HIV Treatment Update

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Case

You are initiating antiretroviral therapy on a recently diagnosed patient with a CD4 count of 54 and a viral load of 168,000 copies/ml. There are no baseline resistance mutations. His creatinine clearance is 65 ml/min and HLAB5701 is negative. Which of the following regimens would be the most appropriate choice based on current DHHS recommended options?

A. Tenofovir/emtricitabine/rilpivarine
B. Abacavir/lamivudine/ritonavir/atazanavir
C. Tenofovir/emtricitabine/cobicistat/elvitegravir
D. Abacavir/lamivudine/dolutegravir
E. Abacavir/lamivudine/ritonavir/darunavir

Learning Objectives

- Describe the HIV Continuum of Care Cascade and the importance of diagnosis, linkage, retention and adherence.
- Review the HIV therapeutic classes and how they are used in combination.
- Discuss recent updates to the Department of Health and Human Services Treatment Guidelines for antiretroviral therapy.
- Analyze a clinical scenario of a patient on antiretroviral therapy

HIV Epidemic: New York State

- Over 154,000 New Yorkers are living with HIV/AIDS
- 132,000 (86%) have been diagnosed
- 21% of persons with diagnosed HIV infection live outside of NYC
- 23% are diagnosed with AIDS, another 6% develop AIDS within 12 months
- While most HIV diagnoses are in people under age 40, 77% of PLWH/A are over age 40 and 47% are over age 50 in NY
- There are higher rates of new infection and prevalence of HIV among Blacks (7-8 fold) and Hispanics (5-6 fold) than whites


Community Viral Load Mirrors Reduced Rate of New HIV Cases in San Francisco

- Retrospective analysis of relationship between community viral load (CVL; mean of summed individual HIV-1 RNA results per yr) and new HIV diagnoses
- P = .005 for association
- Mean CVL
- Newly diagnosed and reported HIV cases

*Data insufficient to prove significant association with reduced HIV incidence.

Transmission Category of Potential Transmission Partners (2001-2012)


Black (n=14,392)  Other (n=1337)  White (n=14,809)

Potential Transmission Category

<table>
<thead>
<tr>
<th>Category</th>
<th>Black</th>
<th>Other</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>47%</td>
<td>3%</td>
<td>47%</td>
</tr>
<tr>
<td>Asian/NHOPI</td>
<td>27%</td>
<td>3%</td>
<td>27%</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>12%</td>
<td>3%</td>
<td>19%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
<td>3%</td>
<td>19%</td>
</tr>
</tbody>
</table>


- North America cohort (n=75,148)
  - On HAART (49.8%)
  - 1799 deaths over 89,521 person-years of follow-up
- Life expectancy at age 20 years
  - Increased
    - Stepwise with each calendar year
    - White and Hispanic versus Black
  - Decreased
    - IDU versus MSM and heterosexuals
- The need to address disparities in life expectancy is an ongoing healthcare need


Improving Efficacy of Initial HAART Regimens

Bartlett et al (AIDS. 2006;20:2051-2064)

**HIV RNA <50 Copies/mL**

- 1998*: 41%
- 1999-2000*: 50%
- 2001-2002*: 56%
- 2003-2004*: 64%
- 2006-2014**: 65% to 90%

**Values are weighted means 1994 to July 2004 (n=14,264 patients). 90 treatment arms from 53 trials: NNRTI (n=38); PI (n=32), NRTI (n=12), boosted PI (n=8). STR: single-tablet regimen.**

Heterosexual HIV Transmission After ART Initiation in Discordant Couples

- Partners for the Prevention of HSV/HIV Transmission study
  - Prospective cohort analysis of discordant couples (n=5381)
  - 7 African countries
- HIV-infected partners starting HAART (n=349)
  - Genetically linked HIV transmission (n=103)
- Follow-up
  - Up to 24 months

- HIV Incidence

- 2.24 (1.84-2.72)
- 0.37 (0.09-2.04)

- 92% Reduction


Challenges: HIV Care Cascade: New York State and the US

- HIV Diagnosed
- Linked to Care
- Retained in Care
- HIV RNA <200 Copies/mL

- US (2009; n=1,542,200)
- New York State (2012; n=154,000)

AIDS Free New York 2020, NYS DOH 2014
HIV Testing Law- New York

Requires that an HIV-related test be **offered to every individual between 13 and 64 years of age** (or younger/older if there is evidence of risk activity) receiving health services as an inpatient or in the emergency department of a hospital or receiving primary care services in the outpatient department of a hospital or freestanding diagnostic treatment center or from a physician, physician assistant, nurse practitioner, or midwife providing primary care.

New HIV Testing Regulations for New York State

- As of April 1, 2014, written informed consent no longer required
- Oral notification with an opportunity to “opt out”
- All HIV tests should be documented in the medical record
- Provide information about HIV testing on posters, brochures, videos or by providers
- Local and state Health Departments may share HIV information to assist in linkage and retention efforts

Techniques to Improve Linkage and Retention

- **NY Links Interventions**
  - Pre-visit contact (Phone, outreach, Project ARTAS- brief strengths based case management intervention)
  - Appointment Reminders and Missed Appointment Follow-up
  - Consistent Team Based Messaging
  - Outreach/Return to Care
  - Peer Support Interventions
- Motivational Interviewing
  
www.newyorklinks.org

Adherence to ART and Hospitalization Risk in the US

1 pill/day had better chance of achieving ≥85% adherence
- 1 versus 2: 47% versus 41% (P=0.019)
- 1 versus >3: 47% versus 34% (P<0.001)

Main results
- 85% adherence was significantly associated with a lower rate of hospitalization, regardless of pill burden (P<0.001)
- Patients receiving 1 pill/day were 24% less likely to have hospitalization compared with those receiving ≥3 pills/day (P=0.003)

Results remained significant after controlling for diagnoses of substance abuse, psychiatric illness, and medical complexity

Factors Associated with Higher Levels of Adherence

- Twice-daily or once-daily regimens
- Belief in own ability to adhere to regimen
- Not living alone
- Dependent on a significant other for support
- History of opportunistic infection or advanced HIV disease
- Belief in efficacy of antiretroviral therapy
- Belief that non-adherence will lead to viral resistance

Combination drugs (simplification)

- Combivir (zidovudine, lamivudine)
- Truvada (tenofovir + emtricitabine)
- Epzicom (abacavir + lamivudine)
- Trizivir (zidovudine + abacavir + lamivudine)
- Kaletra (lopinavir + ritonavir)

Single Tablet Regimens

- Atripla (tenofovir + emtricitabine + efavirenz)
- Complera (tenofovir + emtricitabine + Rilpivirine)
- Striibid (Tenofovir + emtricitabine + cobicistat + elvitegravir)
- Triumeq (abacavir, lamivudine, dolutegravir)
- Cobi/ATA, Cobi/DRV, TAF/FTC/Cobi/DRV (in development)

HAART 2014: 35 Drugs

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>INI</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine</td>
<td>nevirapine (2)</td>
<td>saquinavir (3)</td>
<td>raltegravir</td>
</tr>
<tr>
<td>lamivudine</td>
<td>delavirdine</td>
<td>ritonavir (3)</td>
<td>Elvitegravir/riboviral</td>
</tr>
<tr>
<td>Didanosine (2)</td>
<td>efavirenz</td>
<td>indinavir</td>
<td>dolugavir</td>
</tr>
<tr>
<td>zalcitabine</td>
<td>etravirine</td>
<td>Nelfinavir (2)</td>
<td>CCR5 Antagonist</td>
</tr>
<tr>
<td>stavudine</td>
<td>rilpivirine</td>
<td>amprenavir</td>
<td>maraviroc</td>
</tr>
<tr>
<td>abacavir</td>
<td>lopinavir/ritonavir</td>
<td>Fusion Inhibitor</td>
<td></td>
</tr>
<tr>
<td>tenofovir</td>
<td>Booster</td>
<td>fos-amprenavir</td>
<td>enfuvirtide</td>
</tr>
<tr>
<td>emtricitabine</td>
<td>cobicistat</td>
<td>atazanavir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>tipranavir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>darunavir</td>
<td></td>
</tr>
</tbody>
</table>

What’s New With the DHHS Guidelines?

- New sections
  - HIV and the older patient
  - Antiretroviral drug cost table
- Existing sections
  - ART is recommended for all HIV-infected individuals (strength recommendation varies by pretreatment CD4 cell count)
  - Effective ART has been shown to prevent transmission of HIV
  - HIV-infected women (expanded discussion on hormonal contraception)
  - HIV/HCV coinfection (preliminary recommendations on co-administration of NS3/4A drugs and ART
  - Prevention of secondary HIV transmission

New Drugs

- Triumeq®- Abacavir + lamivudine + dolutegravir STR
- Vitekta® - Elvitegravir (must be combined with co-administered “boosted” PI)
- Tybost®- Cobicistat- boosting agent with no antiretroviral activity (contained in Stribild® and being co-formulated with atazanavir and darunavir)

The Shift Towards Earlier Initiation of Antiretroviral Therapy

- Newer ART regimens
  - Generally better tolerated, more convenient, and more potent than older regimens
- Survival benefit
  - Randomized controlled trials
  - Observational cohort data
- Untreated HIV
  - Maybe associated the development of non-AIDS-defining illness
- Biologic rationale
- Effective ART reduces HIV transmission

2013 DHHS Guidelines: Recommendations for Initiation of ART in Naïve Patients

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4 Cell Count (cells/mm³)</th>
<th>2013 DHHS Guidelines</th>
<th>Strength-Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of Transmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Perinatal Any value</td>
<td>Treat</td>
<td>AII</td>
<td></td>
</tr>
<tr>
<td>- Heterosexual</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Other Risks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatics:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>Treat</td>
<td>AII</td>
<td></td>
</tr>
<tr>
<td>200 to 500</td>
<td>Treat</td>
<td>AII</td>
<td></td>
</tr>
<tr>
<td>&gt;500</td>
<td>Treat</td>
<td>BIII</td>
<td></td>
</tr>
</tbody>
</table>

Patients starting ART should be willing and able to receive treatment and understand the benefits and risks of therapy and the importance of adherence. Providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

2013 Update: DHHS Guidelines on ART for HIV-Infected Adults and Adolescents

- Patients with early infection should be offered ART
  - “Early” HIV infection now refers to acute (after infection, prior to seroconversion) and recent (<6 mos) infections
Mortality Risk: Patients on ART vs. HIV-negative Population

3280 Non-IDU Patients from SMART and ESPRIT

<table>
<thead>
<tr>
<th>Overall</th>
<th>Most Recent Eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 350-500 cells/mm³</td>
<td>suggests higher mortality rates despite ARVs</td>
</tr>
<tr>
<td>CD4 &gt;500/mm³</td>
<td>similar risk to HIV negative population</td>
</tr>
</tbody>
</table>

Conclusions:
- CD4 350-500 cells/mm³ – suggests higher mortality rates despite ARVs
- CD4 >500/mm³ – similar risk to HIV negative population

3280 Non-IDU Patients from SMART and ESPRIT

Observed Death Rates and SMRs Standardized by Age and Sex and Country

Overall Most Recent Eligible

<table>
<thead>
<tr>
<th>CD4 Count Cells/µL</th>
<th>Pt-yrs follow-up</th>
<th>Observed deaths</th>
<th>Expected deaths</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>350-499</td>
<td>12357</td>
<td>28</td>
<td>15.86</td>
<td>1.77 (1.17-2.55)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>3729</td>
<td>34</td>
<td>33.96</td>
<td>1.00 (0.69-1.40)</td>
</tr>
</tbody>
</table>


SMR: Standardized Mortality Ratio

CD4 at Initiation of ARV Therapy Predicts Extent of CD4 Recovery

- 1,378 patients at 10 US clinics followed from 1996-2007
- Median peak CD4 was progressively higher for specific CD4 strata

\[ p < 0.001 \]

CD4 at Initiation of ARV Therapy Predicts Extent of CD4 Recovery

DHHS Guidelines: Recommended Regimens

Regardless of Baseline HIV RNA Level or CD4 Count

**NNRTI**
- Efavirenz/emtricitabine/tenofovir DF*

**PI**
- Atazanavir + ritonavir + emtricitabine/tenofovir DF
- Darunavir + ritonavir + emtricitabine/tenofovir DF

**INSTI**
- Raltegravir + emtricitabine/tenofovir DF
- Elvitegravir/cobicistat/emtricitabine/tenofovir DF*
- Dolutegravir + abacavir/lamivudine
- Dolutegravir + emtricitabine/tenofovir DF

*Available as a once-daily, single-tablet regimen.

Notes:
- Efavirenz: avoid use in women trying to conceive or are sexually active and not using contraception.
- Lamivudine may substitute for emtricitabine or visa versa.
- Tenofovir DF: use with caution in patients with renal insufficiency.
- Atazanavir + RTV: absorption depends on food and low gastric pH.
- Elvitegravir/cobicistat/emtricitabine/tenofovir DF: only for patients with pre-ART creatinine clearance >70 mL/min.
- Darunavir + RTV: absorption depends on food and low gastric pH.
- Raltegravir + abacavir/lamivudine: only for patients who are HLA-B*5701 negative.

DHHS. Paper presented at: 17th CROI; February 16-19, 2010; San Francisco, CA. Abst. 983.

DHHS Guidelines: Recommended Regimens

Additional Options When Baseline HIV RNA <100K Copies/mL

**NNRTI**
- Efavirenz + abacavir/lamivudine
- Rilpivirine/emtricitabine/tenofovir DF*

**PI**
- Atazanavir + ritonavir + abacavir/lamivudine

*Available as a once-daily, single-tablet regimen.

Notes:
- Efavirenz: avoid use in women trying to conceive or are sexually active and not using contraception.
- Abacavir: only for patients who are HLA-B*5701 negative.
- Lamivudine may substitute for emtricitabine or visa versa.
- Tenofovir DF: use with caution in patients with renal insufficiency.
- Rilpivirine/emtricitabine/tenofovir DF: only for patients with pre-ART CD4 >200 cells/mm³.

DHHS. Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

DHHS Guidelines: Alternative Regimens

May Be the Preferred Regimen for Some Patients

**PI**
- Darunavir + ritonavir + abacavir/lamivudine
- Lopinavir/ritonavir (qd or bid) + abacavir/lamivudine or emtricitabine/tenofovir DF

**INSTI**
- Raltegravir + abacavir/lamivudine

Notes:
- Darunavir + ritonavir: avoid use in women trying to conceive or are sexually active and not using contraception.
- Lamivudine may substitute for emtricitabine or visa versa.
- Tenofovir DF: use with caution in patients with renal insufficiency.
- Atazanavir + RTV: absorption depends on food and low gastric pH.
- Rilpivirine/emtricitabine/tenofovir DF: only for patients with pre-ART CD4 >200 cells/mm³.
- Darunavir + RTV: absorption depends on food and low gastric pH.

DHHS. Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.

ART Pill Burden in 2014: Initial Regimens

<table>
<thead>
<tr>
<th>Single-tablet, once-daily</th>
<th>Multipill pills (number of pills/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TDF/FTC/EFV</td>
</tr>
<tr>
<td>1</td>
<td>TDF/FTC/DRV/ABT/3TC/COBI</td>
</tr>
<tr>
<td>2</td>
<td>TDF/FTC/COBI</td>
</tr>
<tr>
<td>3</td>
<td>TDF/FTC/RTV + ABC/3TC</td>
</tr>
<tr>
<td>4</td>
<td>TDF/FTC/RTV + ABC/3TC</td>
</tr>
</tbody>
</table>

Notes:
- When VL < 100,000; CD4 > 200

DHHS. Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 1, 2014.
ACTG A5257 Study: Additional Outcomes

- All 3 arms had equivalent virologic efficacy.
- Atazanavir/r arm was less well tolerated:
  - Largely due to cosmetic hyperbilirubinemia.
- Raltegravir was superior to both PI/r regimens for combined tolerability + virologic efficacy.
- Darunavir/r was superior to atazanavir/r.
- Virologic failure with resistance was rare.
- More frequent with raltegravir.

Trials of ABC/3TC/Dolutegravir

- Randomized, noninferiority phase III studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48

**Spring-3**
- (Placebo controlled)
- ART-naive pts
  - VL ≥ 1000 copies/mL
  - HLA-B*5701 neg
  - CrCl > 50 mL/min
  - N = 822

- DTG 50 mg QD + 2 NRTIs
  - (n = 411)
- RAL 400 mg BID + 2 NRTIs
  - (n = 411)
- EFV/TDF/FTC QD
  - (n = 419)

- 88% DTG Superior

**Single**
- (Placebo controlled)
- ART-naive pts
  - VL ≥ 1000 copies/mL
  - HLA-B*5701 neg
  - CrCl > 50 mL/min
  - N = 484

- DTG 50 mg QD + ABC/3TC QD
  - (n = 242)
- DRV/RTV 800/100 mg QD + 2 NRTIs
  - (n = 242)

- 90% DTG Superior

**Flamingo**
- (Open label)
- ART-naive pts
  - VL ≥ 1000 copies/mL
  - HLA-B*5701 neg
  - CrCl > 50 mL/min
  - N = 584

- DTG 50 mg QD + 2 NRTIs
  - (n = 242)
- EFV/TDF/FTC QD
  - (n = 242)

- 83% DTG Superior
Virologic Success Over Time

Week 48

DTG 88%
RAL 85%

Most Common Adverse Events (≥50%)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>DTG 50 mg QD (n=411)</th>
<th>RAL 400 mg BID (n=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>339 (82%)</td>
<td>340 (83%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>59 (14%)</td>
<td>53 (13%)</td>
</tr>
<tr>
<td>Headache</td>
<td>51 (12%)</td>
<td>48 (12%)</td>
</tr>
<tr>
<td>Nephropathygalactia</td>
<td>48 (12%)</td>
<td>48 (12%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47 (11%)</td>
<td>47 (11%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>26 (6%)</td>
<td>26 (6%)</td>
</tr>
<tr>
<td>Chills</td>
<td>22 (5%)</td>
<td>22 (5%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20 (5%)</td>
<td>20 (5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (5%)</td>
<td>19 (5%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>17 (4%)</td>
<td>17 (4%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>10 (2%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Depression</td>
<td>10 (2%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5 (1%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>4 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

Renal Safety

- No withdrawals due to renal events
- Small increase in creatinine due to blockade of Cr secretion
- DTG does not affect actual glomerular filtration rate (GFR)

Protocol-Defined Virologic Failure (PDVF): Genotype

• Amongst DTG-treated subjects, no integrase nor NRTI mutations were detected throughout Week 48

- INI-r mutations 0/18 (6%)
- NRTI-r mutations 0/19 (21%)

A62A/V (n=1), M184M/I (n=1), M184M/V (n=1)

Phase 2c Study 957

- Subjects receiving DTG +ABC/3TC achieved virologic suppression faster than Atripla, median time to HIV-1 RNA <50 c/mL of 28 days (DTG +ABC/3TC) vs 84 days (Atripla), P<0.0001


Proportion (95% CI) of Subjects <50 c/mL (FDA Snapshot)

- DTG 50 mg +ABC/3TC QD was statistically superior to Atripla at Week 48 (primary endpoint)
- Subjects receiving DTG +ABC/3TC achieved virologic suppression faster than Atripla, median time to HIV-1 RNA <50 c/mL of 28 days (DTG +ABC/3TC) vs 84 days (Atripla), P<0.0001
Proportion <50 c/mL: Snapshot Outcomes

<table>
<thead>
<tr>
<th>Outcome (snapshot) at Week 48</th>
<th>DTG 50 mg + ABC/3TC QD (N=414)</th>
<th>Atripla QD (N=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic success</td>
<td>364 (88)</td>
<td>338 (81)</td>
</tr>
<tr>
<td>Virologic nonresponse</td>
<td>21 (5)</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Data in window not &lt;50 c/mL</td>
<td>6 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>7 (2)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Discontinued for other reason while not &lt;50 c/mL</td>
<td>8 (2)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>No virologic data at Week 48</td>
<td>29 (7)</td>
<td>55 (13)</td>
</tr>
<tr>
<td>Discontinued because of AE or death*</td>
<td>9 (2)</td>
<td>40 (10)</td>
</tr>
<tr>
<td>Discontinued for other reasons</td>
<td>20 (5)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>0</td>
<td>(1 &lt;1)</td>
</tr>
</tbody>
</table>

Note: *Data on virologic data at window not <50 c/mL/subjects who discontinued prior to Week 48 and virologic data at study end but not prior to Week 48 window

Virology: Resistance

Subjects with PDVF: 12% (84/688)

<table>
<thead>
<tr>
<th>PDVF genotypic population</th>
<th>11</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDVF Genotypic (RT Results at Baseline and PDVF)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>NRTI tmt-emergent major mutations</td>
<td>0</td>
<td>1(KESR)</td>
</tr>
<tr>
<td>K103N, G190A*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PDVF Genotypic (IN Results at Baseline and PDVF)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>INi tmt-emergent major substitution</td>
<td>0**</td>
<td>0</td>
</tr>
</tbody>
</table>

*K103N, G190A, K103N, G190A
**K103N, G190A, K103N, G190A

Absolute Change from Baseline in CD4+ Cell Count
Repeated Measures Mixed Model Analysis

 batches: 0 1 (<1%)

Most Common Adverse Events (≥10%)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>DTG 50 mg + ABC/3TC QD (N=414)</th>
<th>Atripla QD (N=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>369 (89)</td>
<td>387 (92)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (2)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>44 (10)</td>
<td>43 (10)</td>
</tr>
<tr>
<td>Headache</td>
<td>55 (13)</td>
<td>56 (13)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>54 (13)</td>
<td>50 (12)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>72 (17)</td>
<td>75 (18)</td>
</tr>
<tr>
<td>Nausea</td>
<td>58 (14)</td>
<td>57 (14)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>35 (9)</td>
<td>43 (10)</td>
</tr>
<tr>
<td>Rash</td>
<td>14 (3)</td>
<td>58 (14)</td>
</tr>
</tbody>
</table>

Proportion <50 c/mL: Snapshot Outcomes

- More responders on DTG vs DRV/r using the Snapshot analysis
- Superiority driven by fewer withdrawals due to AEs and other reasons prior to Week 48

<table>
<thead>
<tr>
<th>Virologic success</th>
<th>DTG 50 mg QD (N=414)</th>
<th>DRV/r 800 mg QD (N=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic success</td>
<td>27 (10)</td>
<td>18 (7%)</td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>15 (6%)</td>
<td>18 (7%)</td>
</tr>
<tr>
<td>Data in window not &lt;50 c/mL</td>
<td>6 (2%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>1 (0%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Discontinued for other reason while not &lt;50 c/mL</td>
<td>3 (1%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Change in ART</td>
<td>9 (2%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>No Week 48 virologic data</td>
<td>10 (5%)</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>Discontinued due to AE or death</td>
<td>1 (0%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Discontinued for other reasons</td>
<td>6 (2%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>1 (0%)</td>
<td>4 (2%)</td>
</tr>
</tbody>
</table>
ART switching for “tolerability”

Canadian cohort study (n=2807)
- Might represent specific patient characteristics
- Provincial location
- Female gender
- Subsequent virologic failure
- Longer duration of ART
- Subsequent ART switch (36%)
- HIV RNA <50 copies/mL
- Initiate first ART 1/2005 through 6/2012

CANOC Cohort: Risk of Virologic Failure in Patients Who Switch First ART for Reasons Other Than Virologic Failure

- Canadian cohort study (n=2807)
  - Initiate first ART 1/2005 through 6/2012
  - HIV RNA <50 copies/mL
  - Subsequent ART switch (36%)
    - Once: 14%
    - ≥2 times: 22%
  - ART switching was associated with
    - Longer duration of ART
    - Subsequent virologic failure
    - Female gender
    - Psychosocial traustration
  - ART switching for “tolerability”
    - Might represent specific patient characteristics
      where ART intolerance is a marker for factors associated with poor adherence versus specific ART concerns

Case

35 year old school teacher, diagnosed with HIV and PCP.
- Baseline VL = 214,000; CD4 = 124.
- Baseline GT: No RT or PI resistance mutations
- She is on TMP/SMX for PCP, completed 3 weeks of initial treatment and steroid taper
- She is initiated on TDF/FTC/cobi/EVG combination tablet.

What would you do next?

A. Send an Integrase Phenotypic Resistance test and stop all ARVs
B. Send an Integrase Genotypic Resistance test and stop all ARVs
C. Provide adherence support and continue current regimen
D. Intensify treatment by adding darunavir
E. Repeat viral load and standard genotype to confirm these unexpected results, continue current regimen pending results
Case

- INI genotype reveals: N155H
- She is brought in to discuss adherence issues, she reports that she had become concerned about taking too many medicines and had skipped several doses, which she regrets.
- Rapid failure: she likely had unmasking of transmitted M184V and subsequent development of INI mutation
- Now initiated TDF/FTC/rtv/DRV/DTG

10/2/2014

Bulk vs Sensitive Genotyping for Detection of Transmitted Drug Resistance

- Re-examination of 1070 de-identified samples in CDC Variant Atypical Resistance HIV Surveillance database of ART-naive pts in 2009-2011
- Use of sensitive testing increased total prevalence of transmitted resistance from 7.9% to 13.6% (P < .0001)
- Analysis of 5 mutations as sentinel markers of transmitted resistance

Bulk vs Sensitive Genotyping for Detection of Transmitted Drug Resistance

Specimens (%)

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<tr>
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<th>Sensitive</th>
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<tbody>
<tr>
<td>K15T</td>
<td>0.6</td>
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<tr>
<td>K15T</td>
<td>2.4</td>
<td>0</td>
</tr>
<tr>
<td>K15T</td>
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</tr>
<tr>
<td>K15T</td>
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</tr>
<tr>
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Legend: K65R Y181C M184V 0.3 1.1 1.5 1.2 0.6 0

K15T = 0

Case

- You are initiating antiretroviral therapy on a recently diagnosed patient with a CD4 count of 54 and a viral load of 168,000 copies/ml. There are no baseline resistance mutations. His creatinine clearance is 65 ml/min and HLAB5701 is negative. Which of the following regimens would be the most appropriate choice based on current DHHS recommended options?

A. Tenofovir/emtricitabine/rilpivvarine
B. Abacavir/lamivudine/ritonavir/atazanavir
C. Tenofovir/emtricitabine/cobicistat/elvitegravir
D. Abacavir/lamivudine/dolutegravir
E. Abacavir/lamivudine/ritonavir/darunavir

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10/2/2014
Thank you!
Joseph McGowan, MD

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