Investigator Initiated Study Program (IISP)
Project Manager

e.g : Title: ANRS 139 TRIO: Pilot study to evaluate antiretroviral therapy combining raltégravir, darunavir/ritonavir and etravirin  in HIV-infected patients in virological failure with multi-resistant viruses.

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Title: ANRS 139 TRIO: Pilot study to evaluate antiretroviral therapy combining raltegravir, darunavir/ritonavir and etravirin in HIV-infected patients in virological failure with multi-resistant viruses

Sponsor: Agence nationale de recherches sur le sida et les hépatites virales (ANRS) (French Agency for Research on AIDS and Viral Hepatitis)

Coordinating Investigator: Yazdan Yazdanpanah

ABSTRACT (205 words)

Background: The recommendation to treat HIV-infected patients on failing antiretroviral therapy is to combine at least two novel active drugs.

Hypothesis: The introduction of the following 3 new antiretroviral agents: raltegravir, etravirine and darunavir/ritonavir, should enable these patients to achieve an undetectable viral load.

Objectives: The objective was to assess the safety and efficacy of this combination.

Methods: TRIO, this non-comparative pilot trial enrolled highly experienced patients having at screening plasma HIV RNA>1000 copies/ml, naïve of the investigational drugs, and having a history of virologic failure on non-nucleoside reverse transcriptase inhibitors (NNRTI), ≥3 primary protease inhibitor (PI) and nucleoside reverse transcriptase inhibitor (NRTI) mutations, and ≤3 darunavir and NNRTI mutations.

Results: Overall 103 patients were enrolled. At baseline, genotypic resistance profiles showed a median of 4 primary PI mutations, 1 NNRTI mutation and 6 NRTI mutations. At week 24, 90% of patients had HIV RNA<50 copies/ml. At week 48, 86% had HIV RNA<50 copies/ml and mean CD4 increase was 129 cells/mm³. Grade 3/4 clinical adverse events were reported in 15 patients, only one discontinued the investigational regimen.

Discussion: In patients with multi-drug resistant virus and few remaining treatment options, the combination of raltegravir, etravirine and darunavir/r is well tolerated and has a rate of virological suppression similar to that reported for treatment-naïve patients.
BACKGROUND
The aim of antiretroviral therapy, whatever the situation (first-line, subsequent lines, including after multiple regimen failures) must be to achieve and maintain a plasma viral load lower than 50 copies/ml. To achieve this goal in patients who are in virological failure, it is recommended to combine at least two novel active drugs, ideally including one which belongs to a therapeutic class which has not yet been used. However, it is not always possible to achieve a viral load lower than 50 copies/ml, particularly in patients who are experiencing multiple regimen failure and for whom no active drug is available. This approach, often necessary because of limited drug options, put patients at high risk of virologic failure and resistance to the new agent, as well as to other agents in the same class. Raltegravir, the first HIV integrase inhibitor, darunavir, a new protease inhibitor, and etravirine, a new non nucleoside reverse transcriptase inhibitor (NNRTI) became available for use in clinical practice. The efficacy of raltegravir has been shown in the BENCHMRK study in which 62.1% of HIV-infected patients with limited treatment options taking raltegravir plus OBT achieved plasma HIV RNA levels > 50 copies/mL at week 48. Etravirine and darunavir have both shown potent in vitro activity against multidrug-resistant strains of HIV-1. No previous data on the efficacy and safety of a combination of 3 new drugs were available for a population of treatment- experienced patients infected with multidrug-resistant HIV.

STUDY HYPOTHESES
The introduction of the following 3 new antiretroviral agents, raltegravir, darunavir and etravirine, and their use in combination should enable treatment-experienced patients, with one or no active drugs available to them, to achieve an undetectable viral load. Before using these compounds in combination in this population, it was necessary to evaluate their efficacy in the context of a study and to determine the predictive factors associated with this efficacy, as well as studying their tolerability and determining the pharmacokinetic interactions which might occur.

OBJECTIVES
Primary objective
The primary objective of this work was to study the virological efficacy at W24 of a combination of retroviral drugs comprising raltegravir, darunavir/r and etravirin, in HIV-1 patients in virological failure with multi-resistant viruses.

Secondary objectives
The secondary objectives were to study the efficacy at W48 and the safety of this combination, to evaluate therapeutic compliance using this combination and to determine socio-demographic, clinical, immunological and virological factors associated with virological success.

METHOD
Study design
This was a non-comparative, prospective, multicenter, national pilot study which has been carried out to evaluate antiretroviral therapy including raltegravir, darunavir combined with low-dose ritonavir, etravirin and optimized therapy (which may include NRTI and enfuvirtide) in patients
Infected with HIV-1, in virological failure and with multi-resistant viruses. The choice of the NRTI(s) was left at the discretion of the clinician managing the patient. The use of enfuvirtide was strongly recommended in enfuvirtide-naive patients, but left at the discretion of the clinician managing the patient. In view of the data available on similar patient populations, it was estimated that fewer than 50% of the patients included with enfuvirtide will be enfuvirtide-naive. Patients have been followed for a period of 48 weeks.

**Eligibility criteria**

Patients who satisfied the following criteria were eligible: infected by HIV-1, plasma HIV-1 RNA >1000 copies/ml; on stable combination antiretroviral treatment (cART) initiated for >8 weeks prior to screening; naïve to the investigational drugs raltegravir, etravirine and darunavir. A genotype resistant test was done at screening and must show more than 3 Protease Inhibitor resistance mutations, defined according to the IASUSA; susceptibility to darunavir, defined according to version 16 of the ANRS resistance algorithm with, at least less than 3 mutations among V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V and L89V; and at least 3 nucleoside reverse transcriptase inhibitor (NRTI) mutations, defined according to the IASUSAvii.

Patients must also had a history of virologic failure while on NNRTI-based therapy but be susceptible to etravirine at screening based on available data at the time this study was designed (more than 3 NNRTI mutations among A98G, L100I, K101Q/P/E, K103H/N/S/T, V106A/M, V108I, E138G/K/Q, V179D/E/F/G/I, Y181C/I/V/C/H/L, Y188C/H/L, G190A/C/E/Q/S, P225H, F227C/L, M230I/L, P236L, K238N/T and Y318F).

Woman of childbearing age not using effective contraception (intrauterine device or contraceptive pill), pregnant woman or breastfeeding mother, patient suffering from an opportunistic infection in the acute phase, or having decompensated cirrhosis (Child-Pugh score, stage B or C), neoplasm currently under treatment by chemotherapy and/or radiotherapy, prohibited concomitant treatments were not eligible. Other exclusion criteria included renal insufficiency (creatinine clearance level < 50 mL/ min), hemoglobin level < 7 g/dL, absolute neutrophil count < 500 cells/mL, and platelet count < 50,000 platelets/mL; the concentration of alkaline phosphatase, ASAT, ALAT or bilirubin ≥ 3 times the upper normal limit (N).

All patients were up to 18 years of age at the screening visit, affiliated to or benefiting from social security insurance, free, informed, and written consent, signed by the patient and the investigator has been obtain from all patient.

**Study treatments**

After the signature of informed consent and verification of the eligibility criteria, patients were included in the study and received from W00 to W48 raltegravir (two 400 mg tablets twice a day), darunavir plus low dose of ritonavir (two 300-mg darunavir tablets plus 100 mg ritonavir twice daily), etravirin (two, 100 mg tablets twice daily at the end of a meal) + plus an optimized therapy which can include NRTI and enfuvirtide but not NNRTI or PI. The choice of the NRTI(s) was left at the discretion of the clinician managing the patient and the use of enfuvirtide was strongly recommended in enfuvirtide-naive patients, but also left at the discretion of the clinician managing the patient.
Endpoints
The primary endpoint was the proportion of patients with plasma HIV-1 RNA levels lower than 50 copies/mL at W24.

The secondary end points were the proportion of patients who reached plasma HIV-1 RNA levels lower than 50 copies/mL at week 48, and those who reached plasma HIV-1 RNA levels lower than 4000 copies/mL at week 24 and week 48, the change in plasma HIV-1 RNA levels and CD4 cell counts from baseline through week 48, and drug tolerability (assessed by number, type and time to onset of grade 3 and 4 adverse events, outcome of clinical and biological metabolic disorders and the evaluation of symptoms perceived). Additional secondary end points like change in drug susceptibility, proviral and circular HIV DNA evolution from baseline to week 48, and pharmacokinetic-pharmacodynamic association between raltegravir, etravirine, and darunavir have also been assessed.

Local laboratories assessed HIV-1 RNA levels and CD4 cell counts at screening, at enrollment (day 0), and at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48. Protease and reverse-transcriptase genes were sequenced at screening to determine the genotypic sensitivity scores of the OBT regimens to know the total number of antiretroviral drugs in the OBT regimen to which a patient’s HIV was susceptible (score, 1), possibly susceptible (score, 0.5), or resistant (score, 0), according to version 16 of the ANRS algorithm. Safety has been measured by conducting physical examinations and blood and urine tests at enrollment and during the study. An independent data and safety monitoring board reviewed available safety and efficacy data.

RESULTS

Overall 170 patients have been screened and 103 enrolled in the study. Among the 103 patients enrolled, 100 patients were taking their therapy at week 24, one died and 3 discontinued their treatment: 1 experienced a grade 4 clinical adverse event and 2 decided to stop taking the study drugs.

Patients characteristics at baseline are shown in Table 1. Among the 103 patients included, 91 were Male. The medium age was 45 years old and the medium duration of their antiretroviral therapy before their enrollment in the study therapy was 13 years. The median CD4 cell count was 255 cells/mL, and the median plasma HIV RNA level was 4.2 log10 copies/mL. The baseline genotypic test did showed that the median number of PI mutations (primary mutations) was 6 (3-4), NRTI mutations was 6 (5-7) and the median number of NNRTI mutations was 1. During the treatment period,
86 patients (84%) received NRTI-containing OBT regimens, and 12 patients (12%) received enfuvirtide-containing OBT regimens.

Figure 1: Proportion of patients with plasma human immunodeficiency virus (HIV) RNA levels >50 copies/mL during the ANRS 139 TRIO trial

The figure 1 shows the proportion of patient with plasma HIV-1 RNA levels ≥50 copies/ml during the trial. At week 4 50% of patient and 90% at week 24, had RNA levels ≥50 copies/ml.

Among the 10% of them who had plasma HIV-1 RNA levels ≥50 copies/ml at week 24, five had plasma HIV-1 RNA between 50 and 400 copies/ml and the five other who had HIV RNA>400 copies/ml included the three patients who discontinued treatment before week 24. At week 48, 89 patients had HIV-1 RNA<50 copies/ml.

The Figure 2 illustrates the mean change in log_{10} HIV-1 RNA copies/ml and CD4 cell count from baseline. Since the mean change in log log_{10} HIV-1 RNA copies/ml at week 48 decrease to −2.4, the mean CD4 cell count increase from baseline to week 48 was 129/mm³.
Adverse Events
2 new AIDS-defining events (HIV encephalopathy and oesophageal candidiasis)(2%) has been declared during the study period and one patient died due to a myocardial infarction syndrome after an aortobifemoral bypass surgery (1%).

<table>
<thead>
<tr>
<th>Clinical adverse events</th>
<th>No. (%) of patients (n = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1 Event</td>
<td>87 (53.8)</td>
</tr>
<tr>
<td>Drug-related event</td>
<td>28 (17.2)</td>
</tr>
<tr>
<td>Severe event</td>
<td>14 (8.6)</td>
</tr>
<tr>
<td>Severe drug-related event</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Grade 3–4 event</td>
<td>15 (9.2)</td>
</tr>
<tr>
<td>Grade 3–4 drug-related event</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Grade 3–4 severe event</td>
<td>19 (11.7)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Event leading to discontinuation</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

Few clinical adverse events has been noticed during the study and reported in table 2, 87 patients (84.5%) reported clinical adverse events of any intensity, 28 (27.2%) of these were considered to be related to one or several of the study drugs and 14 were serious (Table 2). 15 patients (14.6%) reported grade 3/4 clinical adverse events, 4 (3.9%) of these were considered to be drug-related and one resulted in treatment discontinuation. The clinical adverse event that resulted in treatment discontinuation was a grade 4 skin rash, with fever. It was considered to be related to raltegravir by the investigator since the symptoms reoccurred when the patient resumed use of raltegravir and the three NRTIs used at enrollment, but did not when he resumed etravirine and darunavir/r. Five other patients (4.9%) reported skin rashes with a severity classified grade 1 in three patients and grade 2 in two patients, respectively. Overall, 91 patients (88.3%) reported laboratory abnormalities, including 20 patients (19.4%) who reported grade 3/4 laboratory abnormalities. The most frequent grade 3/4 laboratory abnormalities were creatine kinase elevation (n=11), and GGT elevation (n=4). None of the laboratory abnormalities resulted in treatment discontinuation.

DISCUSSION
In patients infected by HIV who had few remaining treatment options and were with multidrug-resistant HIV and, the ART combination containing raltegravir, etravirine and darunavir/r resulted in high suppression rates for at least 48 weeks.

The strategy in case of virologic failure due to multidrug-resistances is to add one or two new and active agents to a failing regimen. TRIO trial was the first clinical trial whose evaluate the efficacy and tolerability of a regimen containing three new agents in patients with highly resistant virus. The suppression rates observed in this trial are higher than those observed in any other study on multidrug-resistant patients and approaches the rates reported among antiretroviral-naïve patients.

Table 2. Clinical Adverse Events and Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Laboratory adverse events</th>
<th>No. (%) of patients (n = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1 Event</td>
<td>91 (55.8)</td>
</tr>
<tr>
<td>Grade 3–4 event</td>
<td>29 (18.1)</td>
</tr>
</tbody>
</table>

Grade 3–4 laboratory adverse events:
- Creatine phosphokinase level >5 × ULN: 11 (6.7%)
- Gamma-glutamyltransferase level >5 × ULN: 4 (2.4%)
- Triglycerides >260 mmol/L: 3 (2.0%)
- Alanine aminotransferase level >6 × ULN: 1 (0.6%)
- Absolute neutrophil count <750 cells/mm³: 1 (0.6%)
- Aspartate aminotransferase level >6 × ULN: 1 (0.6%)
- Glucose level >18.5 mmol/L: 1 (0.6%)

NOTE: ULN upper limit of normal.
As reported in STARTMRK and BENCHMRK investigating the efficacy of raltegravir plus OBT respectively in treatment-naïve and treatment-experienced patients investigational drugs had a rapid antiretroviral effect\textsuperscript{xiv,xiii}. The Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected patients state that virologic failure while on treatment can be defined as confirmed HIV RNA>400 copies/ml after 24 weeks or >50 copies/ml by 48 weeks or a repeated detectable HIV RNA level after prior suppression of viremia\textsuperscript{i}. Given the rapid kinetics of HIV-1 RNA response to new investigational drugs, and especially raltegravir, we can wonder whether a more strict definition of virologic failure should be used or not in clinical practice for treatment-naïve and treatment-experienced patients.

Moreover, the raltegravir, etravirine and darunavir/r combination was well tolerated with most drug-related adverse events proving to be mild or moderate in severity and only one grade 3/4 led to treatment discontinuation. Since there was no control arm, it is difficult to identify which adverse events were related to the investigational drugs. Among the clinical adverse events skin rash was one of the most frequently and clinicians often considered it to be related to the study regimen. The DUET 1 and 2 showed higher rates of skin rashes in the etravirine group than in the control group\textsuperscript{xi, xii}. In the study skin rashes observed were mild to moderate and often resolved without treatment discontinuation, except the grade 4 skin rash observed in the patient who stopped the investigational drugs that was probably not related to etravirine but to raltegravir as stated by the physician. The most frequent grade 3/4 events found were creatine kinase elevations (n=11). Even if a case report acknowledged a case of severe rhabdomyolysis associated with raltegravir use\textsuperscript{v}, the BENCHMRK trials showed a similar proportion of patients with creatine kinase elevation in the raltegravir group than in the control group\textsuperscript{viii}. In this study, all patients with creatine kinase elevations were asymptomatic and none discontinued study treatment.

This study was designed as a single arm clinical trial in which all patients received the three investigational drugs to allow all included patients who harbored multidrug-resistant virus to benefit the three active agents from multiple drug classes, as recommended\textsuperscript{1,vii}.

In conclusion, HIV-infected patients with few remaining treatment options and highly resistant virus can benefit from an ART regimen containing raltegravir, etravirine and darunavir/r and achieve virological suppression comparable to treatment-naïve patients.
REFERENCES


ix Fagard C.1, Descamps D.2, Dubar et al. Efficacy and Safety of raltegravir plus etravirine and darunavir/ritonavir in treatment-experienced patients with multidrug-resistant virus: 48-week results from the ANRS 139 TRIO trial, Poster, IAS 2009


