Is HIV management moving towards personalized medicine?

Carlo Federico Perno
Proportion of patients with a VL≤80 copies/mL at 12 months from starting their first ART regimen by calendar year of initiation
In the long-term management of HIV infection, the stable maintenance of undetectable HIV over the years is more important than the mere success of the first regimen.
Therapy insights today

- Treatment is life-long (or at least for decades)
- Therapy is successful only if maintained for decades, not for months or a few years
- Switch to new ARTs is a natural event in the course of long-term therapies (failure, toxicity, intolerance etc)
- Preservation of future therapeutic options is mandatory in this context
- Avoiding the emergence of resistance / cross resistance is, in this frame, one of the major factors to be considered
  - Otherwise, a clinical price will be paid, although later than in the past....
Therefore . . . . . .

- Our endeavour today has switched from treating the resistant virus to preventing its emergence and consolidation
  - Although resistant viruses are still an issue in a number of patients

- Long-term success will require major attention in this matter
Strategies to Achieve Treatment Goals

Selection of Initial Combination Regimen

Several ARV regimens are recommended for use in ART-naïve patients.

Recommended Regimens for First-line ART

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTI</td>
<td>DTG/ABC/3TC</td>
<td>DTG/ABC/3TC</td>
<td>DTG/ABC/3TC</td>
</tr>
<tr>
<td></td>
<td>DTG + (TAF or TDF)/FTC</td>
<td>DTG + TAF/FTC</td>
<td>DTG + (TAF or TDF)/FTC</td>
</tr>
<tr>
<td></td>
<td>EVG/COBI/(TAF or TDF)/FTC</td>
<td>EVG/COBI/TAF/FTC</td>
<td>EVG/COBI/(TAF or TDF)/FTC</td>
</tr>
<tr>
<td></td>
<td>RAL + (TAF or TDF)/FTC</td>
<td>RAL + TAF/FTC</td>
<td>RAL + (TAF or TDF)/FTC</td>
</tr>
<tr>
<td>Boosted</td>
<td>DRV + RTV + (TAF or TDF)/FTC</td>
<td></td>
<td>DRV + (RTV or COBI) + (TAF or TDF)/FTC</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td>RPV/(TAF or TDF)/FTC</td>
<td></td>
</tr>
</tbody>
</table>

Most of the recommended regimens have comparable efficacy.

However they vary in:
• Pill burden
• Potential for drug interactions and/or side effects
• Propensity to select for resistance mutations if ART adherence is suboptimal

Regimens should be tailored for the individual patient to enhance adherence and support long-term treatment success.
Factors influencing long-term viral suppression

\[ \text{Durability} = \text{Adherence} + \text{Drug Levels} + \text{Genetic Barrier} - \text{Baseline Mutations} - \text{Baseline Viremia} \]

- Patient: Convenience and tolerability, Height and duration of drug exposure, Adverse effects
- Drugs: Number and type of mutations required for resistance development
- Virus: Number and type of mutations present at therapy start, Subtype

Viremia levels at therapy start
By 72 weeks of therapy, patients having **pre-HAART viremia >500,000 copies/mL** showed the lowest probability of achieving VS compared to others pre-HAART viremia ranges.

**Pre-HAART viremia ranges (copies/mL):**

- **<30K**
- **30-100K**
- **100-300K**
- **300-500K**
- **>500K**

**Median time (95% CI) of achieving VS (weeks)**

- 12 (11-13): 98%
- 16 (16-17): 98%
- 20 (19-21): 96.3%
- 23 (21-26): 99.1%
- 27 (24-30): 92.7%

**Probability of VS at 72 weeks**

- 98%
- 98%
- 96.3%
- 99.1%
- 92.7%

 Patients (N=1,734) followed after HAART starting regardless therapy changes or interruptions. CI: confidence interval. HAART: highly active antiretroviral therapy. <30K: <30,000. 30-100K: 30,000-100,000. 100-300K: 100,000-300,000. 300-500K: 300,000-500,000. >500K: >500,000. VS: virological success.
Plasma HIV-1 RNA plays an important role in the selection of an initial ARV

Pre-treatment viral load level is an important factor in the selection of an initial ARV regimen because several currently approved ARV drugs or regimens have been associated with poorer responses in patients with high baseline viral load.

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ART HIV RNA &gt;100,000 copies/mL</td>
<td>Do Not Use the Following Regimens:</td>
<td>Higher rates of virologic failure observed in those with high pretreatment HIV RNA</td>
</tr>
<tr>
<td></td>
<td>• RPV-based regimens</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ABC/3TC with EFV or ATV/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DRV/r plus RAL</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Case: ID 18216 Patient Infected with HIV-1 B subtype


- **Risk Factor**: Sexual
- **Clinical Case**
  - **ID 18216**
  - **Patient Infected with HIV-1 B subtype**
  - **Age**: 28
  - **Sex**: M
  - **Risk Factor**: Sexual
  - **1st Seropositivity**: January 2016
  - **CDC stage**: B2

**CD4 cell count (cells/µl)**

- **CD4: 395 cells/µl**
  - **GRT November 2016 from Plasma**
    - **VL (copies/ml)**: > 10,000,000
    - **CD4**: 395 cells/µl
    - **PR**: L63P V77I I93L
    - **RT**: None
    - **INT**: None
  - **Other mutations**
    - **PR**: N37S R41K I62V I64ILM
    - **INT**: D6N K7E V31I I113V T125A V201I Q216H L234H

- **CD4: 407 cells/µl**
  - **GRT April 2017 from Plasma**
    - **VL (copies/ml)**: 235,745
    - **CD4**: 407 cells/µl
    - **PR**: L63H V77I I93IL
    - **RT**: M184V
    - **INT**: Q140A Q148R
  - **Other mutations**
    - **PR**: N37S R41K I62V
    - **INT**: D6N K7E V31I I113V T125A V201I Q216H L234H

**Viremia (log copies/ml)**

- **Undetectability threshold**
  - **Nov-16**: 7.0
  - **Dec-16**: 6.5
  - **Jan-17**: 6.0
  - **Feb-17**: 5.5
  - **Apr-17**: 5.0

**November 2016 - April 2017**

TDF/FTC/EVG/COB

- **GRT November 2016 from Plasma**
  - **VL**: > 10,000,000 copies/ml
  - **CD4**: 395 cells/µl
  - **PR**: L63P V77I I93L
  - **RT**: None
  - **INT**: None

- **GRT April 2017 from Plasma**
  - **VL**: 235,745 copies/ml
  - **CD4**: 407 cells/µl
  - **PR**: L63H V77I I93IL
  - **RT**: M184V
  - **INT**: Q140A Q148R

**Other mutations**

- **PR**: N37S R41K I62V
- **INT**: D6N K7E V31I I113V T125A V201I Q216H L234H
Overall, by 96 weeks after achieving virological success, the probability of virological rebound was 17.5%.

Patients (N=1,671) followed after achieving VS regardless therapy changes or interruptions. Virological rebound defined as the first of 2 consecutive viremia values >50 copies/mL after achieving VS. VS: virological success.
By 96 weeks after achieving virological success, patients having pre-HAART viremia >500,000 copies/mL showed the highest probability of experiencing virological rebound compared to other pre-HAART viremia ranges.

Pre-HAART viremia ranges (copies/mL):

- Green: <30K
- Bright Green: 30-100K
- Orange: 100-300K
- Brown: 300-500K
- Red: >500K

Probability of VR at 96 weeks:
- 10.3%
- 16.7%
- 19.2%
- 19.3%
- 26.8%

Patients (N=1,671) followed after achieving VS regardless of therapy changes or interruptions. Virological rebound defined as the first of 2 consecutive viremia values >50 copies/mL after achieving VS. <30K: <30,000, 30-100K: 30,000-100,000, 100-300K: 100,000-300,000, 300-500K: 300,000-500,000, >500K: >500,000. HAART: highly active antiretroviral therapy. VS: virological success.
Clinical Case: ID 5060 Patient infected with HIV-1 B subtype

Age: 46  Sex: M  1st Seropositivity: January 1997  Risk Factor: MSM

**GRT October 2006**
- VL: 16,873 cps/mL
- CD4: 506 cells/µl
- PR: L63P V77I I93L
- RT: T69NT K70KR M184IMV K219IK

**Other PR-RT mutations**
- PR: T12AT K14R H69Q K70R

**GRT September 2016**
- VL: 5,874 cps/mL
- CD4: 391 cells/µl
- PR: L63P V77I I93L
- RT: D67N K70R K101P K103N M184V T215Y K219Q
- INT: V151I

**Other mutations**
- PR: L19I H69Q K70R
- INT: D6N K7E I72V T214NT T125AMTV V126LV
Long-life treatment dictates the switch!!!

How we can personalize treatment switch in virologically suppressed patients?
HIV DNA Genotypic Resistance Test is a good tool for therapy optimization in both drug-naïve and drug-experienced patients

Increased requests of HIV DNA GRT in clinical practice over the recent years

Number of PBMCs genotypic resistance tests performed

- Protease & Reverse Transcriptase
- Integrase

Armenia D unpublished data, Update Dec 2016
By exploring plasma cumulative resistance for any class and resistance detected in PBMC, 20.1% of patients harboured major resistance mutations (MRMs) not detected in any of previous GRTs performed in plasma.

Proportion of Patients with MRM in PBMCs and Cumulative Plasma (149 Patients with DNA GRT and ≥2 Plasma GRTs, 9 Patients for INSTI)

Mean (±SD) number of MRM, (PI/NNRTI/NRTI)

<table>
<thead>
<tr>
<th>Class</th>
<th>Mutations detected only in cumulative plasma</th>
<th>Mutations detected in PBMCs and cumulative plasma</th>
<th>Mutations detected only in PBMCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>50.3 (±1.67)</td>
<td>11.4 (±1.66)</td>
<td>38.3 (±1.67)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>43</td>
<td>28.2 (±1.00)</td>
<td>11.4 (±1.66)</td>
</tr>
<tr>
<td>PI</td>
<td>30.2</td>
<td>16.8 (±1.39)</td>
<td>1.3 (±1.33)</td>
</tr>
<tr>
<td>INSTI</td>
<td>11.111.1 (±1.33)</td>
<td>0.3 (±0.33)</td>
<td>0.29 (±0.37)</td>
</tr>
<tr>
<td>Overall</td>
<td>61.1</td>
<td>51</td>
<td>51.2 (±1.67)</td>
</tr>
</tbody>
</table>

Zaccarelli et al., JCV 2016
What about the impact of archived resistance in virologically suppressed patients that need a therapy switch?
PBMC resistance evaluation predicts virological response after therapy switching in treated patients with undetectable HIV-1 RNA

D. Armenia¹, M. Zaccarelli², V. Borghi³, W. Gennari³, D. Di Carlo¹, A. Giannetti², F. Forbici², A. Bertoli¹, C. Gori², L. Fabeni², C. Pinnetti², R. Marocco⁴, A. Latini⁵, F. Ceccherini Silberstein¹, C. Mastroianni⁴, C. Mussini³, A. Antinori², CF. Perno², and MM. Santoro¹

¹University of Rome Tor Vergata, Rome, Italy; ²National Institute for Infectious Diseases L. Spallanzani, IRCCS; ³Polyclinic of Modena, Modena, Italy; ⁴La Sapienza University Polo Pontino, Latina, Italy; ⁵San Gallicano Dermatological Institute, IRCCS, Rome, Italy.
Patients showing at baseline PBMC GRT an intermediate or fully resistant GSS to the regimen administered have a higher probability of experiencing virological rebound compared to those showing full susceptibility.

Kaplan-Meier estimates of virological rebound stratified for GSS
(VR: 2 consecutive HIV-1 RNA \(> 50 \) copies/mL or 1 HIV-RNA \(> 1000 \) copies/mL after therapy switching)

Genotypic susceptibility score
- Fully or intermediate resistant
- Fully susceptible

\[ P = 0.001 \]

Analysis on 227 patients virologically suppressed since a median (IQR) time of 3.7 (0.9-7.0) years.

Armenia et al., ERDW 2017, poster 52
Cox-regression confirmed that a higher hazard of experiencing virological rebound is found in patients with an intermediate or fully resistant GSS in PBMCs as compared to those with a fully susceptible GSS.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude relative hazard of experiencing VR</th>
<th>Adjusted relative hazard of experiencing VR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RH</td>
<td>IC 95.0%</td>
</tr>
<tr>
<td>Nadir CD4 cell count (cells/mm$^3$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq$100$^b$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>$&lt;$100</td>
<td>3.06</td>
<td>1.28</td>
</tr>
<tr>
<td>Time under undetectable HIV-1 RNA before therapy switching (per 1 year lower)</td>
<td>1.13</td>
<td>0.98</td>
</tr>
<tr>
<td>Genotypic susceptibility score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully susceptible$^b$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intermediate or fully resistant</td>
<td>4.04</td>
<td>1.61</td>
</tr>
</tbody>
</table>

a. Adjusted for age, gender, subtype, risk factor, nadir CD4, duration of virological suppression before switching, HIV-RNA baseline target detection, viral blips before therapy switching, number of previous regimens, number of antiretrovirals administered at switch, type of cART administered at switch. Reference (dummy).

Armenia et al., ERDW 2017, poster 52
Pre-existent NRTI and NNRTI resistance impacts on maintenance of virological suppression in HIV-1-infected patients who switch to a tenofovir/emtricitabine/rilpivirine single-tablet regimen

D. Armenia, D. Di Carlo, A. Calcagno, G. Vendemiati, F. Forbici, A. Bertoli, G. Berno, S. Carta, F. Continenza, V. Fedele, R. Bellagamba, S. Cicalini, A. Ammassari, R. Libertone, M. Zaccarelli, V. Ghisetti, M. Andreoni, F. Ceccherini-Silberstein, S. Bonora, G. Di Perri, A. Antinori, C. F. Perno and M. M. Santoro

1Experimental Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy; 2Division of Infectious Diseases, University of Turin, Turin, Italy; 3Antiretroviral Drug Monitoring Laboratory, National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome, Italy; 4Infectious Diseases Division, National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome, Italy; 5Systems Medicine, University of Rome Tor Vergata, Rome, Italy

*Corresponding author. E-mail: santormaria@gmail.com
†D. Armenia and D. Di Carlo equally contributed to this work.

Received 3 August 2016; returned 29 August 2016; revised 28 October 2016; accepted 1 November 2016

Objectives: To evaluate the maintenance of virological suppression (VS) in antiretroviral-treated HIV-1-suppressed patients switching to a tenofovir/emtricitabine/rilpivirine (TDF/FTC/RPV) single-tablet regimen, by considering pre-existent resistance (pRes).

Methods: pRes was evaluated according to resistance on all previous plasma genotypic resistance tests. Probability and predictors of virological rebound (VR) were evaluated.

Results: Three hundred and nine patients were analysed; 5.8% of them showed resistance to both NRTIs and NNRTIs, while 12.6% showed resistance to only one of these drug classes. By 72 weeks, the probability of VR was 11.3%. A higher probability of VR was found in the following groups: (i) patients with NRTI + NNRTI pRes compared with those harbouring NRTI or NNRTI pRes and with those without reverse transcriptase inhibitor pRes (39.2% versus 11.5% versus 9.4%, P < 0.0001); (ii) patients with a virus with full/intermediate resistance to both tenofovir/emtricitabine and rilpivirine compared with those having a virus with full/intermediate resistance to tenofovir/emtricitabine or rilpivirine and those having a virus fully susceptible to TDF/FTC/RPV (36.4% versus 17.8% versus 9.7%, P < 0.001); and (iii) patients with pre-therapy viraemia >500 000 copies/mL compared with those with lower viraemia levels (≥500 000: 16.0%; 100 000–500 000: 9.3%; <100 000 copies/mL: 4.8%, P = 0.009). pRes and pre-therapy viraemia >500 000 copies/mL were independent predictors of VR by multivariable Cox regression.

Conclusions: TDF/FTC/RPV as a treatment simplification strategy shows a very high rate of VS maintenance. The presence of pRes to both NRTIs and NNRTIs and a pre-therapy viraemia >500 000 copies/mL are associated with an increased risk of VR, highlighting the need for an accurate selection of patients before simplification.
Patients with pre-existing both NRTI+NNRTI resistance had a higher probability of experiencing virological rebound compared to those harboring pre-existent NRTI or NNRTI resistance and to those without pre-existent RTI resistance.

Pre-existent RTI-resistance before switching:
- No resistance
- NRTI or NNRTI 12.6%
- NRTI + NNRTI 5.8%

Overall probability of virological rebound 11.3%

p<0.0001
A significant higher hazard ratio of virological rebound was found in patients with pre-existent both NRTI+NNRTI-resistance compared to those without RTI-resistance (or only NRTI or NNRTI-resistance)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio of experiencing virological rebound</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR (95% C.I.) p-value</td>
<td>HR (95% C.I.) p-value</td>
<td></td>
</tr>
<tr>
<td>Pre-existent RTI-resistance before TDF/FTC/RPV switching:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 0.943</td>
<td>1 0.935</td>
<td></td>
</tr>
<tr>
<td>NRTI or NNRTI</td>
<td>1.06 (0.23-4.77) 0.943</td>
<td>1.07 (0.19-5.92) 0.935</td>
<td></td>
</tr>
<tr>
<td>NRTI and NNRTI</td>
<td>7.52 (2.39-23.68) 0.001</td>
<td>7.25 (1.47-29.15) 0.022</td>
<td></td>
</tr>
<tr>
<td>Pre-therapy viremia (copies/mL) as drug-naïve:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100,000-500,000</td>
<td>1.59 (0.43-5.93) 0.488</td>
<td>1.84 (0.44-7.68) 0.401</td>
<td></td>
</tr>
<tr>
<td>&gt;500,000</td>
<td>4.85 (1.46-16.12) 0.010</td>
<td>5.69 (1.31-24.74) 0.020</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for: age, gender, subtype, risk factor, years of virological suppression before TDF/FTC/RPV switching, at least one viral load blip before TDF/FTC/RPV switching, pre-existent RTIs resistance before TDF/FTC/RPV switching, usage of TDF+FTC/3TC at TDF/FTC/RPV switching, third drug of the regimen at TDF/FTC/RPV switching, cumulative experience to NNRTIs before TDF/FTC/RPV switching, baseline and nadir CD4 cell count, number of previous regimens before TDF/FTC/RPV switching and pre-therapy viremia as drug-naïve.  
<sup>b</sup> Reference group (dummy). HR: hazard ratio. Boldface indicates factors that were significantly associated (p<0.05) with virological rebound.

Armenia et al., JAC Jan 2017
A significant higher hazard ratio of virological rebound was found in patients with pre-existent both NRTI+NNRTI-resistance compared to those without RTI-resistance (or only NRTI or NNRTI-resistance) and in patients with pre-therapy viremia >500,000 copies/mL compared to those with pre-therapy viremia <100,000 copies/mL

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio of experiencing virological rebound</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusteda</td>
</tr>
<tr>
<td></td>
<td>HR (95% C.I.)</td>
<td>p-value</td>
</tr>
<tr>
<td>Pre-existent RTI-resistance before TDF/FTC/RPV switching:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noneb</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>NRTI or NNRTI</td>
<td>1.06 (0.23-4.77)</td>
<td>0.943</td>
</tr>
<tr>
<td>NRTI and NNRTI</td>
<td>7.52 (2.39-23.68)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pre-therapy viremia (copies/mL) as drug-naïve:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100,000b</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>100,000-500,000</td>
<td>1.59 (0.43-5.93)</td>
<td>0.488</td>
</tr>
<tr>
<td>&gt;500,000</td>
<td>4.85 (1.46-16.12)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

a Adjusted for: age, gender, subtype, risk factor, years of virological suppression before TDF/FTC/RPV switching, at least one viral load blip before TDF/FTC/RPV switching, pre-existent RTIs resistance before TDF/FTC/RPV switching, usage of TDF+FTC/3TC at TDF/FTC/RPV switching, third drug of the regimen at TDF/FTC/RPV switching, cumulative experience to NNRTIs before TDF/FTC/RPV switching, baseline and nadir CD4 cell count, number of previous regimens before TDF/FTC/RPV switching and pre-therapy viremia as drug-naïve. b Reference group (dummy). HR: hazard ratio. Boldface indicates factors that were significantly associated (p<0.05) with virological rebound.

Armenia et al., JAC Jan 2017
Long-life treatment dictates the switch!!!

What are the best treatment options currently available?
Monotherapy?
Perhaps not the best........
RTIs act at early stage of HIV-1 infection blocking few reverse transcriptase (RT) molecules

An appropriate intracellular drug-concentration, and the low number of targets (1-100) ensures: Drug : Target $1 : 1$
INSTIs act on few pre-integration complexes already translocated in nucleus.

An appropriate intracellular drug-concentration, and the low number of targets (1-100) ensures: Drug : Target 1 : 1.
PIs must inhibit protease enzymes (≈100-200 per particle) acting upon the maturation of hundreds of novel viral particles daily produced.

The high number of HIV proteases daily produced (100-200 per viral particle x hundreds of viral particles produced per day ≈ 20,000-100,000 HIV-PR per cell) needs an adequate intracellular drug concentration to reach Drug : Target 1 : 1.

Thus.....
HIV-1 infected H9 lymphoma cell line

Transmission electron microscopy (TEM) images H9 infected with pNL4.3 (10,000 pg/ml) after 7 days post infection. The production of HIV gag p24 was of 1,200,000 pg/ml.
HIV-1 infected macrophages in presence of darunavir 100nM

TEM images of human primary macrophages infected with HIV (p81.A strain) and treated with darunavir 100nM after 14 days post infection. The production of HIV gag p24 was of 63pg/ml. Near all the viral particles are immature/degradated.
Under PI monotherapy, the inhibition of protease might be incomplete due to the high number of targets.

Drug : Target 1 : 1 ??

PI monotherapy might be unable to block all PR targets, particularly in case of pre-therapy high viral load (high HIV-DNA?) and/or a high number of residual replication cycles. The absence of companion drugs further decreases the potency, thus favouring conditions for virological failure.
Protease inhibitor monotherapy for long-term management of HIV infection: a randomised, controlled, open-label, non-inferiority trial

Nicholas I Paton, Wolfgang Stöhr, Alejandra Arenas-Pinto, Martin Fisher, Ian Williams, Margaret Johnson, Chloe Orkin, Fabian Chen, Vincent Lee, Alan Winston, Mark Gompels, Julie Fox, Karen Scott, David T Dunn, for the Protease Inhibitor Monotherapy Versus Ongoing Triple Therapy (PIVOT) Trial Team

Summary
Background Standard-of-care antiretroviral therapy (ART) uses a combination of drugs deemed essential to minimise treatment failure and drug resistance. Protease inhibitors are potent, with a high genetic barrier to resistance, and have potential use as monotherapy after viral load suppression is achieved with combination treatment. We aimed to assess clinical risks and benefits of protease inhibitor monotherapy in long-term clinical use: in particular, the effect on drug resistance and future treatment options.

Methods In this pragmatic, parallel-group, randomised, controlled, open-label, non-inferiority trial, we enrolled adults (≥18 years of age) positive for HIV attending 43 public sector treatment centres in the UK who had suppressed viral load (<50 copies per mL) for at least 24 weeks on combination ART with no change in the previous 12 weeks and a CD4 count of more than 100 cells per μL. Participants were randomly allocated (1:1) to maintain ongoing triple therapy (OT) or to switch to a strategy of physician-selected ritonavir-boosted protease inhibitor monotherapy (PI-mono); we recommended ritonavir (100 mg)-boosted darunavir (800 mg) once daily or ritonavir (100 mg)-boosted lopinavir (400 mg) twice daily, with prompt return to combination treatment if viral load rebounded. All treatments were oral. Randomisation was with permuted blocks of varying size and stratified by centre and baseline ART; we used a computer-generated, sequentially numbered randomisation list. The primary outcome was loss of future drug options, defined as new intermediate-level or high-level resistance to one or more drugs to which the patient’s virus was deemed sensitive at trial entry (assessed at 3 years; non-inferiority margin of 10%). We estimated probability of rebound and resistance with Kaplan-Meier analysis. Analyses were by intention to treat. This trial is registered with the International Standard Randomised Controlled Trial Number registry, number ISRCTN04857074.

Findings Between Nov 4, 2008, and July 28, 2010, we randomly allocated 587 participants to OT (291) or PI-mono (296). At 3 years, one or more future drug options had been lost in two participants (Kaplan-Meier estimate 0.7%) in the OT group and six (2.1%) in the PI-mono group: difference 1.4% (–0.4 to 3.4); non-inferiority shown. 49 (16.8%) participants in the OT group and 65 (22.0%) in the PI-mono group had grade 3 or 4 clinical adverse events (difference 5.1% [95% CI –1.3 to 11.5]; p=0.12); 45 (six treatment related) and 56 (three treatment related) had serious adverse events.

Interpretation Protease inhibitor monotherapy, with regular viral load monitoring and prompt reintroduction of combination treatment for rebound, preserved future treatment options and did not change overall clinical outcomes or frequency of toxic effects. Protease inhibitor monotherapy is an acceptable alternative for long-term clinical management of HIV infection.
Patients in PI-mono arm showed a significantly higher probability of experiencing virological rebound compared to OT arm.

Paton et al., Lancet 2015
Comprehensive Assessment of Resistance Mutations Selected by Dolutegravir (DTG) in Subjects Failing DTG-Monotherapy after Switching from other Therapies (Redomo Study)

Blanco JL\textsuperscript{1}, Oldenbuettel C\textsuperscript{2}, Thomas R\textsuperscript{3}, Mallolas J\textsuperscript{1}, Wolf E\textsuperscript{2}, Brenner BG\textsuperscript{4}, Spinner CD\textsuperscript{2}, Wainberg MA\textsuperscript{4}, Martinez E\textsuperscript{1}

\textsuperscript{1}Hospital Clinic, Barcelona, Spain. \textsuperscript{2}MVZ Karlsplatz, HIV Research and Clinical Care Centre, Munich, Germany. \textsuperscript{3}Clinique Actuel, Montreal, Quebec, Canada. \textsuperscript{4}McGill AIDS Centre Montreal, Quebec, Canada
Number of HIV-infected individuals controlled in three large Clinical Cohorts: 10440

- HCP (Barcelona, Spain): 5000
- Clinical Care Centre (Munich, Germany): 2500
- Clinique Actuel (Montreal, Canada): 2940

DTG-bi- tri therapy: 1082
- Montreal: 402
- Munich: n.a.
- Barcelona: 680

10%

DTG-Monotherapy: 122
- Montreal: 26
- Munich: 52
- Barcelona: 44

1.17%

VF Monotherapy:

- No GRM: 64
- Yes GRM: 0

VF Bi-therapy:

- No GRM: 2
- Yes GRM: 9

Fisher exact text p=0.17
Odds-ratio VF mono: 1.58 (95% CI: 0.73-3.13)

VFs: 64 (6%; 95% CI: 5-7%)
VFs: 11 (9%; 95% CI: 6-18%)

82% of VFs

GRM: Genotypic resistance mutations
INSTIs antiviral activity elicit an higher constrain on viral replication compared to PI monotherapy in line with a lower rate of virological failure in DTG monotherapy.

...but despite the high genetic barrier, residual replication under DTG monotherapy drives resistance selection.
INSTIs antiviral activity elicit an higher constrain on viral replication compared to PI monotherapy in line with a lower rate of virological failure in DTG monotherapy.

Indeed...
In our experience, by 72 weeks from switch with dual therapy containing dolutegravir in 82 virologically suppressed patients the probability of virological rebound was very low.

Kaplan-Mayer estimates of virological rebound
(as the first of 2 consecutive viremia values >50 copies/mL or 1 single HIV-RNA>1000 copies/mL)

Drugs used with DTG (N=82)
Median (IQR) follow-up: 32 (16-49) weeks

Armenia, Di Carlo and Santoro. Unpublished data
Only 2 patients experienced virological rebound after DTG switch

<table>
<thead>
<tr>
<th>ID</th>
<th>Therapy status at switch</th>
<th>Therapy at switch</th>
<th>HIV-RNA at VR (copies/mL)</th>
<th>Time from switch (months)</th>
<th>INI major RAMs at VR</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11250</td>
<td>INSTI-Naive</td>
<td>DTG+3TC</td>
<td>75</td>
<td>7</td>
<td>-</td>
<td>LLV, switch to DTG+ FTC+3TC</td>
</tr>
<tr>
<td>13884</td>
<td>INSTI-Naive</td>
<td>DTG+3TC</td>
<td>13450</td>
<td>8</td>
<td>-</td>
<td>Intolerance Re-suppression after switch</td>
</tr>
</tbody>
</table>

Armenia, Di Carlo and Santoro. Unpublished data
Modern clinical and virological approach to HIV infection

Driven by the perception of exceedingly high rates of success, (nearly) independent of the drug combination chosen

Driven by knowledge of the pathogenesis of HIV infection and its long-term clinical consequences

The disease is today no longer a big threat

The disease is still very insidious

One pill fits all or........... Same therapy(ies) fit well to everyone

Careful, time (and resource)-consuming approach to define the characteristics of each single patient

Unmet diagnostic needs: pretty irrelevant today

Diagnostic tools: Very relevant!!!!!

EMPIRICAL THERAPY

PERSONALISED THERAPY, DRIVEN BY PATIENT NEEDS

WHICH ONE PROVIDES MORE CHANCES OF LONG-TERM/LIFETIME SUCCESS?

WHICH ONE HAS MORE CHANCES TO BE LONG-TERM SUSTAINABLE?