Treatment failure and PI monotherapy

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• Transparency declaration

• I have served during the past 2 years as a consultant on advisory boards or participated in speakers’ bureaus or conducted clinical trials with BMS, Abbott, Gilead, Janssen, Merck and ViiV
Principles of HIV treatment

Goal of therapy

Maximal, lifelong, and continuous suppression of HIV replication
- Prevent resistance
- Promote immune recovery
- Prevent transmission

Regimen adherence considerations

Convenience

Patient Cost

Toxicity

Tolerability

Minimum requirement

Efficacy

Antiretroviral therapy, 27 years of continuous improvement, 30 drugs, 6 classes...

- **NRTIs**: Zidovudine, Didanosine, Lamivudine, Stavudine
- **NNRTIs**: Zalcitabine, Zidovudine, Stavudine, Lamivudine, Saquinavir, Ritonavir, Indinavir, Delavirdine, Nevirapine, Nelfinavir, Efavirenz, Abacavir, Amprenavir
- **PIs**: Maraviroc, Raltegravir, Darunavir, Tipranavir
- **Fusion inhibitor**: Enfuvirtide, Fosamprenavir, Atazanavir
- **CCR5 inhibitor**: Etravirine, Maraviroc, Raltegravir, Darunavir
- **Integrase inhibitor**: Lopinavir/r, Emtricitabine, Tenofovir, Rilpivirine

- **STR (single tablet regimen)**: Trizivir*, Atripla*, Eviplera*, Stribild*, Triumeq*

* STR (single tablet regimen)

**AIDS, 1st cases**
- 1981

**HIV discovery**
- 1983

**Modified from F Raffi**
Antiretroviral therapy, the future ............... 

2015

TAF (Tenofavir alafenamida) NRTI

Doravirine (MK-1439) NNRTI

DRV/COBI PI

GSK 744 Cabotegravir, Integrasa Inhibidor long acting

TMC 278 LA

BMS-663068 Entry Inhibidor

CENICRIVIROC (CVC)-CCR5/CCR2 antagonist

GENERICS

These diverse consultative processes have generated powerful momentum towards a new narrative on HIV treatment and a set of ambitious, but achievable targets:

- By 2020, 90% of all people living with HIV will know their HIV status.
- By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy.
- By 2020, 90% of all people receiving antiretroviral therapy will have durable viral suppression.

When these targets are achieved, at least 73% of all people living with HIV worldwide will be virally suppressed – a three-fold increase over current estimates of viral suppression. Modelling demonstrates that achieving these targets by 2020 will enable us to end the AIDS epidemic by 2030.

Modified from J. Montaner

2030 End of AIDS Epidemic?
In 11 years (2015-2026) many drugs will be available as individual generics, but co-formulated versions will still maintain the patent

2014: ZDV, 3TC, NVP, EFV, RTV, Combivir – already generic
2016: ABC, LPV/r (soft-gel)
2017: TDF, ATV/r, DRV/r
2019: ETR, ABC/3TC (Kivexa)
2024: TDF/FTC (Truvada)
2025: raltegravir
2026: TDF/3TC/EFV (Atripla), TDF/FTC/RPV (Complera), dolutegravir

Ref: Medecins Sans Frontieres 2014: Untangling the web of ARV price reductions
How to manage long term HIV control?

**Induction**
- 3 or 2 drugs?
- BL VL matters?

**Maintenance therapy**
- To maintain viral suppression, how much potency and how many drugs are required?

- How to individualize therapy to each individual?
  - CD4 nadir
  - Activation status
  - Blood DNA (reservoirs)

The Highest the BL VL
The longest it takes to reach VL<50 c/ml

**Life Cycle and Pathogenesis of HIV**

- HIV-1 Binding
- Reverse transcription of HIV-1 RNA
- CD4+ T cell activation by antigens and cytokines
- Integration of HIV-1 DNA
- Latently infected, resting CD4+ T cell
- Productively infected CD4+ T cell
- Cell death by viral cytopathic effects or CTL

**Viral Rebound After HAART Interruption**

- Survival probability
- HIV-1 Viral Load (Log10 RNA Copies/ml)
- Time Off HAART (Days)
Pivotal ART studies, VL <50 c/mL, 48 weeks ITT, by NRTIs

Efficacy: EFV ZDV 3TC 006 Study 64% Dec 1999

Modified from E Ribera
The 4 rules to have a successful anti-HIV therapy

• No baseline resistance mutations
• Good adherence >95% (less number of pills or STR better….but consider cost and co-packing alternatives)
• No PK interactions with other drugs
• No significant toxicities

If fulfilled…..100% should achieve and maintain VL<40
How can we reduce drug burden?

- Reduced dosing of individual drugs
- PI monotherapy
- Class-sparing strategies
- Dual therapy including 3TC
How can we reduce drug burden?

- Reduced dosing of individual drugs
- PI monotherapy
- Class-sparing strategies
- Dual therapy including 3TC
## Boosted PI monotherapy

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<td>MONOI MONET</td>
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Monotherapy: later looks better...

**DRV/RTV Monotherapy: Noninferior or not noninferior?**

**MONET 96 Wks**

![Graph showing patients meeting primary endpoint (%) for DRV/RTV Mono (74.8%) and DRV/RTV + 2 NRTIs (80.6%) with a noninferiority margin of -5.8% (-16.0% to +4.4%).](image1)

**MONO 48 Wks**

![Graph showing patients meeting primary endpoint (%) for DRV/RTV Mono (92.1%) and DRV/RTV + 2 NRTIs (90.7%) with a noninferiority margin of +1.4% (-5.5% to +8.3%).](image2)

**MONOI 48 Wks**

![Graph showing patients meeting primary endpoint (%) for DRV/RTV Mono (94.1%) and DRV/RTV + 2 NRTIs (99%) with a noninferiority margin of +1.4% (90% CI: 9.9 to 9.1).](image3)

**MONET 96 Wks**

![Graph showing patients meeting primary endpoint (%) for DRV/RTV Mono (92.1%) and DRV/RTV + 2 NRTIs (90.7%) with a noninferiority margin of +1.4% (-5.5% to +8.3%).](image4)

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Antiretroviral Simplification with Darunavir/Ritonavir Monotherapy in Routine Clinical Practice: Safety, Effectiveness, and Impact on Lipid Profile

José R. Santos1,2,*, José Moltó1,2, Josep M. Llibre1,2, Eugenia Negredo1,2, Isabel Bravo1, Arelly Ornelas1,3, Bonaventura Clotet1,4, Roger Paredes1,4

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Abstract

Background: Simplification of antiretroviral treatment (ART) with darunavir/ritonavir (DRV/r) monotherapy has achieved sustained suppression of plasma viral load (pVL) in clinical trials; however, its effectiveness and safety profile has not been evaluated in routine clinical practice.

Methodology/Principal Findings: We performed a retrospective cohort analysis of HIV-1-infected patients who initiated DRV/r monotherapy once daily with a pVL <50 copies/mL under ART and at least 1 subsequent follow-up visit in our clinic. The primary study endpoints were the percentage of patients with virological failure (VF, defined as 2 consecutive pVL>50 copies/mL) at week 48, and time to VF. Other causes of treatment discontinuation and changes in lipid profile were evaluated up to week 48. Ninety-two patients were followed for a median (IQR) of 73 (57–92) weeks. The median baseline and nadir CD4+ T-cell counts were 604 (433–837) and 238 (150–376) cells/mm3, respectively. Patients had previously received a median of 5 (3–9) ART lines and maintained a pVL<50 copies/mL for a median of 76 (32–176) weeks before initiating DRV/r monotherapy. Nine (9.8%) patients developed VF at week 48; time to VF was 47.1 (IQR: 36.1–47.8) weeks among patients with VF. Other reasons for changing ART were gastrointestinal disturbances (n = 3), rash (n = 1), and impaired CD4 recovery (n = 2). Median low-density lipoprotein cholesterol levels increased from 116.1 mg/dL at baseline to 137.3 mg/dL at 48 weeks (p = 0.001).

Conclusions/Significance: Treatment simplification with DRV/r monotherapy seems safe and effective in routine clinical practice. Further research is needed to elucidate the effect of DRV/r monotherapy on cholesterol levels.


92 patients followed for a median of 73wks.

Treatment failure at 48 wks:
-Per protocol 9.8%
RESULTS

VF: 9 (9.8%) patients; 4 (44.4%) reported poor adherence. All were re-suppressed

OT: 77 (83.7%) patients

Full dataset analysis: 77 (81.1%) patients

Blips: 17 (18.5%), no VF.

No factors associated with VF
CONCLUSIONS

• DRV/r monotherapy appears to be safe and effective in patients with sustained viral suppression in routine clinical practice.

• Monotherapy with DRV/r is associated with a low rate of VF. In addition, as in clinical trials, viral resuppression is achieved in almost all patient experiencing VF, mainly by reintroducing NRTIs or other antiretroviral regimens.

• In clinical practice, VF to DRV/r monotherapy is not associated to DRV-resistance development.

• With the possible exception of patients previously receiving LPV/r, DRV/r monotherapy does not seem to confer a clear benefit in the management of dyslipidemia.
Virological Efficacy in Cerebrospinal Fluid and Neurocognitive Status in Patients with Long-Term Monotherapy Based on Lopinavir/Ritonavir: An Exploratory Study

José R. Santos, José A. Muñoz-Moreno, José Moltó, Anna Prats, Adrià Curran, Pere Domingo, Josep M. Llibre, Daniel R. McClernon, Isabel Bravo, Jaume Canet, Victoria Watson, David Back, Bonaventura Clotet

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Abstract

Background: Data on suppression of HIV replication in the CNS and on the subsequent risk of neurocognitive impairment using monotherapy with boosted protease inhibitors are limited.

Methods: Ours was an exploratory cross-sectional study in patients on lopinavir/ritonavir-based monotherapy (LPV/r-MT) or standard triple therapy (LPV/r-ART) for at least 96 weeks who maintained a plasma viral load <50 copies/mL. HIV-1 RNA in CSF was determined by HIV-1 SuperLow assay (lower limit of detection, 1 copy/mL). Neurocognitive functioning was assessed using a recommended battery of neuropsychological tests covering 7 areas. Neurocognitive impairment (NCI) was determined and also a global deficit score (GDS) for study comparisons.

Results: Seventeen patients on LPV/r-MT and 17 on LPV/r-ART were included. Fourteen (82.4%) patients on LPV/r-MT and 16 (94.1%) on LPV/r-ART had HIV-1 RNA <1 copy/mL in CSF (p = 0.601). NCI was observed in 7 patients on LPV/r-MT and in 10 on LPV/r-ART (41% vs 59%; p = 0.494). Mean (SD) GDS was 0.22 (0.20) in patients on LPV/r-MT and 0.47 (0.34) in those on LPV/r-ART (p = 0.012).

Conclusions: Suppression of HIV in CSF is similar in individuals with durable plasma HIV-1 RNA suppression who are receiving LPV/r-MT or LPV/r-ART for at least 96 weeks. Findings for HIV-1 replication in CSF and neurocognitive status indicate that this strategy seems to be safe for CNS functioning.
STUDY MONOKAL

Objective: to compare the presence of HIV replication in CSF and the neurocognitive performance in patients who had been receiving LPV/r-based standard HAART (LPV/r-HAART) or LPV/r-MT for at least 96 weeks.

Methods:
• Single centre cross-sectional, exploratory, case-control study.
• pVL <50 copies/mL.
• Primary endpoint: The proportion of patients with complete virological suppression (HIV RNA <1 copy/mL) in CSF.
• Secondary endpoints:
  - The proportion of patients with neurocognitive impairment (NCI), defined by performing at least 1 SD below the standardized mean in at least 2 neurocognitive areas.
  - Differences on neurocognitive status in terms of GDS, which is a validated method to study compositely impairment on neurocognitive functioning.

PLoS One (2013); 8(7): e70201
RESULTS

Of 162 potential candidates, 37 patients agreed to participate.
Patients with complete CSF-virological suppression (RNA HIV <1 copy/mL)

- The proportion of patients with HIV-1 RNA <1 copy/mL in CSF in the LPV/r-MT group was similar to LPV/r-HAART group.
- 3 patients on LPV/r-MT had determinations of CSF HIV-1 RNA of 1, 75 and 120 copies/mL.
- 1 patient on LPV/r + ABC/3TC (LPV/r-HAART group) had a CSF HIV RNA of 2 copies/mL.
Measured CSF concentrations exceeded the 50% IC50 for WT HIV-1 (0.69 mg/ml) by a median 32.2-fold (IQR: 16.4-45.4)
In the LPV/r-MT group: 7 (41%) patients with NCI while in LPV/r-HAART group: 10 (59%) patients with NCI (p=0.48).

When patients with possible confounding comorbidities were excluded, the results were similar (p=0.43).

Considering neurocognitive functioning, values were mildly better in MT group. In total sample, GDS was 0.23 in MT group and 0.46 in HAART group (p=0.025), and in non-comorbidities sample 0.25 and 0.5 (p=0.04), respectively.
CONCLUSIONS

• The proportion of patients with complete viral suppression (HIV-1 RNA <1 copy/mL) was similar between LPV/r-MT and LPV/r-HAART.

• Although the difference was not statistically significant, there were fewer patients with NCI in the LPV/r-MT group.

• Neurocognitive functioning proved to be slightly better in patients on LPV/r-MT compared to LPV/r-HAART.

• This study suggests that in patients receiving LPV/r-MT for a long time, CSF HIV replication is completely suppressed in most of them. Additionally, the use of LPV/r-MT does not appear to be associated with worse neurocognitive functioning.
Monotherapy with boosted PIs as an ART simplification strategy in clinical practice

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Background: Data on the efficacy of simplifying therapy using darunavir/ritonavir and lopinavir/ritonavir monotherapy in clinical practice remain limited.

Methods: A retrospective single-centre study including patients initiating darunavir/ritonavir or lopinavir/ritonavir monotherapy with a plasma HIV-1 viral load (pVL) <50 copies/mL and at least one subsequent follow-up visit. The primary endpoint was the percentage of patients remaining free of virological failure (VF; defined as a confirmed pVL >50 copies/mL or as any change in the regimen after a single determination with a pVL >50 copies/mL) during the follow-up. We also evaluated the percentage of patients remaining free of treatment failure (TF; defined as VF or the early discontinuation of monotherapy for any reason) and compared the effectiveness of the two regimens. Effectiveness was evaluated using cumulative survival analysis (at Weeks 48 and 96). Factors associated with VF and TF were analysed using Cox regression.

Results: A total of 522 patients were included (309 receiving lopinavir/ritonavir and 213 receiving darunavir/ritonavir). The median follow-up was 64.3 (30.5–143.0) weeks. The percentage of patients free of VF and TF was 94% (95% CI 91%–96%) and 79% (95% CI 75%–82%) at 48 weeks, respectively, and 86% (95% CI 81%–89%) and 62% (95% CI 57%–67%) at 96 weeks, respectively. The risk of VF was similar for the two regimens (HR = 1.0, 95% CI 0.6–1.8; P = 0.962). Lopinavir/ritonavir monotherapy was associated with a 1.5-fold greater risk of TF (95% CI 1.1–2.1; P = 0.012) and a 2.3-fold greater risk of discontinuation of therapy due to adverse events (95% CI 1.3–3.9; P = 0.003).

Conclusions: The virological efficacy of darunavir/ritonavir and lopinavir/ritonavir monotherapy is high in clinical practice. Treatment discontinuation due to safety issues is more frequent with lopinavir/ritonavir.
RESULTS

Outcomes of patients according to cumulative survival analysis

1a. Virological failure (VF)

Similar percentage of patients on LPV/r and DRV/r who were free of VF at 48 and 96 weeks (HR=1.0, 95% CI 0.6–1.8; P=0.962).

Occurrence of blips, CD4+ nadir <100 cells/mm3, prior failure with PIs or a duration of virological suppression <24 weeks were not associated to VF.
RESULTS

Outcomes of patients according to cumulative survival analysis

• LPV/r free of TF at 48 and 96 weeks: 76% (95% CI 71%–81%) and 59% (95% CI 53%–65%), respectively.
• DRV/r free of TF at 48 and 96 weeks: 86% (95% CI 76%–88%) and 68% (95% CI 59%–75%), respectively.
• Patients on LPV/r had a 1.5-fold greater risk (95% CI 1.1–2.1; P=0.012) of TF.
• TF was not associated with any of the other factors.

RESULTS

Safety

- AEs were registered as the main reason for the discontinuation (23.6% of patients on LPV/r and 7.5% of patients on DRV/r).

- The most frequent AE leading to treatment discontinuation were GI disturbances (43.8%) and dyslipidaemia (38.2%)

- The AEs were usually mild and none was Grade 3–4.

- Patients on LPV/r were at significantly greater risk than those on DRV/r of experiencing AE leading to a discontinuation of treatment (HR=2.3, 95% CI 1.3–3.9; P=0.003).

- No cases of HIV-related encephalopathy or other serious CNS AEs
CONCLUSIONS

• Monotherapy with LPV/r or DRV/r seems to be safe and effective in HIV-1-infected patients with sustained viral suppression in clinical practice.

• Better tolerability and convenience of administration suggest that DRV/r might be the preferred option for PI monotherapy.

• The proper selection of candidates for PI monotherapy is mandatory in order to minimize the risk of failure.
LONG-TERM CHANGES IN BONE MINERAL DENSITY AFTER SWITCHING TO A PROTEASE INHIBITOR MONOTHERAPY IN HIV-INFECTED SUBJECTS.

Eugènia Negredo\textsuperscript{1}, Anna Bonjoch\textsuperscript{1}, Jordi Puig\textsuperscript{1}, Patricia Echeverría\textsuperscript{1}, Carla Estany\textsuperscript{1}, José R Santos\textsuperscript{1}, José Moltó\textsuperscript{1}, Nuria Pérez-Álvarez \textsuperscript{1}, Arelly Ornelas\textsuperscript{2}, Bonaventura Clotet\textsuperscript{1,3}.

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\textsuperscript{2} Statistics and Operations Research Department, Universitat Politècnica de Catalunya, Barcelona, Spain

\textsuperscript{3} Irsicaixa Foundation, Germans Trias i Pujol University Hospital, Badalona, Spain

\textbf{Short title}: Protease inhibitor monotherapy on BMD

\textit{New Microbiol 2015 (ACCEPTED 2015)}
OBJECTIVE

- To evaluate changes in BMD by dual-energy X-ray absorptiometry (DXA) in HIV-infected patients after 1, 2, or 3 years since the switch from triple ART to PI monotherapy (LPV/r or DRV/r).
METHODS

• A single-centre longitudinal study including 46 HIV-infected patients.

• Inclusion criteria:
  – Treatment with PI monotherapy (LPV/r BID or DRV/r QD) for at least 1 year
  – Triple ART at the moment of the switch to the PI monotherapy
  – DXA scan close to the date of the switch to the PI monotherapy (from 4 months before to 2 months after starting the monotherapy).

• Exclusion criteria:
  – Concomitant treatment for osteoporosis/osteopenia (bisphosphonates), or secondary causes of low bone mineralization (testosterone deficit, thyroid disease) during the monotherapy
  – Any change or interruption of the treatment

New Microbiol 2015 (in revision)
RESULTS

Median percentage of change from baseline in Bone mineral density in total femur and lumbar spine.

- In the one-year group, the median percentage of change was 0.20 (IQR, -2.29 to 2.08, p=0.910) in total femur BMD and -0.08 (IQR, -5.55 to 4.32, p=0.955) in lumbar spine BMD.

- There were no significant changes in two- or three-year groups.
CONCLUSIONS

• Treatment with PI monotherapy (both LPV/r and DRV/r) during 1, 2, or 3 years leads to the stabilization of BMD in patients with long-term virological suppression.

• Prospective comparative studies are necessary
Rules for a successful switch to PI Monotherapy

- Nadir CD4 > 200/mm3 (ideally > 300/mm3)
- Low proviral DNA at the time of switching
- No baseline resistances to PIs (no primary resistances)
- No treatment failures to any PI based approach
Antiretroviral treatment switch strategies for lowering the costs of antiretroviral therapy in subjects with suppressed HIV-1 viremia in Spain

This article was published in the following Dove Press journal: ClinicoEconomics and Outcomes Research 22 May 2013

Background: The current economic recession in European countries has forced governments to design emergency measures to reduce spending on drugs, including antiretroviral therapy (ART). Switching antiretroviral drugs for others that have the same efficacy and safety profile at a lower cost (cost-reduction measures, CRM) could prove to be a valid means of generating savings.

Methods: Descriptive study of prospective consensus-based CRM undertaken in 2011 in a Catalonian hospital HIV unit among patients with prolonged plasma HIV-1 RNA <50 copies/mL.

Results: During the study period, we made 673 switches (87.5% more than the previous year), of which 378 (56.2%) were CRM (16% of all patients treated), leading to a savings of €87,410/month. Switching tenofovir/emtricitabine for abacavir/lamivudine was the most common CRM (129, 31.3%), followed by simplification to boosted protease inhibitor monotherapy (bPImono, 102, 26%). The CRM that generated the greatest saving were switching to bPImono (38%), withdrawal or replacement of raltegravir (24%), switching tenofovir/emtricitabine for abacavir/lamivudine (13%), and switching to nevirapine (5%). Cost savings with CRM were slightly higher than those achieved with medication paid for by clinical trial sponsors (€80,333/month) or through discount arrangements (€76,389/month).

Conclusion: Proactively switching antiretroviral therapy in selected treated patients with sustained virological suppression can generate significant cost savings in pharmacy spending in developed countries. These findings have implications for decision makers in designing safe strategies that maintain HIV-1 suppression at lower costs.

Keywords: health economics, cost analysis, antiretroviral agents economics, antiretroviral therapy highly active, protease inhibitor monotherapy
Figure 1 Correlation between the number of switches identified as cost-saving measures and the costs saved with them (shown as percentages).

Abbreviations: ABC/3TC, abacavir/lamivudine; ATV, atazanavir; DRV/r, darunavir/ritonavir; EFV, efavirenz; ETR, etravirine; FDC, fixed-dose combinations; FPV, fosamprenavir; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; RAL, raltegravir; TDF/FTC, tenofovir/entecavir; TPV, tipranavir; 3TC gen, generic lamivudine.
How can we reduce drug burden?

• Reduced dosing of individual drugs
• PI monotherapy
• Class-sparing strategies
• Dual therapy including 3TC
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<td>DRV/RTV or LPV/r</td>
<td>DRV/RTV or LPV/r</td>
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GARDEL: Study design

Phase III, randomized, international, controlled, open-label study
- Study included adult patients from Argentina, Chile, Mexico, Peru, Spain, US.

ARV-naive patients, 
≥18 years 
HIV-1 RNA >1000 copies/ml 
No IAS-USA defined NRTI or PI resistance at screening*
HB(s)Ag negative (N = 426)

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

DT: LPV/r 400/100mg BID + 3TC 150 mg BID (n=217)

TT: LPV/r 400/100mg BID + 3TC or FTC and a third investigator-selected NRTI in fixed-dose combination (n=209)

Wk 24 interim analysis
Wk 48 primary endpoint

*Defined as > 1 major or > 2 minor LPV/r mutations
LPV major mutations include the following mutations: V32I; I47V/A; L76V; V82A/F/T/S

Cahn, Lancet Inf. Dis, 2014
Viral load <50 copies/mL at week 48 (ITTe)

(p = 0.171, difference +4.6%
[Cl_{95\%}: -2.2\% to +11.8\%])
Viral load <50 copies/mL at week 48 (ITT), baseline VL > 100,000 copies/mL

(p = 0.145, difference +9.3% [CI95%: -2.8% to +21.5%])
CD4 increase from BL to W48

- BSL: Baseline
- W4, W12, W24, W36, W48: Weeks 4, 12, 24, 36, 48

- DT: Red line
- TT: Blue line

- + 227 cells/mm³
- + 217 cells/mm³

p = 0.625
### Virologic Outcome at W48

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<th>DT (n=214)</th>
<th>TT (n=202)</th>
<th>P [IC95%]</th>
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<tr>
<td>HIV – RNA &lt; 50 copies/mL (n; %)</td>
<td>189 (88.3%)</td>
<td>169 (83.7%)</td>
<td>0.171 [-2.2%; +11.8%]</td>
</tr>
<tr>
<td>HIV – RNA &gt;50 copies/mL (n; %)</td>
<td>10 (4.7%)</td>
<td>12 (5.9%)</td>
<td>0.720 [-6.1%; +3.5%]</td>
</tr>
<tr>
<td>No Virologic data at week 48 window</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reasons:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued study due to adverse</td>
<td>2 (0.9 %)*</td>
<td>10 (4.9 %)**</td>
<td>0.03 [-7.8%; -3.0%]</td>
</tr>
<tr>
<td>event or death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued study for other</td>
<td>13 (6.1%)</td>
<td>11 (5.4%)</td>
<td>0.948 [-4.3; +5.6]</td>
</tr>
<tr>
<td>reasons***</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 1 death: Sepsis, 1 nephrotic syndrome
** 2 Rash, 3 anemia, 5 GI intolerance

*** (Non compliance with study procedures, consent withdrawal, adherence, opportunistic infection, lost to follow-up, pregnancy)
Protocol Defined Virologic Failure and Emergent Resistance Mutations

PDVF: 2 measurements of HIV-1 RNA at least 1 week apart
- >400 copies/mL at week 24
- >50 copies/mL at week 48
Emergent resistance mutations, in samples successfully amplified:
- DT: 2 out of 5 both M184V
- TT: 0 out of 8

<table>
<thead>
<tr>
<th>Number of patients, n (%)</th>
<th>DT (N=214)</th>
<th>TT (N=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed virological failures</td>
<td>10 (4.6 %)</td>
<td>12 (5.9 %)*</td>
</tr>
<tr>
<td>HIV-1 RNA at failure (copies/ml) (median-IQR)</td>
<td>236 (183-17,687)</td>
<td>1027 (123-4,880)</td>
</tr>
<tr>
<td>Never suppressed</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Rebounders</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Primary PI RAMs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NRTI RAMs (M184V)</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*p=0.72
DUAL THERAPY EFFICACY IN KEY SUBGROUPS OF TREATMENT-NAIVE PATIENTS IN THE GARDEL STUDY

Fig 2: Proportion with plasma HIV-1 RNA <50 cC/ml at week 48 according nucleosides based therapy

- Δ+ 9.3% (95% CI: +0.1%, +18.9%; p=0.037)
- +Δ-0.9% (95% CI: -9.3%, +7.5%; p=0.968)

- 88.3% DT
- 79% AZT/3TC
- 89.2% TDF/FTC or ABV/3TC

Rolon et al: IAC 2014; Abstr WePe 080
Our results demonstrate that DT with LPV/r+3TC was non-inferior to triple therapy after 48 weeks of treatment, regardless of baseline viral load.

The DT regimen showed fewer discontinuations due to safety and tolerability.

Virologic failure, occurring at similarly low levels in both treatment arms, did not result in PI resistance development, preserving a wide range of drugs for 2\textsuperscript{nd} line ARV therapy.

These results suggest that a dual LPV/r+3TC regimen warrants further clinical research and consideration as a potential therapeutic option for ARV naïve subjects.
OLE:Study design

• 48-week multicenter, prospective, randomized, open-label, non-inferiority trial (n:250)

• Eligibility criteria

HIV-infected patients with plasma HIV-1 RNA < 50 copies/ml for ≥ 6 months on TT with LPV/r + 3TC/FTC + NRTI and no resistance to LPV/r or 3TC/FTC

Randomization 1:1

- LPV/r BID + 3TC/FTC QD (DT)
- LPV/r BID + 3TC/FTC QD + NRTI (TT)

• Primary endpoint:

  - Proportion of patients free of therapeutic failure at 48 weeks, in the m-ITT population defined as two consecutive viral load measurements >= 50 copies/ml, death, progression to new AIDS defining disease, loss to follow-up or change or
Primary endpoint

Therapeutic response (< 50 copies/ml) at 48 weeks and causes of therapeutic failure

<table>
<thead>
<tr>
<th>mITT</th>
<th>AE's</th>
<th>Lost</th>
<th>Other</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>91.5%</td>
<td>90.9%</td>
<td>0.8%</td>
<td>3.3%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

No. at risk: 118 121

Difference (95% CI)
-0.6% (-6.9% to +8.1%)
# Resistance mutations

<table>
<thead>
<tr>
<th></th>
<th>DT (n=118)</th>
<th>TT (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with protocol-defined virologic failure*</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Patients with virological failure and VL &gt; 500 copies/mL</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Patients with blip</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Patients with any detectable viral load (&gt;50 copies/mL)</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

*Protocol defined VF: 2 consecutive VL >50 copies/mL

<table>
<thead>
<tr>
<th></th>
<th>DT (n=118)</th>
<th>TT (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients analyzed for resistance</td>
<td>1/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Patients with data available</td>
<td>1/3</td>
<td>-</td>
</tr>
<tr>
<td>Patients with resistance to ARV regimen</td>
<td>1 (103N and 184V)</td>
<td>-</td>
</tr>
</tbody>
</table>
How can we reduce drug burden?

• Reduced dosing of individual drugs
• PI monotherapy
• **Class-sparing strategies**
• Dual therapy including 3TC
Dual therapy under investigation

- PI/r + integrase inhibitor
- PI/r + CCR5 inhibitor
- PI/r + 3TC/FTC
- PI/r + NNRTI
- Integrase inhibitor + NNRTI
- Integrase Inhibitor + 3TC/FTC