COPEDOL: a two-year French multicentric, observational, longitudinal retro-prospective study in pretreated HIV-1-infected patients starting dolutegravir based regimen due to treatment failure

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INTRODUCTION

- Dolutegravir (DTG) is a 2nd-generation integrase strand transfer inhibitor (INSTI) effective against HIV strains resistant to other INSTIs [1].
- In Phase III trials, PLWHIV failing previous ART can achieve viral suppression following DTG treatment [2,3].
- After launch of DTG in 2014 in France, it is important to collect real-world data on the effectiveness and tolerability of DTG.

OBJECTIVES

- To assess the virological response in patients switched to a DTG-based regimen following treatment failure.
- To evaluate sustained virological response and safety.

METHODS

- COPEDOL is an observational, longitudinal, study conducted in hospitals treating PLWHIV in France.
- Adult patients infected with HIV and starting DTG treatment following previous ART failure were eligible.
- Patients were stratified into two groups according to the reason for previous ART failure:
  - EV group: failure due to inadequate virological control (viral load >50 copies/ml).
  - TOX group: failure due to unacceptable adverse events.
  - The TOX group was divided into patients with (TOX-VL+) and without (TOX-VL-) measurable viral load (>50 copies/ml).
- Patients were followed up for 2 years.
- Viral load and CD4 cell count were assessed at each visit.
- Outcome measures were the % of patients achieving viral suppression and the time to viral suppression.

RESULTS

Patients

- 50 centres included 459 patients (EV group: N=222; TOX group: N=237; TOX-VL+: N=19; TOX-VL-: N=218).
- Patient characteristics are presented in Table 1.

Table 1. Patient characteristics at DTG initiation

	EV Group (N = 222)	TOX Group (N = 237)
Age (years; mean ± SE)	49 ± 12	51 ± 10
Gender (men)	132 (60%)	162 (68%)
BMI (kg/m²; mean ± SE)	23.9 ± 4.5	24.0 ± 4.4
Comorbidities (3 or more)*	41 (19%)	59 (25%)
Time since diagnosis (yrs; mean ± SE)	18 ± 8	15 ± 9
Duration of ART (yrs; mean ± SE)	14 ± 7	12 ± 7
CD4 cell count (mean ± SE)	449 ± 325	697 ± 359
Viral load (log copies/ml; mean ± SE)	3.2 ± 1.2	2.0 ± 1.0
Genotypic Sensitivity Score ≤1	57/186 (31%)	34/125 (27%)

*Most frequently dyslipdaemia (39% overall); hypertension (22%) and CRF (10%)

Treatment duration

- 31 patients in the EV group (14%) and 37 in the TOX group (16%) discontinued DTG after a median interval of 6.2 months.

Effectiveness

- In the EV group, two-thirds of patients achieved viral suppression by Month 1 and the proportion of responders stabilised at ~80% from Month 6 onwards (Figure 1).
- In the TOX-VL+ group, viral suppression was achieved in all patients (Figure 1).
- In the TOX-VL- group, viral suppression was maintained in >90% of patients (Figure 1).
- The median time to viral suppression was 70 days in the EV group and 89 days in the TOX-VL+ group.
- In the EV group, virological response was sustained in 67% of patients. Treatment failure following viral suppression was observed in 24 patients, with a median delay of 424 days after initiation of DTG.
- In the EV and TOX-VL+ groups, CD4 cell count increased over the course of the study (Figure 2).

Figure 1. Virological response rate

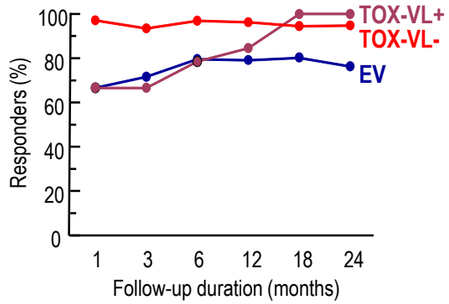


Figure 2. Evolution of CD4 count

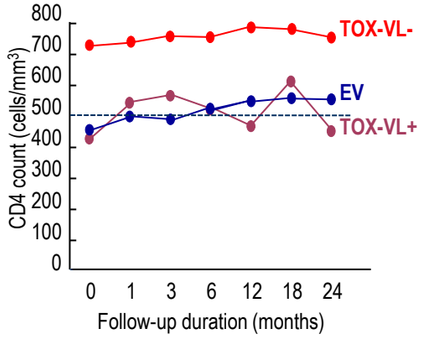
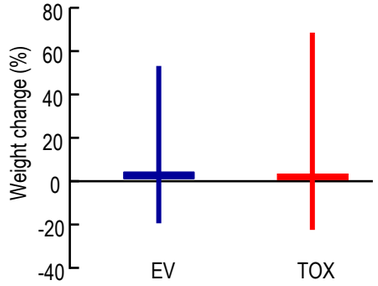


Figure 3. Evolution of body weight



Safety

- Around one-third of patients presented at least one adverse event (AE) during the study; most of these were considered unrelated to DTG (Table 2).
- 12 patients presented serious AEs considered related to DTG, notably 4 cases of renal failure.
- 11 patients in the EV group and 17 in the TOX group discontinued DTG due to the occurrence of an AE.
- In the majority of patients, glomerular filtration rate remained stable.
- On treatment, body weight increased by 1 kg (median) in both groups (Figure 4).
- 29% of patients in the EV group and 25% of those in the TOX group gained ≥5% body weight over the study.
- 4 patients in the EV group (2%) and 3 in the TOX group (1%) died. None of the deaths were considered related to DTG.

Table 2. Adverse events

	EV Group (N = 220)	TOX Group (N = 237)
Any AE	68 (31%)	80 (34%)
AEs related to DTG	21 (10%)	44 (19%)
Serious AEs	51 (23%)	42 (18%)
Serious AEs related to DTG	3 (1%)	9 (4%)
DTG discontinuation due to AEs	11 (5%)	17 (7%)

Emergence of resistance mutations

- At inclusion, 37 patients presented INSTI resistance mutations, including 1 patient in the TOX group with a DTG resistance mutation.
- During follow-up, 5 patients acquired new INSTI resistance mutations.

CONCLUSION

Effectiveness and safety were consistent with the findings of interventional clinical trials [3,4].

Few patients experienced virological failure with emergent INSTI resistance mutations.

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References

1, Kandel et al. Drug Des Devel Ther. 2015; 9: 3547-55. 2. Cahn et al. Lancet 2013; 382: 700-8. 3. Castagna et al. J Infect Dis. 2014; 210: 354-62.