Pretreatment drug resistance and new treatment paradigms in first-line ART
Disclosures/disclaimers

- 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
Factors influencing drug resistance

Drug toxicities
Social / personal issues

Poor adherence

Drug stockouts
Increasingly stretched healthcare systems

Insufficient drug level

Interruption of treatment
Poor potency
Adding 1 drug to failing regimen

Prolonging a failing regimen
Treatment with < 3 drugs
Inappropriate drug selection

Viral replication in the presence of drug

HIV DR

TDR = transmitted drug resistance
Levels of pretreatment HIVDR (PDR)

**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

Prevalence estimates of pretreatment HIV DR

PDR in treatment-naïve patients in selected countries

• Most pretreatment DR is **NNRTI resistance**

NNRTI and dual-class resistance detected amongst patients enrolled according to prior ART exposure (SA)

HIVDR: 37% in ART starters with prior exposure to ARVs
15% in ARV-naive
Magnitude of effect of PDR on long-term virological outcomes

- Cohort data 2007–09; 6 countries in sub-Saharan Africa\(^1\)
- PDR results available for 2579 patients
  - 2404 (93%) had no pretreatment DR
  - 123 (5%) had PDR to ≥ 1 prescribed drug
  - 52 (2%) had PDR and received fully active ART
- \textbf{CD4+ count} increased less in patients with PDR than in those without (\(\bigtriangleup\) 35 cells/\(\mu\)L at 12 months; 95% CI 13–58; \(p = 0.002\))

- A separate retrospective study of 801 HIV-1-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\(^2\)

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VF = virologic failure
More recently

- 1,148 HIV-positive treatment-naïve patients enrolled in trial clinics in rural KwaZulu-Natal
- Pretreatment drug resistance prevalence was 9.5% (109/1,148) at 20% interval and 12.8% (147/1,148) and 5% thresholds
- Median of 1.36 years (IQR 0.91-2.13), mostly on TDF/FTC/EFV

No difference between those with only NNRTI PDR vs. no PDR at the 5% threshold

Odds ratio (OR) 1.05, 95%CI=0.82–1.34

WHO technical update and 2018 guidelines

<table>
<thead>
<tr>
<th>Population</th>
<th>First-line regimens</th>
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<th>Third-line regimens</th>
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<td>Adults and adolescents (incl. women of childbearing potential and pregnant women)</td>
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- Guidelines include recommendations on the selection of ARV drugs in response to high levels of DR\(^1\)
  - Recommend countries consider changing their first-line ART regimens away from NNRTIs if levels of NNRTI DR reach 10%

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- Guidelines include recommendations on the selection of ARV drugs in response to high levels of DR\(^1\)
  - Recommend countries consider changing their first-line ART regimens away from NNRTIs if levels of NNRTI DR reach 10%

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**Primary objective**

- Non inferiority of DTG at W48: % HIV RNA < 50 copies/mL by ITT, snapshot analysis (1-sided significance level of 2.5%, lower margin of the 95% CI for the difference = -10%, 90% power)

**Conclusions**

- Virologic superiority of DTG + ABC/3TC over TDF/FTC/EFV was confirmed at Weeks 96 and 144
DTG in first-line treatment when NNRTI DR is prevalent

- Rate of HIV DR acquisition of DTG at a similar level to that of ATV/r
- DTG generally found to be associated with lower risk of toxicity than both EFV and PIs
  - Risk of neurological toxicity is half that of EFV → reduced risk of toxicity → less discontinuation

Countries in sub-Saharan Africa with substantial prevalence of NNRTI drug resistance in ART initiators should transition from EFV to DTG in first-line ART regimens

Dolutegravir NTD signal
Tsepamo study, Botswana

Neural tube defects in 4/426 pregnancies (0.94%)

Updated data since 01 May 2018: 4/596 (0.67%)

95% CI still does not overlap with other groups

<table>
<thead>
<tr>
<th>NTDs/Exposures</th>
<th>DTG-Conception</th>
<th>Any Non-DTG ART-Conception</th>
<th>EFV-Conception</th>
<th>DTG Started During Pregnancy</th>
<th>HIV-NEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/426</td>
<td>14/11,300</td>
<td>3/5,787</td>
<td>0/2,812</td>
<td>61/66,057</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% with NTD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.94% (0.37%, 2.4%)</td>
</tr>
<tr>
<td>0.12% (0.07%, 0.21%)</td>
</tr>
<tr>
<td>0.05% (0.02%, 0.15%)</td>
</tr>
<tr>
<td>0.00% (0.00%, 0.13%)</td>
</tr>
<tr>
<td>0.09% (0.07%, 0.12%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevalence Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ref</td>
</tr>
<tr>
<td>-0.82% (-0.24%, -2.3%)</td>
</tr>
<tr>
<td>-0.89% (-0.31%, -2.3%)</td>
</tr>
<tr>
<td>-0.94% (-0.35%, -2.4%)</td>
</tr>
<tr>
<td>-0.85% (-0.27%, -2.3%)</td>
</tr>
</tbody>
</table>

Zash, TUSY15
Guidance on the use of DTG in women

Approach to use of DTG across different guideline making bodies

<table>
<thead>
<tr>
<th>ART history</th>
<th>Clinical scenarios</th>
<th>DHHS</th>
<th>BHIVA</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART-naive or using a non-DTG containing regimen</td>
<td>Early pregnancy*</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Late pregnancy</td>
<td>Yellow</td>
<td>Blue</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Childbearing age potential, not using contraception</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Childbearing age potential, using effective/consistent contraception</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>On DTG containing regimen</td>
<td>Early pregnancy*</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
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<td></td>
<td>Late pregnancy</td>
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<td>Red</td>
<td>Red</td>
</tr>
</tbody>
</table>

* The definition of early pregnancy period varies in different guidelines. DHHS: < 8 weeks from LMP; BHIVA: 1st trimester; WHO: < up to 8 weeks from conception.

Safety and Efficacy of DTG and EFV600 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
LPV/r in first-line treatment when NNRTI DR is prevalent

In RLS, LPV/r-based regimen was associated with significantly fewer virologic failures and resistance mutations.

- At baseline, major DRMs were found in 3/27 NVP-failing patients and in 0/13 patients who failed in the LPV/r group.

In RLS, LPV/r-based regimen was associated with significantly fewer virologic failures and resistance mutations.

- Additionally, high levels of NNRTI resistance observed in children in South Africa and Togo support WHO’s 2013 recommendation that all children < 3 years be started on LPV/r-based regimens, irrespective of PMTCT exposure.

Clumeck N et al, AIDS. 2014; 28: 1143–53

DIAMOND: Study design

- DIAMOND is an ongoing, phase 3, single-arm, open-label, prospective, multicentre study evaluating DRV/Cobi/FTC/TAF in a rapid initiation model of care over 48 weeks
- Objective: Assess efficacy and safety of DRV/Cobi/FTC/TAF in a rapid initiation model of care in newly diagnosed, HIV-1–infected, treatment-naive patients; baseline viral resistance in the study population

*Evaluations could be performed sooner based on the availability of results; †Interim analyses were performed once all patients had been assessed for safety at Day 3 and resistance at Week 4, and were updated when all patients continuing treatment reached Week 24
DIAMOND: Week 24 efficacy

**FDA Snapshot (N=109)**
- 91% (99/109) of patients continued treatment through Week 24 – No patients discontinued due to receipt of baseline resistance and only 3 discontinued due to safety stopping rules
  - No patients discontinued due to lack of efficacy and no patients had protocol-defined virologic failure; there was only 1 discontinuation due to an AE

**Observed (n=98)**
- Mean HIV-1 RNA decreased from baseline to Week 24 by 3.08 log_{10} copies/mL
- Mean ± SE CD4 count was 413 ± 24 at baseline and 589± 30 cells/mm³ at Week 24

**Week 24: Change from baseline in log_{10} HIV-1 RNA (Observed)**

These findings, together with the demonstrated **efficacy, high barrier to resistance, safety profile, and convenience** of the DRV/Cobi/FTC/TAF single-tablet regimen, suggest that D/C/F/TAF should be considered a recommended treatment option in a rapid initiation model of care.

Huhn G et al. IAC Congress 2018; Poster WEPEC200
Most prevalent HIVDR mutations contributing to PDR in South Africa

- Pretreatment HIVDR: 17.5%
- 13.9% had NNRTI resistance
- 3.1% of participants had NNRTI and NRTI resistance
- 0.5% are resistant to NRTI
- Three participants harboured single major PI mutations (I54V, I84V)

Hunt et al 2017

Most prevalent HIVDR mutations contributing to PDR in South Africa

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- 3.1% of participants had NNRTI and NRTI resistance
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- Three participants harboured single major PI mutations (I54V, I84V)
Rilpivirine? – active against K103N

- Successful switch to RPV/TDF/FTC in HIV-1-infected patients with an isolated K103N mutation acquired during prior NNRTI therapy

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**Drug Resistance Interpretation: RT**

<table>
<thead>
<tr>
<th>NRTI Resistance Mutations:</th>
<th>None</th>
</tr>
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<tr>
<td>NNRTI Resistance Mutations:</td>
<td>K103N</td>
</tr>
<tr>
<td>Other Mutations:</td>
<td>None</td>
</tr>
</tbody>
</table>

**Nucleoside RTI**
- lamivudine (3TC): Susceptible
- abacavir (ABC): Susceptible
- zidovudine (AZT): Susceptible
- stavudine (D4T): Susceptible
- didanosine (DDI): Susceptible
- emtricitabine (FTC): Susceptible
- tenofovir (TDF): Susceptible

**Non-Nucleoside RTI**
- efavirenz (EFV): High-level resistance
- etravirine (ETR): Susceptible
- nevirapine (NVP): High-level resistance
- **rilpivirine (RPV)**: Susceptible

**RT Comments**
- NNRTI
  - K103N causes high-level resistance to NVP, and EFV. It has no effect on ETR or RPV susceptibility.

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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

ARV-naïve
Baseline viral load
HIV RNA < 100 000 copies/mL

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

Other future options?
Doravirine retains antiviral potency against the most prevalent NNRTI-associated resistant viruses

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


Other future options?
Bictegravir and cabotegravir show activity against InSTI- and NNRTI-associated resistant viruses

Cabotegravir has shown efficacy against five different NNRTI-resistant or NRTI-resistant viruses, with activity equivalent to that against wild-type virus (fold change values ranged from 0.9 to 1.4)

Reduced drug regimens in ARV-naïve patients

- DTG + 3TC (Paddle) (2015)
- DTG + RPV (SWORD) (2016)
- DTG + 3TC (GEMINI & TANGO) (ACTG 5353 & ASPIRE) (Lamidol)
- CABT LA + RPV LA (LATTE-2) (2017)
- CABT LA + RPV LA (FLAIR & ATLAS)

Courtesy: J Arribas
## DTG-based dual therapy regimens

<table>
<thead>
<tr>
<th>Name</th>
<th>Design</th>
<th>Regimen(s)</th>
<th>N</th>
<th>Population</th>
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<tr>
<td><strong>SWORD 1 and 2</strong></td>
<td>Open label RCT switch</td>
<td>DTG/RPV versus continue regimen</td>
<td>1024</td>
<td>Virologically suppressed; no prior VF</td>
</tr>
<tr>
<td><strong>PADDLE</strong></td>
<td>Pilot</td>
<td>DTG/3TC</td>
<td>20</td>
<td>ARV-naïve; VL &lt; 100 000 copies/mL</td>
</tr>
<tr>
<td><strong>ACTG 5353</strong></td>
<td>Single arm</td>
<td>DTG/3TC</td>
<td>120</td>
<td>ARV-naïve; VL = 1000 – 500 000 copies/mL</td>
</tr>
<tr>
<td><strong>GEMINI 1 and 2</strong></td>
<td>RCT double blind</td>
<td>DTG/3TC versus DTG + TDF/FTC</td>
<td>1433</td>
<td>ARV-naïve; VL = 1000 – 500 000 copies/mL</td>
</tr>
<tr>
<td><strong>LAMIDOL ANRS 167</strong></td>
<td>Single arm</td>
<td>DTG/3TC</td>
<td>104</td>
<td>Virologically suppressed on first line 2 NRTIs + PI/ NNRTI/InSTI</td>
</tr>
<tr>
<td><strong>ASPIRE</strong></td>
<td>RCT switch</td>
<td>DTG/3TC versus continue regimen</td>
<td>89</td>
<td>Virologically suppressed</td>
</tr>
<tr>
<td><strong>TANGO</strong></td>
<td>Open label RCT switch</td>
<td>DTG/3TC versus TAF-based regimen</td>
<td>750</td>
<td>Virologically suppressed on TAF-based regimen</td>
</tr>
</tbody>
</table>
GEMINI: DTG + 3TC noninferior at 48 weeks

Parallel randomised double blind phase 3 non-inferiority studies

- No treatment-emergent InSTI or NRTI mutations in patients with VF in either arm
- Confirmed VF with DTG + 3TC: n = 6; Confirmed VF with DTG + TDF/FTC: n = 4
- Bone and kidney safety markers more favourable with DTG + 3TC vs DTG + TDF/FTC

DTG + 3TC was noninferior versus 3-drug therapy; no resistance in either arm

*Adjusted for HIV-1 RNA (≤ vs > 100 000 copies/mL), CD4+ cell count (≤ vs > 200 cells/μL), and study (GEMINI-1 vs GEMINI-2).

†PP = the ITT-E population excluding significant protocol violations

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

Objectives: To evaluate the efficacy and safety of DTG + RPV compared with continuation of current ART regimen (CAR) for 48 weeks in a large randomised population with suppressed viral load

Primary endpoint: Proportion of participants with virologic failure (HIV-1 RNA ≥ 50 copies/mL)
SWORD 1 and 2: Switch from current ART to DTG + RPV dual regimen

Baseline characteristics

<table>
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<tr>
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<th>DTG + RPV (n=513); n (%)</th>
<th>CAR (n=511); n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>43 (11.1)</td>
<td>43 (10.2)</td>
</tr>
<tr>
<td></td>
<td>147 (29)</td>
<td>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/uL (median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤500</td>
<td>611</td>
<td>638</td>
</tr>
<tr>
<td></td>
<td>165 (32)</td>
<td>149 (29)</td>
</tr>
<tr>
<td></td>
<td>348 (68)</td>
<td>362 (71)</td>
</tr>
<tr>
<td>&gt;500</td>
<td></td>
<td></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></td>
<td>275 (54)</td>
<td>278 (54)</td>
</tr>
<tr>
<td></td>
<td>105 (20)</td>
<td>97 (19)</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>InSTI</td>
<td></td>
<td></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></td>
<td></td>
</tr>
<tr>
<td></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%)

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.

# DUAL: DRV/3TC vs DRV/r + 2NRTIs

## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DRV/r + 2NRTI N = 123</th>
<th>DRV/r + 3TC N = 126</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CD4+/uL, median</td>
<td>568</td>
<td>596</td>
</tr>
<tr>
<td>Nadir CD4+/uL, median</td>
<td>240</td>
<td>253</td>
</tr>
<tr>
<td>Duration of HIV RNA &lt; 50 copies/mL (weeks), median</td>
<td>113 (p = 0.014)</td>
<td>79.5</td>
</tr>
<tr>
<td>HCV coinfection, %</td>
<td>22.8</td>
<td>25.4</td>
</tr>
<tr>
<td>N(t)RTI at baseline, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Discontinued at Week 48, N (%)</td>
<td>4 (3.3)</td>
<td>9 (7.1)</td>
</tr>
<tr>
<td>AE / confirmed VF</td>
<td>2 / 0</td>
<td>1 / 2</td>
</tr>
<tr>
<td>Withdrew / lost to f-up</td>
<td>1 / 1</td>
<td>3 / 3</td>
</tr>
</tbody>
</table>

## Week 48 efficacy

![Week 48 efficacy chart](chart.png)

- Dual therapy with **DRV/r plus 3TC was non-inferior** regarding maintenance of viral suppression and **equally well tolerated** as DRV/r plus TDF/FTC (or ABC/3TC)
- Persistent virological suppression was maintained after switching to dual therapy with DRV/r plus 3TC

Pulido F, Clin Infect Dis 2017; 65:2112-8
Prevalence of NNRTI pretreatment resistance by calendar year across studies

Increasing trends in levels of DR observed

Will they continue to increase?

Most DR strains arise independently → ARV regimens with a high genetic barrier to resistance and improved patient adherence may mitigate DR increases by reducing the generation of new ARV-resistant strains

Addressing PDR

↓ chance of transmitting resistant virus

- **Improve adherence**
  - Strengthen adherence support

- **Potent fixed-dose combination regimens**
  - Suppress HIV-RNA
  - High adherence

- **VL monitoring**
  - Promptly switch individuals with confirmed VF to second-line treatment
  - Minimise time spent on a failing regimen with resistant virus
  - Perform viral load monitoring
  - HIV-DR testing with failure

- **Use agents with high genetic barrier**
  - Change first-line regimen at a national level, from an NNRTI-based regimen to DTG- or PI/r-based regimen

Which is the more cost-effective strategy?

http://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf
Factors influencing drug resistance

**Poor adherence**

- Drug toxicities
- Social / personal issues

**Insufficient drug level**

- Interruption of treatment
- Poor potency
- Adding 1 drug to failing regimen

- Prolonging a failing regimen
- Treatment with < 3 drugs
- Inappropriate drug selection

**Viral replication in the presence of drug**

**HIV DR**

- Drug stockouts
- Lack of API, drug supply and delivery
- Lack of continuous support and monitoring

**Increasingly stretched healthcare systems**

**Lack of continuous support and monitoring**

**TDR = transmitted drug resistance**
Factors influencing drug resistance

Drug toxicities

Social / personal issues

Poor adherence

Lack of API, drug supply and delivery

Lack of continuous support and monitoring

Insufficient drug level

Interruption of treatment

Poor potency

Adding 1 drug to failing regimen

Viral replication in the presence of drug

HIV DR

TDR = transmitted drug resistance
Acknowledgements
Pretreatment drug resistance and new treatment paradigms in first-line ART

Michelle Moorhouse
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