Once-daily etravirine/raltegravir (400/800 mg) as maintenance regimen

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ETRAL QD

Romain PALICH[1], Yasmine DUDOIT[1], Gilles PEYTAVIN[2], Minh LE[2], Cathia SOULIE[3], Roland TUBIANA[1], Clotilde ALLAVENA[4], Laurence WEISS[5], Ana MONTOYA FERRER[6], Claudine DUVIVIER[7], Olivier BOUCHAUD[8], Julie BOTTERO[9], Aurore Durand[10], Anne-Geneviève MARCELIN[3], Lambert ASSOUMOU[10], Christine KATLAMA[1], for the ETRAL QD study group

1. Sorbonne University, Infectious Diseases department, Pitié-Salpêtrière hospital, AP-HP, Pierre Louis Epidemiology and Public Health institute (iPLESP), INSERM 1136, Paris, France. 2. Paris 7 University, Toxicology and Pharmacology department, Bichat-Claude Bernard hospital, INSERM 1137, Paris, France. 3. Sorbonne University, Virology department, Pitié-Salpêtrière hospital, AP-HP, Pierre Louis Epidemiology and Public Health institute (iPLESP), INSERM 1136, Paris, France. 4. Infectious Diseases department, University hospital, Nantes, France. 5. Paris Descartes University, Clinical Immunology department, Georges Pompidou hospital, AP-HP, INSERM 976, Paris, France. 6. Infectious Diseases department, University hospital, Montpellier, France. 7. University of Paris, Infectious Diseases department, Necker hospital, AP-HP, INSERM 1016, Paris, France. 8. Infectious Diseases department, Avicenne hospital, AP-HP, Paris, France. 9. Infectious Diseases department, Jean Verdier hospital, Paris, France. 10. Sorbonne University, Pierre Louis Epidemiology and Public Health institute (iPLESP), INSERM 1136, Paris, France

BACKGROUND

- Dual therapies based on integrase strand transfer inhibitors (INSTIs) are increasingly used to avoid cumulated toxicity of protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs).
- The ANRS ETRAL study has demonstrated the potency of the etravirine / raltegravir given as twice daily regimen (200/400 mg BID) in maintaining viral load suppression in patients over 45 years with long history of ART. Viral suppression was maintained in 99.4% and 98.7% of participants at week 48 and week 96, respectively, with an improvement in lipid profile.
- **We aimed to evaluate whether switching etravirine / raltegravir given as twice daily to a once daily one (400/800 mg QD) will maintain the viral suppression over 48 weeks.**

METHODS

- Prospective, multicenter, open-label, single arm French study.
- Inclusion criteria: HIV-positive patients ≥18 years under etravirine / raltegravir 200/400 mg BID for at least 96 weeks, with HIV plasma viral load (pVL) <50 copies/mL for at least 96 weeks.
- **Primary outcome: virological failure rate (protocol-defined virological failure, PDVF = confirmed plasma viral loads [pVL] ≥50 copies/mL or single pVL ≥400 copies/mL) at W48.**
- Secondary outcomes: tolerability, study treatment success rate (no PDVF and no treatment discontinuation), plasma drugs concentrations and resistance profile in case of VF.

Flow chart

Included patients, D0 (n=111) → **Patients with pVL ≤50 copies/mL at W48 (n=96)**

- 2 virological failures (W24 and W48)
- 7 study treatment discontinuations for non virological reasons: adverse events (n=2, W4), investigator decision (n=2, W12 and W48), patient decision (n=1, W4), death (n=1, W48), pregnancy (n=24)
- 3 lost to follow-up

RESULTS

Patients' characteristics at baseline (n=111)	*median (IQR) or n (%)*
Age, years	57 (52-62)
Gender	
Men	85 (76.6)
Women	26 (23.4)
Country of birth, n (%)	
Caucasian	83 (74.8)
Sub-saharan Africa	12 (10.8)
Other	16 (14.4)
Transmission group	
MSM	56 (50.5)
IV drug users	10 (9.0)
Heterosexual	35 (31.5)
Other	10 (9.0)
Body mass, kg	76.0 (64.6-84.5)
HIV diagnosis, years	24.4 (18.6-28.4)
Raltegravir/etravirine BID duration, months	29 (6-40)
CD4 nadir, cells/mm^3	183 (90-269)
Pretherapeutic viral load, log$_{10}$ copies/mL, n=53	4.7 (4.2-5.2)
CDC C	34 (30.6)
Duration of virological suppression, years, n=109	7.9 (5.9-10.7)
CD4, cells/mm^3, n=104	710 (501-919)
CD4/CD8 ratio, cells/mm^3, n=102	0.93 (0.66-1.27)

- **Virological failure rate:** 2 PDVF occurred, leading to a proportion of patients who presented viral suppression under raltegravir/etravirine QD of **2.0% (95%CI 0.5-7.8) at week 48**. The virological success rate was 98.0% (95%CI 92.2-99.5) at W48.
- **Study treatment success rate:** 7 treatment discontinuations occurred for reasons other than virological failure: two for adverse events (nausea, headache), two for investigator decision, one for patient decision, one for death (myocardial infarction) and one for pregnancy, leading to a strategy success rate of **91.7% (95%CI 84.6-95.6) at W48.**
- **No significant change in CD4 count:** +2.5 cells/mm3 (IQR -72 to 84, p=0.75), **and in CD4/CD8 ratio:** +0.03 (-0.07 to 0.10, p=0.16).
- **No significant change in body weight:** -0.11 kg (-0.9 to 1.1, p=0.84)

- **Plasma antiretroviral concentrations (n=50, performed at W4):** median (IQR) C_{24h} values of etravirine 400 mg and raltegravir 800 mg QD were 401 ng/mL (286-591) and 51 ng/mL (26-93), respectively.

Virological success, treatment success and virological failure rates



- **First PDVF:** W24, pVL=7,950 copies/mL, concomitant low plasma concentrations for raltegravir (C_{24h}: 34 ng/mL) and etravirine (C_{24h}: 99 ng/mL), acquisition of resistance mutations associated to INSTI (L74I, G140A and Q148H). Previous HIV-RNA genotypes showing only K103N and 100I mutations.
- **Second PDVF:** W48, single pVL=156 copies/mL, concomitant adequate plasma concentrations for raltegravir (C_{24h}: 102 ng/mL) and etravirine (C_{24h}: 367 ng/mL), followed with etravirine/raltegravir discontinuation. No acquired resistance mutation. Previous HIV-RNA genotypes showing several resistance mutations associated to NNRTI (A98G, K101R and G190E/Q), which reduce the viral potency of etravirine.

CONCLUSIONS

- **A dual therapy combining raltegravir and etravirine, given once daily, represents a highly effective and safe strategy, even in a context of prior use of NNRTIs, with high level of virological success rate (98.0%).**
- The recent NNRTI doravirine opens perspectives to evaluate new dual therapies, for example with raltegravir.

Corresponding author: Dr Romain PALICH, Infectious Diseases department, Pitié-Salpêtrière hospital, AP-HP, France, romain.palich@aphp.fr

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