Michelle Moorhouse
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SAHCS Conference

NNRTIs: an update
Disclosures

- Speaker fees and honoraria from Gilead Sciences, AbbVie, Cipla, Mylan, Aspen, Sanofi, Pfizer and Janssen
- Conference sponsorship from BD, Gilead, Janssen, Merck, Cipla and Mylan
- Part of ART optimisation collaborations
- Funding from USAID, Unitaid, SAMRC and study drug donations from ViiV Healthcare and Gilead Sciences for ART optimisation studies
Flashback to 2016: Safest NNRTI

Rilpivirine
Safest NNRTI:

• Rilpivirine is the safest NNRTI for first-line
• EFV is more effective, so this should remain first choice
• Rilpivirine could replace nevirapine as the second choice NNRTI in first-line and could be used in third-line
WHO’s recommendations on country response to NNRTI PDR

- **Are nationally representative PDR data available?**
  - **YES**
    - Implement viral load monitoring; prevent HIVDR emergence and transmission
    - ≥10% PDR to EFV/NVP
      - Is it feasible to introduce non-NNRTI first-line ART for ALL starters?
        - **YES**
          - Urgently consider using non-NNRTI first-line ART for ALL starters
        - **NO**
          - Consider introducing pretreatment HIVDR testing
    - <10% PDR to EFV/NVP
      - Prioritize use of non-NNRTI containing first-line ART in people reporting prior exposure to ARV drugs
  - **NO**
    - Implement nationally representative PDR survey

**ART**: antiretroviral therapy  
**ARV**: antiretroviral (drug)  
**EFV/NVP**: efavirenz or nevirapine  
**HIVDR**: HIV drug resistance  
**PDR**: pretreatment HIV drug resistance  
**NNRTI**: non-nucleoside reverse-transcriptase inhibitor

Levels of pretreatment HIVDR (PDR): NNRTI

**EFV/NVP pretreatment HIVDR**

In several low- and middle-income countries,

1 in 10 adults starting HIV treatment harbour resistant virus

3 in 10 adults restarting first-line ART with prior exposure to antiretroviral drugs harbour resistant virus

**Women**

Starting first-line ART are **two times more** likely than men to harbour a resistant virus

5 in 10 young children newly diagnosed with HIV harbour resistant virus

**EFV/NVP pretreatment DR in key populations**

Meta-analysis of 50 studies globally

People who inject drugs  | Men who have sex with men  | Sex workers  | Prisoners

Men who have sex with men vs general population  | Commercial sex workers vs general population  | People who inject drugs vs general population

Thanks: Silvia B (WHO)
Pretreatment NNRTI drug resistance in special populations

- In children < 18 months, NNRTI resistance = 63.7%
  (95% CI: 59.0–68.4)
  (single study, South Africa, 2014–16)

- In children 0–18 years starting ART, NNRTI resistance = 49.3%
  (range 7.5–100%)
  (meta-analysis, 2014–17)
  - Particularly in PMTCT-exposed children (4/7 studies found > 50% of PMTCT-exposed children had NNRTI DR)

- Prevalence of any TDR and NNRTI resistance is higher among women than men in the majority of surveys

PDR in treatment-naïve patients in selected countries

- Most pretreatment DR is **NNRTI resistance**

WHO’s recommendations on country response to NNRTI PDR

Recommendation: Countries should consider changing their first-line ART regimens away from NNRTIs if levels of NNRTI DR reach 10%.
Most prevalent HIVDR mutations contributing to PDR in South Africa

- PDR: 17.5%
  - NNRTI: 13.9%
  - NNRTI and NRTI: 3.1%
  - NRTI: 0.5%
- Three participants harboured single major PI mutations (I54V, I84V)

Hunt et al 2017
Magnitude of effect of PDR on long-term virological outcomes

- Cohort data 2007–09; 6 countries in sub-Saharan Africa\(^1\) with PDR results for 2579 patients
  - 2404 (93%) had no pretreatment DR
  - 123 (5%) had PDR to \(\geq 1\) prescribed drug
  - 52 (2%) had PDR and received fully active ART

- A separate retrospective study of 801 HIV-infected ARV-naive patients from 2001–09
  - Presence of transmitted NNRTI resistance \(\rightarrow\) 1.5-fold increased risk for treatment failure in the first 48 weeks after ART initiation\(^2\)

- People with PDR NNRTI are 4.5 times more likely to have unsuppressed VL (systematic review, GDG WHO meeting, 2017)

\(\text{OR for VF} = 2.13\ (95\% \text{ CI 1.44–3.14})\quad p < 0.0001\)
\(\text{OR for acquired resistance} = 2.30\ (95\% \text{ CI 1.55–3.40})\quad p < 0.0001\)

VF = virologic failure
SA has largest ARV programme: > 5 million

Diagram:

- TDF + XTC + EFV
- ZDV + 3TC + PI/r (LPV or ATV)
- Failure

Failure:
- XTC, other nukes
  - Darunavir
  - Dolutegravir
  - Etravirine
So what are the options?

- NVP
- RPV
- ETR
- EFV
Safety and efficacy of EFV$_{600}$ versus DTG in first-line ART (summary 2018 WHO Systematic Review and NMA)

<table>
<thead>
<tr>
<th>Major outcomes</th>
<th>DTG vs EFV$_{600}$</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral suppression (96 weeks)</td>
<td>DTG better</td>
<td>moderate</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>DTG better</td>
<td>high</td>
</tr>
<tr>
<td>CD4+ recovery (96 weeks)</td>
<td>DTG better</td>
<td>moderate</td>
</tr>
<tr>
<td>Mortality</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>AIDS progression</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>SAE</td>
<td>comparable</td>
<td>low</td>
</tr>
</tbody>
</table>

Reference: Steve Kanters, For WHO ARV GDG, 16-18 May 2018
ECHO/THRIVE study results: TDF/FTC/RPV vs TDF/FTC/EFV

ECHO and THRIVE Week 48 analysis: VL < 50 copies/mL by baseline VL (ITT-TLOVR)

• N(t)RTI background had no effect on virologic response
• No differences between treatment groups in virologic response by gender, region or race
Real-world data: Swedish cohort study 2009–2014: treatment-naïve patients

- 2541 treatment-naïve patients started 2583 episodes of treatment with a new third agent
- Compared with EFV, patients on RPV were least likely to discontinue treatment, whilst patients on LPV/r were most likely to discontinue treatment, followed by RAL
ICONA: Comparison of durability of first-line EFV and RPV with TDF/FTC

• After adjustment, compared to those starting RPV, patients treated with EFV were more likely to discontinue at least one drug
  • for any cause [relative hazard (RH) 4.09; 95% CI 2.89 – 5.80]
  • for toxicity (RH 2.23; 95% CI 1.05 – 4.73)
  • for intolerance (RH 5.17; 95% CI 2.66 – 10.07)
  • for proactive switch (RH 10.96; 95% CI 3.17 – 37.87)

• RPV was better tolerated, less toxic and showed longer durability than EFV, without a significant difference in rates of discontinuation because of failures

<table>
<thead>
<tr>
<th>Discontinue ≥ 1 drug in regimen</th>
<th>EFV with TDF/FTC</th>
<th>RPV with TDF/FTC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>26%</td>
<td>13%</td>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Rilpivirine versus efavirenz

- Similar efficacy for virological suppression at 48 and 96 weeks
- Less discontinuations with rilpivirine relative to efavirenz
Where does rilpivirine fit in?

**TABLE 4: Preferred first-line regimen options.**

<table>
<thead>
<tr>
<th>Options</th>
<th>Preferred</th>
<th>Alternative</th>
<th>One of</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI backbone</td>
<td>TDF + FTC/3TC</td>
<td>ABC† + 3TC</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>AZT‡ + 3TC</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>d4T§ + 3TC</td>
<td>–</td>
</tr>
<tr>
<td>Third drug</td>
<td>–</td>
<td>–</td>
<td>EFV</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>DTG</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>RPV¶</td>
</tr>
</tbody>
</table>

Eligible for third line ART?
- PI score > 15

DRV/r PLUS 3TC/FTC PLUS
- AZT/TDF (lowest score)

TDF/AZT 30 – 59 OR DRV > 15
- Add InSTI

TDF/AZT > 29 AND DRV > 15
- AND ETR ≤ 29
- Add ETR

But not in WHO or SA national guidelines
And etravirine?

- **TDF/AZT > 29 AND DRV > 15 AND ETR ≤ 29**
  - Add InSTI
- Add ETR
Reduced drug regimens in ARV-naïve patients

- **DTG + 3TC (Paddle)** (2015)
- **DTG + RPV (SWORD)** (2017)
- **DTG + 3TC (GEMINI & TANGO) (ACTG 5353 & ASPIRE) (Lamidol)**

**CABT LA + RPV LA (LATTE-2)**

**CABT LA + RPV LA (FLAIR & ATLAS)**

**ISTI + NNRTI**

**ISTI + 3TC**

Courtesy: J Arribas
SWORD 1 and 2: Switch from current ART to DTG + RPV dual regimen

Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DTG + RPV (n=513); n (%)</th>
<th>CAR (n=511); n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) ≥ 50 years</td>
<td>43 (11.1) 147 (29)</td>
<td>43 (10.2) 142 (28)</td>
</tr>
<tr>
<td>Female</td>
<td>120 (23)</td>
<td>108 (21)</td>
</tr>
<tr>
<td>Race, non-white</td>
<td>92 (18)</td>
<td>111 (22)</td>
</tr>
<tr>
<td>CD4+ cell count, cells/μL (median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤500</td>
<td>611</td>
<td>638</td>
</tr>
<tr>
<td>&gt;500</td>
<td>165 (32)</td>
<td>149 (29)</td>
</tr>
<tr>
<td></td>
<td>348 (68)</td>
<td>362 (71)</td>
</tr>
<tr>
<td>Baseline 3rd-agent class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>133 (26)</td>
<td>136 (27)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>275 (54)</td>
<td>278 (54)</td>
</tr>
<tr>
<td>InSTI</td>
<td>105 (20)</td>
<td>97 (19)</td>
</tr>
<tr>
<td>Baseline TDF use</td>
<td>374 (73)</td>
<td>359 (70)</td>
</tr>
<tr>
<td>Months of ART prior to Day 1, median</td>
<td>51</td>
<td>53</td>
</tr>
</tbody>
</table>

Week 48 efficacy

- **DTG + RPV (n=513)**
- **Baseline ART (n=511)**

Treatment difference: -0.2% (95% CI: -3.0%–2.5%)

- <1
- 1
- 5
- 4

DTG + RPV was non-inferior to CAR (current ART regimen) over 48 weeks in participants with HIV suppression. Results support the use of this two-drug regimen to maintain HIV suppression.

Future options?

Using clinically relevant concentrations of each drug corrected for protein binding, no viral breakthrough was detected with *doravirine* in resistance selections using K103N, Y181C, and K103N/Y181C mutants.

Doravirine retains antiviral potency against the most prevalent NNRTI-associated resistant viruses.

Doravirine

Key entry criteria:
- HIV-1 RNA ≥1000 copies/mL within 45 days before Day 1
- Antiretroviral-naïve
- No genotypic resistance to any study drugs
- Stratification factors: HIV-1 RNA >100,000 copies/mL and chronic hepatitis B or C infection status

Primary analysis time point

Screening begins

Group 1
N=340

W0

DOR 100 mg/3TC 300 mg/TDF 300 mg QD + PBO

14-day follow-Up

Group 2
N=340

W24

EFV 600 mg/FTC 200 mg/TDF 300 mg QD + PBO

14-day follow-Up

W96

Safest NNRTI

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• Rilpivirine is the safest NNRTI for first-line

• EFV is more effective, so this should remain first choice NNRTI

• Rilpivirine should replace nevirapine as the second choice NNRTI in first-line and is used in third-line

• With increasing NNRTI PDR, we are moving into the InSTI era
NNRTIs: an update

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