State of ART
New therapy options
Implications for women living with HIV

Dr Sharon Walmsley
University Health Network
Toronto, Ontario
Objectives

• To review the newer therapy options available for the management of HIV

• To discuss the relative risks, benefits and unknowns of these therapies for women
Current status of HIV therapy

- Newer agents continue to evolve
- Life expectancy continues to increase
- Duration of exposure to therapy increased
Key issues with ARV therapy

- Efficacious
- Tolerable
- Safety - both long and short term
- Affordable

- And for women
  - Safe in pregnancy
  - Compatible with contraceptive choices
### DHHS Guidelines: October 2013

**Preferred Regimens**

<table>
<thead>
<tr>
<th>NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ EFV/TDF/FTC</td>
</tr>
<tr>
<td>▪ ATV/RTV + TDF/FTC</td>
</tr>
<tr>
<td>▪ DRV/RTV + TDF/FTC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ RAL + TDF/FTC</td>
</tr>
<tr>
<td>▪ EVG/COBI/TDF/FTC</td>
</tr>
<tr>
<td>▪ DTG + ABC/3TC</td>
</tr>
<tr>
<td>▪ DTG + TDF/FTC</td>
</tr>
</tbody>
</table>

**Alternative Regimens**

<table>
<thead>
<tr>
<th>Booster PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ EFV + ABC/3TC</td>
</tr>
<tr>
<td>▪ RPV/TDF/FTC or RPV + ABC/3TC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ ATV/RTV + ABC/3TC</td>
</tr>
<tr>
<td>▪ DRV/RTV + ABC/3TC</td>
</tr>
<tr>
<td>▪ FPV/RTV + (TDF/FTC or ABC/3TC)</td>
</tr>
<tr>
<td>▪ LPV/RTV + (TDF/FTC or ABC/3TC)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ RAL + ABC/3TC</td>
</tr>
</tbody>
</table>

Special concerns of the recommended therapy options for women

Efavirenz

• potential teratogenicity
• Increased adverse events especially CNS (? Drug levels)

Atazanavir/r

• ACTG 5202- higher risk of virologic failure than women on efavirenz or men assigned to ATZ/r

Darunavir/r

• GRACE study showed higher rates of discontinuation in women relative to men

New therapy options

Integrase inhibitors

- raltegravir, elvitegravir, dolutegravir

Non Nucleoside Reverse Transcriptase Inhibitors

- rilpivirine
Are we doing any better getting women into pivotal clinical trials?

<table>
<thead>
<tr>
<th>Study</th>
<th>New Agent</th>
<th>Comparator</th>
<th>% women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Startmrk</td>
<td>Raltegravir</td>
<td>Efavirenz</td>
<td>19%</td>
</tr>
<tr>
<td>Single</td>
<td>Dolutegravir</td>
<td>Efavirenz</td>
<td>16%</td>
</tr>
<tr>
<td>Spring -2</td>
<td>Dolutegravir</td>
<td>Raltegravir</td>
<td>15%</td>
</tr>
<tr>
<td>Flamingo</td>
<td>Dolutegravir</td>
<td>Darunavir/r</td>
<td>13%</td>
</tr>
<tr>
<td>Gilead 102</td>
<td>Elvitegravir</td>
<td>Efavirenz</td>
<td>22%</td>
</tr>
<tr>
<td>Gilead 103</td>
<td>Elvitegravir</td>
<td>Atazanavir/r</td>
<td>8%</td>
</tr>
<tr>
<td>ECHO</td>
<td>Rilpivirine</td>
<td>Efavirenz</td>
<td>23%</td>
</tr>
<tr>
<td>Thrive</td>
<td>Rilpivirine</td>
<td>Efavirenz</td>
<td>26%</td>
</tr>
<tr>
<td>Star</td>
<td>Rilpivirine</td>
<td>Efavirenz</td>
<td>7%</td>
</tr>
</tbody>
</table>
STARTMRK - Proportion (%) of patients (95% CI) with HIV RNA <50 copies/mL through 240 weeks (non-completer = failure)
FOREST PLOTS SHOWING THE VIROLOGIC AND IMMUNOLOGIC EFFICACY OF Raltegravir RELATIVE TO Efavirenz AT WEEK 48 BY BASELINE FACTORS (OBSERVED-FAILURE APPROACH)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Raltegravir</th>
<th>Efavirenz</th>
<th>Difference in Response Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>241/263 (92)</td>
<td>230/258 (89)</td>
<td></td>
</tr>
<tr>
<td>Baseline Plasma HIV RNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50,000 copies/mL</td>
<td>71/75 (95)</td>
<td>66/76 (87)</td>
<td>Efavirenz Better</td>
</tr>
<tr>
<td>&gt;50,000 copies/mL</td>
<td>170/188 (90)</td>
<td>162/180 (90)</td>
<td></td>
</tr>
<tr>
<td>≤100,000 copies/mL</td>
<td>111/120 (93)</td>
<td>114/128 (89)</td>
<td>Raltegravir Better</td>
</tr>
<tr>
<td>&gt;100,000 copies/mL</td>
<td>130/143 (91)</td>
<td>116/130 (89)</td>
<td></td>
</tr>
<tr>
<td>Screening Plasma HIV RNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50,000 copies/mL</td>
<td>66/70 (94)</td>
<td>61/70 (87)</td>
<td>Efavirenz Better</td>
</tr>
<tr>
<td>&gt;50,000 copies/mL</td>
<td>175/193 (91)</td>
<td>169/188 (90)</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 Cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50 cells/mm³</td>
<td>21/25 (84)</td>
<td>24/28 (86)</td>
<td>Efavirenz Better</td>
</tr>
<tr>
<td>&gt;50 to ≤200 cells/mm³</td>
<td>85/95 (89)</td>
<td>83/97 (86)</td>
<td></td>
</tr>
<tr>
<td>&gt;200 cells/mm³</td>
<td>135/143 (94)</td>
<td>122/132 (92)</td>
<td>Raltegravir Better</td>
</tr>
<tr>
<td>Hepatitis B/C Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B or C positive*</td>
<td>16/17 (94)</td>
<td>14/16 (88)</td>
<td>Efavirenz Better</td>
</tr>
<tr>
<td>Both B and C negative</td>
<td>225/246 (91)</td>
<td>216/242 (89)</td>
<td></td>
</tr>
<tr>
<td>Age (years)**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td>126/137 (92)</td>
<td>129/145 (89)</td>
<td></td>
</tr>
<tr>
<td>&gt; Median</td>
<td>115/126 (91)</td>
<td>101/113 (89)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>194/214 (91)</td>
<td>188/213 (88)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>47/49 (96)</td>
<td>42/45 (93)</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>100/109 (92)</td>
<td>100/107 (93)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>24/27 (89)</td>
<td>20/22 (91)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>31/34 (91)</td>
<td>26/30 (87)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>54/58 (93)</td>
<td>53/62 (85)</td>
<td></td>
</tr>
<tr>
<td>Multiracial</td>
<td>31/34 (91)</td>
<td>30/36 (83)</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>88/97 (91)</td>
<td>81/96 (84)</td>
<td>Efavirenz Better</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>30/32 (94)</td>
<td>26/28 (93)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>63/70 (90)</td>
<td>70/76 (92)</td>
<td>Raltegravir Better</td>
</tr>
<tr>
<td>Europe/Australia</td>
<td>60/64 (94)</td>
<td>53/58 (91)</td>
<td></td>
</tr>
<tr>
<td>Viral Subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clade B</td>
<td>186/206 (90)</td>
<td>185/209 (89)</td>
<td>Efavirenz Better</td>
</tr>
<tr>
<td>Non-Clade B</td>
<td>52/54 (96)</td>
<td>40/44 (91)</td>
<td></td>
</tr>
</tbody>
</table>

*An arrow end implies the upper limit of 95% CI exceeding the maximum of x-axis
**Median age: 37 for Raltegravir group vs. 36 for Efavirenz

Rockstroh, JAIDS, 2013
REALMRK- Raltegravir

% with HIV RNA <50 copies/mL by Gender: (2) Previously Treated Patients, Intolerant

% with HIV RNA <50 copies/mL by Gender: (3) Treatment-Naive Patients
Study 102: Stribild vs Atripla
Primary Endpoint: HIV-1 RNA < 50 copies/mL

Elvitegravir:
Study 103: Stribild vs TDF/FTC + ATV/r – Week 48

Primary endpoint: HIV RNA < 50 c/ml (ITT, snapshot)

- **Virologic success**:
  - Quad: 90%
  - TDF/FTC + ATV/r: 87%

- **Virologic non-suppression**:
  - 5 in Quad
  - 5 in TDF/FTC + ATV/r

- **No data at W48**:
  - 5 in Quad
  - 8 in TDF/FTC + ATV/r

**Diff: 3.5%**
(95% CI: -1.0 to 8.0)
Difference in Efficacy by Subgroup: Combined Study 102 and 103 – Week 96

Differences in Percentages (95% CI)

OVERALL
Age
<40 years
≥40 years

Sex
Male
Female

Race
White
Non-White

Baseline HIV-1 RNA
≤100,000 c/mL
>100,000 c/mL

Baseline CD4 count
≤350 cells/mm³
>350 cells/mm³

Study Drug Adherence*
<95%
≥95%
WAVES Study
EVG/COBI/FTC/TDF in Treatment-naïve Women

Phase 3b, multicenter, international, randomized, blinded, double dummy 48-week study

ART-naïve subjects
HIV RNA ≥500 c/mL
No CD4 restrictions
eGFR > 70mL/min

n=255
n=255

EVG/COBI/FTC/TDF
Single-Tablet Regimen

48 Weeks

ATV + RTV + FTC/TDF
Multi-Pill Regimen

Primary Endpoint: Non-inferiority (12% margin) of EVG/COBI/FTC/TDF to comparator arm by FDA snapshot analysis HIV-1 RNA <50 copies/mL at Week 48

Secondary Endpoints: Change in CD4 cell count at Week 48

Stratification by HIV RNA (≥ or ≤100,000 c/mL)

ClinicalTrials.gov identifier: NCT01705574

Enrolling
SPRING-2: Raltegravir vs Dolutegravir in ARV naive

Figure 2: Proportion of patients with HIV-1 RNA less than 50 copies per mL. Error bars show 95% CIs.

Raffi, Lancet, 2013
SINGLE: Dolutegravir vs Atripla:
Proportion (95% CI) of Subjects <50 c/mL (FDA Snapshot)

- DTG 50mg +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 <50c/mL of 28 days (DTG +ABC/3TC) vs 84 days (Atripla), P<0.0001

Walmsley S, NEJM 2013
Results were confirmed in per protocol analysis: 91% DTG versus 84% DRV/r, Δ (CI): 7.4 (1.4 - 13.3)
### Dolutegravir by gender

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DTG</th>
<th>Comparator</th>
<th>Study</th>
<th>Favors comparator</th>
<th>Favors DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Viral Load ≤100,000 c/mL</td>
<td>267/297 (90)</td>
<td>264/295 (89)</td>
<td>SPRING-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Viral Load &gt;100,000 c/mL</td>
<td>160/181 (88)</td>
<td>157/181 (87)</td>
<td>FLAMINGO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 count &lt;350 cells/mm³</td>
<td>84/96 (88)</td>
<td>80/75 (80)</td>
<td>FLAMINGO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 count ≥350 cells/mm³</td>
<td>170/194 (91)</td>
<td>164/198 (83)</td>
<td>SINGLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background NRTI: ABC/3TC</td>
<td>145/169 (86)</td>
<td>142/164 (87)</td>
<td>SPRING-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background NRTI: TDF/FTC</td>
<td>216/242 (89)</td>
<td>209/247 (85)</td>
<td>SPRING-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>57/67 (85)</td>
<td>50/56 (82)</td>
<td>SINGLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>308/348 (89)</td>
<td>305/355 (86)</td>
<td>SPRING-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;50 y</td>
<td>319/361 (88)</td>
<td>302/375 (81)</td>
<td>SINGLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥50 y</td>
<td>192/214 (90)</td>
<td>167/206 (81)</td>
<td>FLAMINGO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>306/346 (88)</td>
<td>301/352 (86)</td>
<td>SPRING-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American/ African heritage</td>
<td>41/49 (84)</td>
<td>33/39 (85)</td>
<td>SPRING-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Proportion of patients, %

- DTG
- RAL
- EFV/TDF/FTC
- DRV/r

#### Difference in proportion, %

-20 -15 -10 -5 0 5 10 15 20 25 30 35 40
ARIA Study Design

- Phase IIIb, parallel group, open-label, (N=474; 237 per arm)
- 1:1 randomized, regimen-to-regimen comparison
- Stratified by HIV-1 RNA and CD4+ cell count

HIV-infected, ART-naive women
HIV-1 RNA ≥500 c/mL
HLA-B*5701 negative

DTG/ABC/3TC

ATV + RTV + TDF/FTC

 DTG/ABC/3TC

Screening visit
~Day -14
Randomization
Day 1
Analysis
Week 48

Screening period
Randomized phase
Continuation phase
Rilpivirine: COMPLERA

Primary Efficacy Endpoint (<50 c/mL TLOVR): Pooled Week 48 results for the FTC/TDF subset from ECHO and THRIVE

• Non-inferiority (at the 12% margin) of RPV to EFV was demonstrated when given in combination with FTC/TDF as the background N(t)RTI
Effect of gender on the week 48 findings in treatment-naïve, HIV-1-infected patients enrolled in the randomized, phase III trials ECHO and THRIVE.

(a) Gender analysis

<table>
<thead>
<tr>
<th></th>
<th>RPV (n = 518)</th>
<th>Failure</th>
<th></th>
<th>RPV (n = 168)</th>
<th>Failure</th>
<th></th>
<th>RPV (n = 163)</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>9</td>
<td>2</td>
<td>4</td>
<td></td>
<td>83</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td></td>
<td>83</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

- **Responder**: RPV, EFV
- **Failure**: Virological failure, Discontinued because of AE/death, Discontinued because of other reasons
Effect of gender and race on the week 48 findings in treatment-naïve, HIV-1-infected patients enrolled in the randomized, phase III trials ECHO and THRIVE
Adverse events by gender

No adverse events or lab abnormalities were found to be statistically different by gender in any of the pivotal trials of the new agents.
Integrase inhibitors

• Well tolerated
• Minimal risk of drug interactions
• Good lipid profile

• Safety in pregnancy unclear
• Rapid viral load reduction of uncertain clinical significance
Cobisistat as booster

- Cyp 3A4 inhibitor
- Increases progesterone concentrations in oral contraceptives
- Similar adverse events as with ritonavir
Rilpivirine

- Well tolerated
- Needs 500 kcal food for optimal absorption
- Potency? - not as effective for those with high viral loads (late presenters)
- Cyp 3A4 inducer
What do we know about safety in pregnancy?- Animal data

• Raltegravir
  Class C- no teratogenicity in development studies in rats and rabbits
  supernumary ribs in later rat studies
• Dolutegravir
  • Class B – no teratogenicity in rats or rabbits
• Elvitegravir
  Class B- no teratogenicity in rat or rabbit studies
• Rilpivirine
  • Class B- no teratogenicity in rat and rabbit studies
• Cobisitat
  • Class B- no teratogenicity in rat and rabbit studies

The concern: with changing treatment guidelines more women will become pregnant on ARV
Is the rapid reduction of viral load with integrase clinically useful for the prevention of MTCT?

- Interventional, randomized, phase 2/3, open-label, n=44.
- Primary endpoint: HIV Viral load at delivery
- Randomly assigned to receive AZT+3TC+Raltegravir or AZT+3TC+LPV/r.

NCT01618305: A Phase IV Randomized Trial to Evaluate the Virologic Response and Pharmacokinetics of Three Different Potent Regimens in HIV Infected Women Initiating Triple ARV Between 28 and 36 Weeks of Pregnancy for the Prevention of MTCT
- Interventional, randomized, open-label, phase 4
- Primary endpoints: Rapid viral load decrease, tolerability of study drugs,
- Randomly assigned to one of three arms.
  - Arm A: combivir + LPV/r
  - Arm B: combivir + efavirenz
  - Arm C: combivir + Raltegravir
Ageing as a woman with HIV

- Women living with HIV face all the challenges that the general population faces when growing older **PLUS:**
  - Hormonal changes
  - Cardiovascular events
  - Non-AIDS-defining infections
    - Renal disease
  - Non-AIDS-defining cancers/malignancy
  - Muscular and skeletal changes
  - Non-AIDS-dementias, neurocognitive changes, mood and CNS disorders

The consequences of longer exposure to HIV treatment regimens

The consequences of living longer with HIV
Tenofovir Alafenamide (TAF)
Next Generation Prodrug of Tenofovir
Tenofovir Alafenamide (TAF) vs. Tenofovir DF (TDF), + FTC/EVG/c Percent Change in Bone Mineral Density (DEXA)

- Proportion of subjects with no change in BMD
  - **Spine:** TAF/EVG/c/FTC, 38%; TDF/EVG/c/FTC, 12%
  - **Hip:** TAF/EVG/c/FTC, 41%; TDF/EVG/c/FTC: 23%
Tenofovir Alafenamide (TAF) vs Tenofovir DF (TDF), + FTC/EVG/c

Median Estimated GFR (Cockcroft-Gault)

- Change in eGFR at Week 24
  - TAF/FTC/EVG/c: -4.8 mL/min
  - TDF/FTC/EV/G/c: -11.8 mL/min ($P=0.04$)

Zolopa A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 99LB.
FIG. 2. Treatment priorities among HIV-infected women. Participants’ answers to: “When thinking about your HIV treatment options, how important are each of the following to you?” Base: all women. *p<0.05 versus other two subgroups.
Its not just the ARV

- WISE study 2006-2011
- N=887 women, 46% virologic failure
- Risk factors for failure:
  - African American race
  - Lower income
  - Lack of health insurance
  - Depression

Need to continue to develop strategies to reduce disparities in therapy outcomes

McFall et al; JAIDS, 2013
Choosing ART for women: is there a preferred option?

- **Efficacy**: data suggests no difference
- **Toxicity**: gender specific differences still to be determined
- **Individualize**: characteristics of the individual drugs vs patient
  - Drug interactions (contraception)
  - Co-morbidities (menopause, osteoporosis)
  - Reproductive intent (current, future)
- Strategies to increase female representation and retention in clinical trials need to be continually developed
- Gender specific reporting improving

We as a voice for women with HIV are making a difference!