PK and virological efficacy of DTG (50 mg BID) containing regimen in association with RIF in HIV–infected patients using DBS: ANRS–12313 NAMSAL sub–study in Cameroon

Lê MP,1,2 Cournil A,3 Kouanfack C,4 Lem S,5 Le Gac S,5 Delaporte E,3 Peytavin G,1,2 for the NAMSAL study group

1AP–HP, Hopital Bichat, Pharmacology–Toxicology, Paris, France, 2IAME, UMR 1137, INSERM, Université Paris Diderot, Sorbonne Paris Cité, Paris, France, 3TransVIHMI, IRD, INSERM, Université de Montpellier, Montpellier, France, 4Hopital Central, Yaoundé, Cameroon, 5ANRS, Yaoundé, Cameroon
Rationale (1)

- Efficacy of dolutegravir (DTG) has been demonstrated in several randomized control trials conducted among naïve of antiretroviral treatment (ART) (Single, Spring, Flamingo)\(^1\)\(^-\)\(^3\) and experienced patients (Striiving, Dawning)\(^4\),\(^5\)

- DTG is associated with a more rapid viral suppression and higher genetic resistance barrier, when compared with 1\(^{st}\) generation NNRTIs

- It is also effective against HIV-2 (which is naturally resistant to NNRTIs)\(^6\)

- WHO’s recent systematic reviews and meta-analysis have showed that DTG-based regimens are better tolerated when compared with EFV 600 mg QD\(^7\)

- DTG is becoming the 1\(^{st}\) line alternative to efavirenz (EFV) in the WHO guidelines for ART

\(^1\) Walmsley S et al, JAIDS 2013
\(^2\) Van Lunzen J et al, Lancet Infect Dis 2012
\(^3\) Clotet B et al, Lancet 2014
\(^4\) Trottier B et al, Antivir Ther 2017
\(^5\) Aboud M, Dawning study, IAS 2017
\(^6\) Descamps D, CID 2015
\(^7\) Kanters S et al, Lancet HIV 2016
Tuberculosis (TB) is the first cause of death in HIV–infected patients and clinical trials have clearly shown that ART should be initiated early after TB diagnosis to reduce mortality. However, it is necessary to assess the potential drug interaction with TB drugs, particularly rifampin:

- DTG is substrate of UGT1A1 and CYP3A4 while rifampin is a strong inducer of these enzymes.

References:

7. WHO guidelines on TB, 2017
8. Dooley KE et al, JAIDS 2013
ANRS–12313 NAMSAL study

- **NAMSAL**: New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-income countries
- The ANRS–12313 NAMSAL is a non-inferior multicenter study evaluating DTG 50mg QD versus EFV 400mg QD containing regimen as first-line treatment in HIV–1 infected patients from Cameroon

**Study and design**

- **Trial Study design**
  - Randomized, non-inferior, open-label
  - 3 study sites: Yaounde, Cameroon
  - Primary outcome: Viral load < 50 cp/ml at Week 48

- **Support studies**
  - PK study:
    - to assess ARV concentrations in pregnant women and in TB-coinfected patients receiving rifampicin
  - Economic substudy:
    - to assess the cost-effectiveness of a DTG-based first-line strategy and the economic impact of its introduction in LIC

- **Participants**
  - 606 participants
  - HIV-1
  - Age ≥ 18 years
  - ARV naïve
  - Contraception for women
  - Cr clearance ≥ 50 ml/min

- **Regimens**
  - DTG 50mg + TDF/3TC
  - EFV 400mg + TDF/3TC
Objectives

- to assess the steady state pharmacokinetics and efficacy of DTG 50mg BID containing regimen in association with rifampin (600 mg QD) based TB treatment
- to verify the good adherence of anti-TB drugs in same samples
The capillary blood samples obtained by finger stick was spotted onto filter paper (no. 903 Protein Saver cards, Whatman, five spots of ~50 μL per card), air-dried, and stored in sealed bags at 4 to 8 °C with desiccant material.

The antiretrovirals (ARV) were extracted from a dried blood spots (DBS) of 0.6 cm diameter punched out, corresponding to approximately 50 μL of full blood.

DBS were collected at least 4 weeks after the start of ART (steady-state).

Time between last drug intake and sampling was recorded.

Antiretroviral DBS concentrations and TB DBS drugs were determined using UPLC–MS/MS (LOQ <10ng/mL and <50ng/mL, respectively).
Drugs concentrations were interpreted after blood to plasma correction:

- **For DTG:**
  \[ Plasma_{ARV} = F_{bpp} \times \left( \frac{DBS_{ARV}}{1 - Hematocrit} \right), \]

  where \( F_{bpp}(DTG) = 0.99 \) were set as 99% for dolutegravir.

- **For 3TC and TFV:**
  - correction factor (0.88 and 1.57 for lamivudine and tenofovir, respectively)

- DTG C12h was interpreted using a 10-fold protein adjusted IC90 (~640 ng/mL) and the inhibitory quotient (C12h/IC90).

- Median trough plasma concentrations (C12h and C24h) and HIV-1 RNA (VL) levels (IQR) are presented.

---

10De Truchis et al, JAC 2016
11Waitt C et al, JAC 2018
**Results (1): Patients’ characteristics**

- 12 HIV-1/TB patients from the DTG arm
  - 2 losts to follow-up
  - 2 pregnancies
- 8 HIV-1/TB patients analyzed

<table>
<thead>
<tr>
<th></th>
<th>N (%) or median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Women</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>40 (34–45)</td>
</tr>
<tr>
<td>Bodyweight, kg</td>
<td>58.5 (51.8–63.5)</td>
</tr>
<tr>
<td>Haematocrit, %</td>
<td>34.0 (31.3%–37.5%)</td>
</tr>
<tr>
<td>Baseline plasma HIV-1 RNA, c/mL</td>
<td>520,440 (352,735–826,763)</td>
</tr>
</tbody>
</table>
Results (2): virological and PK data

- n=8 patients
- N=23 DBS (W12–W24–W36)

<table>
<thead>
<tr>
<th>ARV</th>
<th>Median (IQR) from mean/patient</th>
<th>BSV (%)</th>
<th>WSV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG C12h</td>
<td>1,123 (820–1,746)</td>
<td>63%</td>
<td>72%</td>
</tr>
<tr>
<td>3TC C24h</td>
<td>25 (20–41)</td>
<td>48%</td>
<td>25%</td>
</tr>
<tr>
<td>TFV C24h</td>
<td>75 (65–118)</td>
<td>55%</td>
<td>29%</td>
</tr>
</tbody>
</table>

BSV: between subject variability
WSV: within subject variability

- At W48, all patients presented pVL<200 copies/mL
- Anti–TB drug concentrations (rifampin/isoniazid/ethambutol/pyrazinamid) suggested good adherence to TB therapy
Results (2): virological and PK data

- At W48, all patients presented pVL < 200 copies/mL
- Anti-TB drug concentrations (rifampin/isoniazid/ethambutol/pyrazinamid) suggested good adherence to TB therapy

Interpretation of DTG C12h:
- 10-fold DTG IC\textsubscript{90} (WT HIV-1) = 640ng/mL
- DTG C12h > 640 ng/mL
- DTG C12h < 640 ng/mL

### ARV

<table>
<thead>
<tr>
<th>ARV</th>
<th>Median (IQR) from mean/patient</th>
<th>BSV (%)</th>
<th>WSV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG C12h</td>
<td>1,123 (820–1,746)</td>
<td>63%</td>
<td>72%</td>
</tr>
<tr>
<td>3TC C24h</td>
<td>25 (20–41)</td>
<td>48%</td>
<td>25%</td>
</tr>
<tr>
<td>TFV C24h</td>
<td>75 (65–118)</td>
<td>55%</td>
<td>29%</td>
</tr>
</tbody>
</table>

BSV: between subject variability
WSV: within subject variability

n=8 patients
N=23 DBS (W12–W24–W36)
Discussion Conclusion (1)

Our results are in accordance with those from INSPIRING\(^{12}\) study: interim W24 results show that DTG 50mg BID is effective and well–tolerated in HIV/TB co–infected adults receiving rifampin based TB therapy.

![Virologic Results in the ITT-E Population Through Week 24](image)

**Pharmacokinetic Data**

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>DTG Conc (ng/mL) Geomean (90%CI) %CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 8</td>
<td>41</td>
<td>852 (208–2340) 118</td>
</tr>
<tr>
<td>Wk 24</td>
<td>22</td>
<td>942 (19–3380) 276</td>
</tr>
</tbody>
</table>

INSPIRING DTG C\(_{tau}\) when administered twice daily with RIF were similar to DTG 50 mg once daily without RIF and to previously reported data for DTG 50 mg once daily in Phase 2/3 HIV trials.

\(^{12}\)Dooley et al. CROI 2018; Boston, MA.
WHO briefnote on DTG fixed-dose combination (April 2018) suggests the use of double dose of dolutegravir in HIV/TB co-infected patients

Variability of DTG C12h and IQ might suggest that DTG–RIF should only be associated in HIV-naïve patients with fully susceptible virus to DTG and maximally adherent to both HIV and anti-TB drugs
Thank you for your attention

- We thank everyone who has contributed to the success of this study, including
  - All study participants and their families
  - The NAMSAL study team