Management of ART Failure

EACS Advanced HIV Course 2015
Dr Nicky Mackie
Outline

• Defining treatment success
• Defining treatment failure
• Reasons for ART failure
• Management of ART failure
• Choice of second line therapy
Defining treatment success

• Reduce HIV-associated morbidity and prolong the duration and quality of survival
• Restore and preserve immune function
• Prevent HIV transmission
• Maximally and durably suppress plasma HIV viral load*

*Includes treatment-experienced patients with ART failure +/- drug resistance
The goal of antiretroviral therapy

- Treatment guidelines: The goal of therapy is to achieve & maintain viral load suppression below detection limits\(^1-^4\)

**Probability of viral load suppression among patients starting first-line therapy in the UK (n=1550)\(^5\)**

**CD4 count recovery among patients starting first-line therapy in the UK (n=1550)\(^5\)**

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Which of the following correctly defines virological failure?

1. Any confirmed HIV RNA detection
2. Confirmed viral load >50 cps
3. Confirmed viral load >200 cps
4. Confirmed viral load >400 cps
5. Confirmed viral load >1000 cps
Definitions of virological failure vary

**EACS 2014:** Confirmed >50 cps ≥6 months after ART initiation or modification

**DHHS 2014:** Inability to achieve or maintain <200 cps

**IAS-USA 2014:** HIV-1 RNA level >200 cps should prompt evaluation of factors leading to failure and consideration of switching ART

**BHIVA 2015 (draft):** Incomplete virological response after commencing treatment or evidence of confirmed virological rebound to >200 copies/ml

**WHO 2014:** Confirmed >1000 cps after ≥6 months of ART
Treatment Failure

Immunological treatment failure

- This includes a fall in CD4 count towards pre-treatment levels or a blunted or 'discordant' CD4 response despite suppressed viral load

Clinical Treatment Failure

- For example a new AIDS-defining illness
A virological blip is defined as a single measurement of detectable viraemia which is preceded and followed by an undetectable result without any change in therapy.
Viral Load Blips

• Confirm with a repeat sample within 4-6 weeks

• A single detectable viral load, preceded and followed by an undetectable viral load, is usually not a cause for clinical concern

• Resistance testing should be considered for those with ‘large’ or repeated blips
Viral load rebound during therapy

Low level viraemia is defined as persistent detectable low level viraemia over a sustained period of time.
HIV-1 RNA kinetics after starting ART

Median months to cut-off (95% CI)

- <50 cps: 4.1 (3.3, 5.1)
- <40 cps: 4.4 (3.7, 5.4)
- <10 cps: 6.2 (5.4, 7.2)

HIV-1 RNA kinetics after starting ART

- **Phase 1 (days)**
- **Phase 2 (weeks)**
- **Phase 3 (months)**

**VL (Viral Load)**

**Cut-off**

**Latently infected cell**

**Sanctuary sites**
HIV-1 RNA kinetics after starting ART

Phase 1 (days)

Phase 2 (weeks)

Phase 3 (months)

Cut-off

VL

Sanctuary sites

Latently infected cell
Consequences of LLV

• If reflects on-going viral replication
  – May predict VL rebound (may be dependent on level of VL)
  – Potential for viral genetic evolution and emergence of drug resistance
  – Immune activation/inflammation
  – May signal suboptimal control in certain compartments
Reasons for ART Failure

**Patient**
- Non-adherence
- Tolerability
  - Low nadir CD4
- Comorbidities*
  - Rx history

**Virus**
- High baseline VL
- Resistance (TDR or acquired)
- Fitness

**ART**
- Suboptimal potency
- Suboptimal pK
- Food requirements
- Pill burden
- Drug/food interactions

*Includes active substance abuse, psychiatric disease, neurocognitive defects
Types of resistance

- **Acquired drug resistance**: resistance of HIV to drugs in individuals on treatment

- **Primary drug resistance (transmitted drug resistance, TDR)**: resistance of HIV to drugs in individuals who have never received treatment
Prevalence of TDR in UK

Practical point: use regimens with high genetic barriers, e.g. PI-based, in individuals with TDR

- Transmitted resistant species persist prior to initiating treatment, and represent a risk for onward transmission and sub-optimal response to treatment
- Current levels 7-8% in UK
Management of ART failure (1)

• Review the patient

• Assess:
  – Adherence
  – Drug tolerability/toxicity
  – Lifestyle, health beliefs
  – Drug-drug or drug-food interactions
  – Co-morbidities including renal/liver disease and mental health/drug dependency problems
  – ARV potency
Management of ART failure (2)

• Assess:
  – Treatment history
  – Prior and current drug resistance test results
  – HIV VL/CD4 over time

• Tests
  – Repeat VL
  – Perform resistance test (ideally whilst patient on treatment or within 2-4 weeks of discontinuation)
  – Tropism testing
  – ?consider TDM

• Change regimen as required
## Genetic barrier and cross-resistance

<table>
<thead>
<tr>
<th>Class</th>
<th>ARVs</th>
<th>Genetic barrier</th>
<th>Cross Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>ZDV/3TC, d4T/3TC</td>
<td>+/+++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>ABC/3TC, TDF/3TC</td>
<td>+</td>
<td>+++</td>
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<td></td>
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<tr>
<td>NNRTIs</td>
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<td></td>
<td>+/+++</td>
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<td>PIs</td>
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<td></td>
<td>+++/++++</td>
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<td></td>
<td>Unboosted</td>
<td></td>
<td>+++/++</td>
</tr>
<tr>
<td></td>
<td>Boosted</td>
<td></td>
<td>++/+++</td>
</tr>
<tr>
<td>Fusion inhibitors</td>
<td>T20</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>CCR5 antagonists</td>
<td>MVC</td>
<td>+/+++</td>
<td>NA</td>
</tr>
<tr>
<td>Integrase inhibitors</td>
<td>RAL, EVG</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>DTG</td>
<td>++/+++</td>
<td>++</td>
</tr>
</tbody>
</table>

**LLV on a low genetic barrier regimen may warrant prompt regimen change**
Mr CM starts Atripla™ in September 2010
Baseline RT: wild-type; suppresses within 3 months
First ART failure: NNRTIs

• Resistance patterns
  – No resistance (WT virus).
  – 3TC/FTC resistance (M184V/I) following any first-line therapy, including TDF/FTC or ABC/3TC.
  – NNRTI resistance (e.g. K103N, Y181C/I/V, or E138K) and/or 3TC/FTC resistance
  – Extended RT resistance (e.g. K65R/L74V or thymidine analogue mutations)
Genotypic and Phenotypic Characterization of HIV-1 Isolates Obtained From Patients on Rilpivirine Therapy Experiencing Virologic Failure in the Phase 3 ECHO and THRIVE Studies: 48-Week Analysis

Laurence Rimsky, PhD,* Johan Vingerhoets, PhD,* Veerle Van Eygen, MSc,* Joseph Eron, MD,† Bonaventura Clotet, MD,‡ Annemie Hoogstoeel, MSc,* Katia Boven, MD,§ and Gaston Picchio, PhD§

*J Acquir Immune Defic Syndr 2012;59:39–46
% experiencing VF by week 48

<table>
<thead>
<tr>
<th></th>
<th>RPV</th>
<th>EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;100k</td>
<td>368</td>
<td>330</td>
</tr>
<tr>
<td>VL &gt;100k</td>
<td>318</td>
<td>352</td>
</tr>
<tr>
<td>All</td>
<td>686</td>
<td>682</td>
</tr>
</tbody>
</table>
% of VF developing resistance

% of all virological failures

RPV <100k, RPV >100k, RPV total, EFV <100k, EFV >100k, EFV total

NNRTI, NRTI, Both
First ART failure: NNRTIs

• Resistance patterns
  – No resistance (WT virus).
  – 3TC/FTC resistance (M184V/I) following any first-line therapy, including TDF/FTC or ABC/3TC.
  – NNRTI resistance (e.g. K103N, Y181C/I/V, or E138K) and/or 3TC/FTC resistance
  – Extended RT resistance (e.g. K65R/L74V or thymidine analogue mutations)

• Options:
  – Review adherence, ?TDM
  – **Switch to a bPI-based regimen is optimal**
  – To include NRTIs or another ARV(s)??
Activity of ETV with a weak backbone
Study TMC125-C227: 2 NRTIs + ETV or PI

**TMC125-C227: Change in viral load (observed)**

Initial 1.3 log decline in viral load was not sustained past 8 weeks, possibly affected by limited activity of the background regimen.

**ART-experienced, PI-naive patients with documented NNRTI resistance**

Ruxrungtham, HIV Med 2008
SECOND-LINE: LPV/RTV + RAL vs LPV/RTV + NRTIs After First-line VF

- Randomized, open-label, international, multicenter trial

- Stratified by clinical site, baseline HIV-1 RNA (≤ or > 100,000 copies/mL)

- HIV-infected pts with virologic failure on first-line regimen of 2 NRTIs + NNRTI (N = 541)

- Wk 48 primary endpoint

- Lopinavir/Ritonavir 400/100 mg BID + Raltegravir 400 mg BID (n = 270)

- Lopinavir/Ritonavir 400/100 mg BID + 2-3 NRTIs QD or BID (n = 271)

SECOND-LINE: Noninferiority of LPV/RTV + RAL vs LPV/RTV + NRTIs

- Similar high levels of virologic suppression with each strategy in primary mITT analysis\(^1\)
- LPV/r once daily or twice daily
- Non-inferiority demonstrated
- No effect of baseline VL
- 83% vs. 81% <200 cps at wk 48
- No major safety issues
- RAL arm significantly larger CD4 gains: +167 vs. +132 (NB: ZDV use in 45% of control patients)
- RAL arm significantly higher total cholesterol, HDL, LDL
- Non-inferiority also confirmed at week 96
- 80% vs 76% <200 cps

SECOND-LINE Subanalysis: Resistance to NRTIs and Risk of Virologic Failure

- Resistance analysis of randomized, open-label, multicenter trial

- Primary analysis: LPV/RTV + RAL noninferior to LPV/RTV + 2-3 NRTIs after VF of initial NNRTI regimen

- 46% with high-level NRTI resistance at baseline by global genotypic sensitivity score

- Risk of VF at Wk 96 in both treatment arms higher among pts with lower levels of NRTI resistance by gGSS

**VF at Wk 96 by BL Resistance Level, %**

<table>
<thead>
<tr>
<th></th>
<th>LPV/RTV + 2-3 NRTIs*</th>
<th>LPV/RTV + RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Moderate</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Low</td>
<td>43</td>
<td>38</td>
</tr>
</tbody>
</table>

*NRTIs selected by genotypic resistance test or by algorithm.

**EARNEST: Second-line LPV/RTV-Based ART After Initial NNRTI Failure**

- Randomized, controlled, open-label, phase III trial

**Baseline demographics (medians):** HIV-1 RNA 69,782 copies/mL; CD4+ 71 cells/mm³; time on ART 4 yrs

*Including clinical, CD4+ cell count (HIV-1 RNA confirmed), or virologic criteria.†Selected by physician according to local standard of care.

Paton et al, NEJM 2014; 371: 234-47
**EARNEST: Clinical Outcomes at Wk 96**

- "Good disease control" at Wk 96 defined as pt alive, no new WHO 4 events from Wks 0-96, and CD4+ cell count > 250 cells/mm³, and HIV-1 RNA < 10,000 copies/mL or > 10,000 copies/mL without PI resistance mutations.

Paton et al, NEJM 2014; 371: 234-47
Impact of NRTI Cross-Resistance on Second-line PI + NRTI Therapy Outcomes in Africa

N. Paton¹,⁷, C.Kityo², L. Bagenda², A. Kambugu³, J. van Oosterhout⁴,⁵, J. Hakim⁶, J.Thompson⁷, A. Hoppe⁷, S. Walker⁷, for the EARNEST Trial Team

¹Dept. Of Medicine, National University of Singapore, Singapore
²Joint Clinical Research Centre, Kampala, Uganda
³Infectious Diseases Institute, Kampala, Uganda
⁴Coll. of Med., Univ. Malawi, Blantyre, Malawi
⁵Dignitas International, Zomba, Malawi
⁶University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe
⁷MRC Clinical Trials Unit at UCL, London, UK
Methods: VL and resistance analysis

• **Viral load**
  – Batch tested on stored samples
  – In PI/NRTI & PI/RAL group to week 144, PI-mono to week 96
  – Central lab at JCRC Kampala, Uganda using Abbott m2000rt assay

• **Resistance**
  – Batch tested on stored samples
  – All PI/NRTI group at baseline
  – WHO-accredited reference lab at JCRC Kampala, Uganda using WHO-approved PCR assay
  – Mutations classified using Stanford algorithm
  – Calculated predicted activity of NRTIs in prescribed 2nd line PI/NRTI regimen:
    1) Number of “active” NRTIs (without int/high resistance) in prescribed regimen
    2) GSS of NRTIs in prescribed regimen:
      • Score activity of individual NRTI drugs used
        – High-level resistance 0
        – Intermediate level resistance 0.25
        – Low-level resistance 0.5
        – Potential low-level resistance 0.75
        – Susceptible 1
      • Added scores & categorised total as: 0, 0.25-0.75, 1-1.75, ≥2
Predicted activity of NRTIs in regimens

• **Number of predicted “active” NRTIs in prescribed second-line Rx*:**
  
<table>
<thead>
<tr>
<th>Number of NRTIs</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>230 (59%)</td>
</tr>
<tr>
<td>1</td>
<td>128 (33%)</td>
</tr>
<tr>
<td>≥2</td>
<td>33 (8%)</td>
</tr>
</tbody>
</table>

  *NRTI predicted “active” if no int./high level resistance by Stanford

• **GSS for NRTIs in prescribed second-line Rx:**
  
<table>
<thead>
<tr>
<th>GSS Range</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>114 (29%)</td>
</tr>
<tr>
<td>0.25-0.75</td>
<td>177 (45%)</td>
</tr>
<tr>
<td>1-1.75</td>
<td>73 (19%)</td>
</tr>
<tr>
<td>≥2</td>
<td>27 (7%)</td>
</tr>
</tbody>
</table>
VL response by number of active NRTIs in the regimen

- PI/NRTI(0) (N>149)
- PI/NRTI(1) (N>86)
- PI/NRTI(2-3) (N>17)
- PI + RAL (N>280)
- PI Monotherapy (N>374)

Within PI+NRTIs global p=0.02
NRTI() = number or active(susceptible-low resistance) NRTIs

Global p<0.0001

Percent with VL<400 copies/ml

Weeks from switch to second-line

88% 85%
81% 77%
61%

88% 85%
81% 77%
61%
VL response by GSS of NRTIs in the regimen

Weeks from switch to second-line

Percent with VL<400 copies/ml

Global p<0.0001
Within PI+NRTIs global p=0.007
Conclusions

- **Even when no predicted activity due to resistance, NRTIs have major beneficial effect in PI (LPV/r)/NRTI 2\textsuperscript{nd}-line therapy**
  - with clear added activity over a PI alone
  - equivalent to adding a new drug class
  - NRTI contribution may not be direct drug effect (fitness?)

- **Paradoxical relationship between resistance and VL suppression**
  - Confounding by adherence (although persists after adjustment)
  - Also consistent with fitness effect

- **Algorithmic NRTI drug selection + attention to adherence can achieve excellent outcomes from 2\textsuperscript{nd}-line therapy in public health approach**
  - Resistance testing to select NRTIs is of little added value.
Mr CM starts Truvada + Raltegravir in September 2010
Baseline RT: wild-type; suppresses within 3 months
First ART failure: IIs

• Resistance patterns
  – No resistance (WT virus).
  – 3TC/FTC resistance (M184V/I) following any first-line therapy, including TDF/FTC or ABC/3TC.
  – INI resistance (e.g. K143C/R, Q148R/H, or N155H) and/or 3TC/FTC resistance (following first-line therapy with RAL or ELV-based regimen, including TDF/FTC or ABC/3TC)
Study Design
Stribild Phase 3 Studies

- Multicentre, randomised, Phase 3, blinded, 192-week studies

Primary endpoint: HIV-1 RNA <50 c/mL at Week 48; FDA Snapshot analysis with non-inferiority margin of 12%


C-G: Cockcroft-Gault
Primary Endpoint
Study GS-102 – 48-week Virologic Efficacy

Stribild was **non-inferior** to EFV/FTC/TDF at Week 48

### Study GS-102 – 48-week Virologic Efficacy

**Primary Endpoint**

**Study GS-102 – 48-week Virologic Efficacy**

Stribild was **non-inferior** to EFV/FTC/TDF at Week 48

**STB** (n=348) vs **EFV/FTC/TDF** (n=352)

#### Outcome (snapshot) at Week 48

<table>
<thead>
<tr>
<th>Outcome (snapshot) at Week 48</th>
<th>STB (n=348)</th>
<th>EFV/FTC/TDF (n=352)</th>
<th>Prop Diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic success</td>
<td>88%</td>
<td>84%</td>
<td>3.6% (−1.6%, 8.8%)</td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>7%</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Data in window not &lt;50c/mL</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>1%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Discontinued for other reason while not &lt;50c/mL</td>
<td>2%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td><strong>No virologic data at Week 48</strong></td>
<td>5%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Discontinued because of AE or death</td>
<td>3%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Discontinued for other reasons</td>
<td>2%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>0%</td>
<td>&lt;1%</td>
<td></td>
</tr>
</tbody>
</table>

*Includes patients who had ≥50 copies/mL in the Week 48 window, patients who discontinued early due to lack or loss of efficacy, patients who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥50 copies/mL

**FDA Snapshot**


Data on file (STBUK1303)
<table>
<thead>
<tr>
<th>Mutation, n (%)</th>
<th>STB (combined, n=701)</th>
<th>Mutation</th>
<th>EFV/FTC/TDF (n=352)</th>
<th>ATV+RTV+FTC/TDF (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wk 48</td>
<td>Wk 48–96</td>
<td>Wk 48</td>
<td>Wk 48–96</td>
</tr>
<tr>
<td>Resistance analysis population at Week 96</td>
<td>36 (5.1%)</td>
<td>23 (5.1%)</td>
<td>16 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Any emergent resistance</td>
<td>13 (1.9%)</td>
<td>+3 (+0.4%)</td>
<td>8 (2.3%)</td>
<td>+2 (+0.6%)</td>
</tr>
<tr>
<td>Any primary integrase resistance</td>
<td>11 (1.6%)</td>
<td>+3 (+0.4%)</td>
<td>Any NNRTI resistance</td>
<td>8 (2.3%)</td>
</tr>
<tr>
<td>E92Q</td>
<td>8</td>
<td>+1</td>
<td>K103N</td>
<td>7</td>
</tr>
<tr>
<td>N155H</td>
<td>3</td>
<td>+2</td>
<td>K101E</td>
<td>0</td>
</tr>
<tr>
<td>Q148R</td>
<td>3</td>
<td>0</td>
<td>V108I</td>
<td>2</td>
</tr>
<tr>
<td>T66I</td>
<td>2</td>
<td>0</td>
<td>Y188F/H/L</td>
<td>1</td>
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<td></td>
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<td></td>
<td>M230L</td>
<td>0</td>
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<td></td>
<td>V90I</td>
<td>0</td>
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<td></td>
<td>G190A</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P225H</td>
<td>0</td>
</tr>
<tr>
<td>Any primary NRTI resistance</td>
<td>12 (1.7%)</td>
<td>+3 (+0.4%)</td>
<td>2 (0.6%)</td>
<td>+1 (+0.3%)</td>
</tr>
<tr>
<td>M184V/I</td>
<td>12</td>
<td>+3</td>
<td>2</td>
<td>+1</td>
</tr>
<tr>
<td>K65R</td>
<td>4</td>
<td>+1</td>
<td>2</td>
<td>+1</td>
</tr>
</tbody>
</table>

Zolopa A. Presented at CROI 2013, poster 553
**DTG Phase III Clinical Trials in Treatment-Naïve Adult Patients**

**FDA Snapshot Response Rates (48-Week Data; Primary Endpoint)**

<table>
<thead>
<tr>
<th>Trial</th>
<th>DTG</th>
<th>EFV</th>
<th>RAL</th>
<th>DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SINGLE</strong></td>
<td>364/414</td>
<td>338/419</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SPRING-2</strong></td>
<td>361/411</td>
<td>351/411</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FLAMINGO</strong></td>
<td>217/242</td>
<td>200/242</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **SINGLE**: 414 patients received DTG +ABC/3TC.\(^1\)
- **SPRING-2**: On Day 1 in the DTG arm, 242 and 169 patients received TDF/FTC or ABC/3TC, respectively; in the RAL arm 247 and 164 patients received TDF/FTC and ABC/3TC, respectively.\(^2\)
- **FLAMINGO**: On Day 1 in the DTG arm, 163 and 79 patients received TDF/FTC or ABC/3TC, respectively; in the DRV/r arm 162 and 80 patients received TDF/FTC and ABC/3TC, respectively.\(^3\)

**Percent (% of patients HIV-1 RNA <50 copies/ml)**

- **DTG** 88/414
- **EFV** 81/414
- **RAL** 88/411
- **DRV/r** 90/242

**Statistical Significance**

- **SINGLE**: DTG is statistically superior vs EFV/TDF/FTC \(p = 0.03\)
- **SPRING-2**: Non-inferior vs RAL +2NRTIs\(^†\)
- **FLAMINGO**: Statistically superior vs DRV/r +2NRTIs\(^†\) \(p = 0.025\)

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Resistance profile of DTG in treatment-naïve studies

- DTG has demonstrated a favourable resistance profile in several studies to date.

### Treatment-emergent mutations observed in trials with treatment-naïve patients

<table>
<thead>
<tr>
<th>Study</th>
<th>INI resistant mutations</th>
<th>NRTI-resistant mutations</th>
<th>NNRTI-resistant mutations</th>
<th>EFV/IDV/FTC QD (N=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGLE study (144 weeks)¹</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>SPRING-2 study (96 weeks)²</td>
<td>0</td>
<td>0</td>
<td>6 (K101E, K103N, K103K/N, G190G/A)⁺</td>
<td></td>
</tr>
<tr>
<td>FLAMINGO study (96 weeks)³</td>
<td>0</td>
<td>4⁺</td>
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<th>Study</th>
<th>INI-resistant mutations</th>
<th>NRTI-resistant mutations</th>
<th>EFV/IDV/FTC QD (N=419)</th>
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<tbody>
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<td>SINGLE study (144 weeks)¹</td>
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<td>SPRING-2 study (96 weeks)²</td>
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**Notes:**
- SINGLE: *n=1 with K101E, n=2 with K103N, n=2 with K103K/N, n=2 with G190G/A (n=1 with K103N and G190G/A)

References:
First ART failure: IIs

• Resistance patterns
  – No resistance (WT virus).
  – 3TC/FTC resistance (M184V/I) following any first-line therapy, including TDF/FTC or ABC/3TC.
  – INI resistance (e.g. K143C/R, Q148R/H, or N155H) and/or 3TC/FTC resistance (following first-line therapy with RAL or ELV-based regimen, including TDF/FTC or ABC/3TC)

• Options:
  – Switch to a bPI-based regimen is optimal
Thanks?