
</tbody>
</table>

- Infectious causes of death
  - Early: 1 (gastroenteritis)
  - Standard: 17 (7 gastroenteritis, 5 TB, 4 pneumonia, 1 cholangitis/sepsis)
- More toxicity from ART and intensive need for lab f/u for deferred grp
- WHO start guidelines now modified to <350 cells/uL

### NA-ACCORD: Risk of Death with ART Deferral

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>351-500 CD4+</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deferral of ART</td>
<td>1.7</td>
<td>1.3, 2.3</td>
<td>&lt;0.001</td>
<td></td>
<td>1.9</td>
<td>1.4, 2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.2</td>
<td>0.9, 1.6</td>
<td>0.24</td>
<td></td>
<td>1.9</td>
<td>1.3, 2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Older Age (per 10 years)</td>
<td>1.7</td>
<td>1.5, 1.9</td>
<td>&lt;0.001</td>
<td></td>
<td>1.8</td>
<td>1.6, 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline CD4 count (per 100 cells/mm³)</td>
<td>1.1</td>
<td>0.7, 1.8</td>
<td>0.59</td>
<td></td>
<td>0.9</td>
<td>0.9, 1.0</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>&gt;500 CD4+</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deferral of ART</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Sex</td>
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<td></td>
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</tr>
<tr>
<td>Baseline CD4 count (per 100 cells/mm³)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Ultimate CD4 Cell Count Depends on Where You Start

ATHENA National Cohort

Weeks From Starting ART

0 48 96 144 192 240 288 336

0 200 400 600 800 1000

≥500
350-500
200-350
50-200
<50

SMART: Changes in D-Dimer and IL-6 Levels

- Suggests HIV viremia effect on endothelium, leading to increased tissue factors and initiation of coagulation cascade

* DC patients on ART at baseline with HIV RNA ≤400 copies/mL

HPTN 052: Immediate vs Delayed ART in Serodiscordant Couples

HIV-infected, sexually active serodiscordant couples; CD4+ cell count of the infected partner: 350-550 cells/mm$^3$ (N = 1763 couples)

Immediate ART
Initiate ART at CD4+ cell count 350-550 cells/mm$^3$ (n = 886 couples)

Delayed ART
Initiate ART at CD4+ cell count ≤ 250 cells/mm$^3$* (n = 877 couples)

*Based on 2 consecutive values ≤ 250 cells/mm$^3$.

- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and use of condoms

HPTN 052: Linked HIV Transmission Events

n=27; incidence rate
1.7 per 100 p-y (95% CI 1.1, 2.5)

n=1; incidence rate
0.1 per 100 p-y (95% CI 0.0, 0.4)

### When to Start Treatment

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4 Count (cells/mm³)</th>
<th>HIV RNA (copies/mL)</th>
<th>2/13/13 DHHS Guidelines</th>
<th>2012 IAS-USA Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness or severe symptoms</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>≤500</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td></td>
<td>&gt;500</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>HIV-associated nephropathy</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>HIV/HBV coinfection when HBV treatment is indicated</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
<td>Treat</td>
</tr>
</tbody>
</table>

*Unless elite controller (HIV RNA <50 copies/mL) or has stable CD4 cell count and low-level viremia in absence of therapy.*

The IAS-USA guidelines also recommends initiating antiretroviral therapy in HIV-infected patients with active hepatitis C virus infection, active or high risk for cardiovascular disease, and symptomatic primary HIV infection.

What to Start?
According to the most recent DHHS ARV Treatment guidelines, which of the following is not a preferred drug to be combined with tenofovir DF/emtricitabine as first-line therapy?

1. Efavirenz
2. Rilpivirine
3. Raltegravir
4. Atazanavir/ritonavir
5. Darunavir/ritonavir
Factors to consider in choosing first-line therapy

- Patients' willingness to commit to therapy
- Baseline resistance
- Comorbid conditions
- Efficacy data
- Tolerability
- Convenience
- Consequences of failure (resistance)
- Since the introduction of potent ARV therapy preferred regimens all include NRTIs + third drug
HIV replication cycle and sites of drug activity

**Capsid proteins and viral RNA**

**HIV Virions**

**NRTIs**
- AZT (Zidovudine-Retrovir)
- ddI (Didanosine-Videx)
- ddC (Zalcitabine-Hivid)
- d4T (Stavudine-Zerit)
- 3TC (Lamivudine-Epivir)
- ABC (Abacavir-Ziagen)
- FTC (Emtricitabine, Emtriva)

**NNRTIs**
- Efavirenz (Sustiva)
- Nevirapine (Viramune) (XR)
- Etivirine (Intalense)
- Rilpivirine (Edurant)

**Protease Inhibitors**
- Indinavir (Crixivan)
- Ritonavir (Norvir)
- Saquinavir (Fortovase)
- Nelfinavir (Viracept)
- Lopinavir/ritonavir (Kaletra)
- Atazanavir (Reyataz)
- Fos Amprenavir (Lexiva)
- Tipranavir (Aptivus)
- Darunavir (Prezista)

**Reverse Transcriptase**

**Integrate**

**Protease**

**Attachment**

**Uncoating**

**Reverse Transcription**

**Integration**

**Transcription**

**Translation**

**Assembly and Release**

**New HIV particles**

**CD4 Receptor**

**Fusion Inhibitor T-20 (Enfuvirtide, Fuzeon)**

**CCR5 Antagonist Maraviroc (Celsentri)**

**Integrate Inhibitor**
- Raltegravir (Isentress)
- Elvitegravir / COBI

**Integrate**

**Reverse Transcription**

**Viral RNA**

**Unintegrated double stranded Viral DNA**

**Integrated Viral DNA**

**Viral mRNA**

**gag-pol polyprotein**

**Cellular DNA**

**nRTI**
- Tenofovir DF (Viread)

**Integrate Inhibitor**
- Raltegravir (Isentress)

**Assembly and Release**

**New HIV particles**

**Capsid proteins and viral RNA**

**Protease**

**Translated protein**

**Assembly and Release**

**New HIV particles**
Nucleoside/tide Reverse Transcriptase Inhibitors
NRTIs: TDF or ABC

• ABC limitations
  – Potentially less active than TDF in patients with high viral loads on ATV/r or EFV
  – Conflicting data on ABC and CV risk

• TDF limitations
  – associated with greater decline in bone mineral density
  – associated with variable decline in renal function
Third Drug to Combine with NRTIs

- Reverse Transcriptase
- Protease
- Integrase
- CCR5 Chemokine Receptor
Boosted-Protease Inhibitors

**KLEAN**
(ITT-E, TLOVR)
48 weeks

- LPV/r 400/100 QD
- FPV/r 700/100 BID

**ARTEMIS**
(ITT, TLOVR)
96 weeks

- LPV/r QD or BID
- DRV/r 800/100 QD

**CASTLE**
(ITT, NC=F)
96 weeks

- LPV/r 400/100 BID
- ATV/r 300/100 QD

ATV/r vs. EFV
Primary Endpoint

### STARTMRK: RAL vs. EFV

**Rockstroh J, et al, 19th IAC; Washington, DC; July 22-27, 2012; Abst. LBPE19.**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
<th>120</th>
<th>144</th>
<th>168</th>
<th>192</th>
<th>216</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients with HIV RNA Levels &lt;50 Copies/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir 400 mg BID</td>
<td>281</td>
<td>278</td>
<td>279</td>
<td>280</td>
<td>281</td>
<td>281</td>
<td>277</td>
<td>280</td>
<td>281</td>
<td>281</td>
<td>277</td>
<td>279</td>
</tr>
<tr>
<td>Efavirenz 600 mg QHS</td>
<td>282</td>
<td>282</td>
<td>282</td>
<td>281</td>
<td>282</td>
<td>282</td>
<td>281</td>
<td>281</td>
<td>282</td>
<td>282</td>
<td>282</td>
<td>279</td>
</tr>
</tbody>
</table>

**CD4 Change:** RAL +374 vs. EFV +312

**ITT, NC=F**

**Twice per day vs. Once per day**

**BUT**

**Less side effects**
Pooled ECHO and THRIVE: Virologic Response (ITT-TLOVR)

- Mean change in CD4 cell count from baseline at Week 48 (NC=F⁺): TMC278: +192 vs. EFV: +176 cells/mm³
### Pooled ECHO and THRIVE: Virologic Response (ITT-TLOVR)

<table>
<thead>
<tr>
<th>Outcome at Week 48, %</th>
<th>Pooled</th>
<th>ECHO</th>
<th>THRIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TMC278 N=686</td>
<td>EFV N=682</td>
<td>TMC278 N=346</td>
</tr>
<tr>
<td>VL &lt;50 copies/mL</td>
<td>84.3</td>
<td>82.3</td>
<td>82.9</td>
</tr>
<tr>
<td>Virologic failure‡</td>
<td>9.0</td>
<td>4.8</td>
<td>11.0</td>
</tr>
<tr>
<td>- Rebounder</td>
<td>3.5</td>
<td>2.2</td>
<td>4.6</td>
</tr>
<tr>
<td>- Never suppressed</td>
<td>5.5</td>
<td>2.6</td>
<td>6.4</td>
</tr>
<tr>
<td>Discontinued due to AE</td>
<td>2.0</td>
<td>6.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Discontinued for other reasons§</td>
<td>4.5</td>
<td>5.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Death</td>
<td>0.1</td>
<td>0.4</td>
<td>0.0</td>
</tr>
</tbody>
</table>
GS102 & GS103: EVG/COBI/TDF/FTC vs. EFV/TDF/FTC or ATV/RTV + TDF/FTC

Randomized, Phase III, Double-blind, Double Dummy, Active-controlled, International Studies

GS 102
- ~89% men
- 33% >10^5 c/mL
- CD4= ~385 c/uL

Treatment Naïve
- HIV-1 RNA ≥5,000 c/mL
- Any CD4 cell count
- eGFR ≥70 mL/min

GS 103

Quad QD
- EFV/FTC/TDF Placebo QD
- EFV/FTC/TDF QD
- Quad Placebo QD
- Quad QD
- ATV/r +TDF/FTC Placebo QD
- QUAD Placebo QD
- ATV/r +TD/FTC QD

48 weeks
192 weeks

Study 236-102: Primary Endpoint: HIV-1 RNA < 50 copies/mL

Virologic Success: Quad 88% vs. EFV/FTC/TDF 84%

Virologic Non-Suppression: Quad 7% vs. EFV/FTC/TDF 7%

No W48 Data: Quad 5% vs. EFV/FTC/TDF 9%

CD4+ change: Quad +239 vs. EFV +206 c/mm³ (p=0.009)

No difference by baseline characteristics

## Study 236-102: Common Adverse Events

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Events in ≥ 10% of subjects (%)</th>
<th>Quad (n=348)</th>
<th>EFV/FTC/TDF (n=352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>23%</td>
<td>19%</td>
</tr>
<tr>
<td>Nausea *</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Abnormal Dreams ^</td>
<td>15%</td>
<td>27%</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Insomnia *</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Depression</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Dizziness ^</td>
<td>7%</td>
<td>24%</td>
</tr>
<tr>
<td>Rash #</td>
<td>6%</td>
<td>12%</td>
</tr>
</tbody>
</table>

* p<0.05; ^ p<0.001; # p=0.009

# DHHS Guidelines for Adolescents/Adults: What to Start

| Preferred Regimens | • EFV/TDF/FTC  
|• ATV/r + TDF/FTC  
|• DRV/r (once daily) + TDF/FTC  
|• RAL + TDF/FTC  
|[Pregnant Women Only: LPV/r (twice daily) + ZDV/3TC] |

| Alternative Regimens | • EFV + ABC/3TC  
|• RPV + (TDF or ABC)/(FTC or 3TC)  
|• ATV/r or DRV/r + ABC/3TC  
|• FPV/r or LPV/r (qd or bid) ABC/3TC or TDF/FTC  
|• RAL + ABC/3TC  
|• EVG/COBI/TDF/FTC |

| Acceptable Regimens | • EFV or RPV + ZDV/3TC  
|• NVP + TDF/FTC or ZDV/3TC or ABC/3TC  
|• ATV + (ABC or ZDV)/3TC  
|• ATV/r, DRV/r, LPV/r, FPV/r, RAL + ZDV/3TC  
|• MVC + ZDV or ABC/3TC  
|• SQV/r + TDF/FTC or ABC/3TC or ZDV/3TC (with caution) |

ART: What to Start
IAS–USA Recommendations, 2012

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI plus nRTIs</td>
<td>• Efavirenz/tenofovir/emtricitabine (Ala)</td>
</tr>
<tr>
<td></td>
<td>• Efavirenz plus abacavir/lamivudine (Ala) in HLA-B*5701-negative patients with baseline plasma HIV-1 RNA &lt;100,000 copies/mL</td>
</tr>
<tr>
<td>PI/r plus nRTIs</td>
<td>• Darunavir/r plus tenofovir/emtricitabine (Ala)</td>
</tr>
<tr>
<td></td>
<td>• Atazanavir/r plus tenofovir/emtricitabine (Ala)</td>
</tr>
<tr>
<td></td>
<td>• Atazanavir/r plus abacavir/lamivudine (Ala) in patients with plasma HIV-1 RNA &lt;100,000 copies/mL</td>
</tr>
<tr>
<td>InSTI plus nRTIs</td>
<td>• Raltegravir plus tenofovir/emtricitabine (Ala)</td>
</tr>
</tbody>
</table>
Prevention
Which of the following has been shown to be the most effective means of preventing HIV transmission?

1. Preexposure prophylaxis of uninfected partner with tenofovir DF/emtricitabine
2. Vaginal tenofovir gel for uninfected women
3. Rectal tenofovir gel for uninfected man who has sex with men
4. HIV vaccine
5. Antiretroviral therapy for HIV-infected partner
Robert Gallo and Heckler Press Conference 4/23/1984: “I think the agent is at hand that produces the disease.” Projected vaccine within 5 years

Note. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.
HPTN 052: Linked HIV Transmission Events

n=27; incidence rate 1.7 per 100 p-y (95% CI 1.1, 2.5)
n=1; incidence rate 0.1 per 100 p-y (95% CI 0.0, 0.4)
# Efficacy Rates of Prevention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size, Percent (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART for prevention; HPTN 052, Africa, Asia, Americas</td>
<td>96 (73-99)</td>
</tr>
<tr>
<td>PrEP for discordant couples; Partners PrEP, Uganda, Kenya</td>
<td>73 (49-85)</td>
</tr>
<tr>
<td>PrEP for heterosexual men and women; TDF2, Botswana</td>
<td>63 (21-84)</td>
</tr>
<tr>
<td>Medical male circumcision; Orange Farm, Rakai, Kisumu</td>
<td>54 (38-66)</td>
</tr>
<tr>
<td>PrEP for MSMs; iPrEX, Americas, Thailand, South Africa</td>
<td>44 (15-63)</td>
</tr>
<tr>
<td>Sexually transmitted diseases treatment; Mwanza, Tanzania</td>
<td>42 (21-58)</td>
</tr>
<tr>
<td>Microbicide; CAPRISA 004, South Africa</td>
<td>39 (6-60)</td>
</tr>
<tr>
<td>HIV vaccine; RV144, Thailand</td>
<td>31 (1-51)</td>
</tr>
<tr>
<td>PrEP for women; FEM-PrEP, Kenya, SA, Tanzania</td>
<td>0 (-69-41)</td>
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Future Issues
Work Towards a Cure

New Hope of a Cure for H.I.V.

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VIRUS-FREE Timothy Brown of San Francisco had two bone-marrow transplants to treat leukemia, and H.I.V. can no longer be detected in his body. (Heidi Schumann for The New York Times)

Procedure and Events

• Ablative chemotherapy
• Total body XRT
• Graft vs. host
• Transplant with CCR5Δ32 homozygous donor
Summary

• Current U.S. guidelines recommend early initiation of therapy
• First-line regimens are numerous with multiple one-pill once-per day options
• Preferred regimens all highly efficacious with differences between men and women still to be explored
• Major advances and options for prevention have recently emerged with treatment being at the forefront
• Despite progress, there remains much work to do both domestically and internationally
Thank You!!