Long-Term Efficacy and Safety of Raltegravir, Etravirine, and Darunavir/Ritonavir in Treatment-Experienced Patients: Week 96 Results From the ANRS 139 TRIO Trial

Catherine Fagard, MD,¶¶ Céline Colin, MSc,*¶¶ Charlotte Charpentier, PharmD, PhD,†‡ Agathe Rami, MD,§ Christine Jacomet, MD,|| Patrick Yeni, MD, PhD,† Daniel Vittecoq, MD, PhD,¶ Christine Katlama, MD, PhD,#** Jean-Michel Molina, MD, PhD,†† Diane Descamps, MD, PhD,†‡ Geneviève Chêne, MD, PhD,*‡‡¶¶ Yazdan Yazdanpanah, MD, PhD,§§||||*
and The ANRS 139 TRIO Trial Group

Abstract: Among 103 patients with multidrug-resistant HIV who initiated raltegravir, etravirine, and darunavir/ritonavir-containing regimen in the ANRS 139 TRIO trial, 100 participated in extended follow-up and continued study treatment until week 96. Among them, 87 (87%) received an optimized background therapy including either nucleoside reverse transcriptase inhibitors or enfuvirtide, they were 78 (78%) at week 96. At week 96, 88% achieved durable virologic response (<50 copies/mL). CD4 response was maintained (median change of +150 cells/mm^3). No major toxicity was reported. This triple drug combination showed sustained efficacy and thus should be strongly considered for patients with multiclass-resistant virus.

Key Words: multidrug resistant, HIV, raltegravir, etravirine, darunavir/ritonavir

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From the *INSERM, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, F-33000 Bordeaux, France; †Laboratoire de Virologie, AP-HP, Groupe hospitalier Bichat-Claude Bernard, Hôpitaux Universitaires Paris Nord Val de Seine, Paris, France; ‡EA 4409 Université Paris-Diderot, Paris, France; §Hôpital Lariboisière, Paris, France; ||Hôpital Gabriel Montpied, Clermont-Ferrand, France; ¶Service des maladies infectieuses, APHP, Hôpitaux universitaires Paris Sud, Bicêtre, France; #Hôpital Pitié-Salpêtrière, Paris, France; **Université Pierre et Marie Curie UPMC Hôpital Pitié-Salpêtrière, Paris, France; ††Hôpital Saint Louis and Université de Paris Diderot Paris 7, Paris, France; ‡‡CHU de Bordeaux, Pôle de santé publique, Service d'information médicale, F-33000 Bordeaux, France; §§Hôpital Tourcoing, Lille School of Medicine, Lille, France; ||||ATIP-AVENIR Inserm U995, Université Lille Nord de France, Lille, France; and ¶¶Université Bordeaux, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, F-33000 Bordeaux, France.

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The members of the ANRS 139 TRIO Trial Group are listed in Appendix I.

Correspondence to: Catherine Fagard, MD, INSERM U897, Université Bordeaux Segalen, 146 rue Léo Saignat Case 11, 33076 Bordeaux cedex, France (e-mail: catherine.fagard@isped.u-bordeaux2.fr).

INTRODUCTION

Recent clinical trials reported on the findings of new antiretroviral combinations with a dramatic increase in the proportion of patients safely achieving virologic response despite harboring multidrug-resistant HIV-1 viruses.[1] Among these investigations, the ANRS 139 TRIO trial reported that 86% of patients reached HIV-1 RNA <50 copies/mL at week 48 with a salvage regimen containing raltegravir, etravirine, and darunavir/ritonavir and optimized background therapy with nucleoside reverse transcriptase inhibitors (NRTIs) or enfuvirtide.[2] This level of success may be compared with previous studies on treatment-naive patients receiving a triple combination regimen including raltegravir.[3,4] However, as highly potent combinations were only recently introduced in treatment-experienced patients, data on the long-term efficacy and safety of these regimens are scarce. Consequently, we report here the 96-week efficacy and safety of raltegravir, etravirine, and darunavir/ritonavir in patients enrolled in the ANRS 139 TRIO trial.

METHODS AND STATISTICAL ANALYSIS

The ANRS 139 TRIO trial was a phase II noncomparative, multicenter trial with 103 treatment-experienced patients with multidrug-resistant HIV viruses. Details of the study eligibility criteria were reported elsewhere.[2] In short, patients were included if they presented with HIV-1 RNA

>1000 copies/mL, were on stable antiretroviral therapy for at least 8 weeks, were naive to the study drugs, and had the following resistance profile: ≥3 primary protease inhibitor (PI) mutations, ≥3 NRTI mutations, ≤3 darunavir mutations, and ≤3 nonnucleoside reverse transcriptase inhibitor mutations.[2] All patients received raltegravir (one 400-mg tablet twice daily), etravirine (two 100-mg tablets twice daily), and darunavir/ritonavir (two 300-mg/100-mg tablets twice daily). An optimized background regimen with NRTIs or enfuvirtide was given at the physician's discretion. At week 48, patients were invited to participate in the extended follow-up until week 96 to assess the durability of efficacy and safety of this antiretroviral combination.

The protocol amendment was reviewed and approved by the Nord Ouest III, France ethics committee, and health authority. All patients participating in the extended follow-up signed an additional consent form. Follow-up study visits after week 48 were scheduled at weeks 60, 72, 84, and 96.

The protocol-defined endpoints were the proportions of patients with HIV-1 RNA <50 copies/mL at weeks 48 and 96 (virologic success), with virologic failure defined by HIV-1 RNA ≥50 copies/mL at week 24 (primary endpoint), or with viral rebound defined by 2 consecutive measurements of HIV-1 RNA ≥50 copies/mL between week 24 and week 96. Other endpoints were changes in HIV-1 RNA levels and CD4+ cell counts from baseline and incident clinical and biological events.

All patients participating in the extended follow-up were included in the statistical analysis. For patients discontinuing the trial, data were included up to the date of the final visit. For HIV-1 RNA analysis, missing data were imputed as >50 copies/mL (missing equal failure), while the analysis of CD4+ counts was performed on available data only.

The incidence of clinical and laboratory adverse events comprised all events occurring during the trial. The severity of clinical and laboratory abnormalities was graded according to the ANRS scale for grading the severity of adverse events in adults.

All statistical analyses were performed using SAS, version 9.1.3 service pack 2 (SAS Institute).

RESULTS

Of the 103 patients, 100 consented to participate in the extended follow-up. Among the 3 other patients, 1 died at week 40, 1 was unable to consent due to mental confusion and multiple injuries after an accident, and 1 refused to participate. Overall, 98 of the 100 enrolled patients completed follow-up until week 96, whereas 2 patients withdrew their participation due to reasons unrelated to the trial drugs.

Among the 100 patients enrolled, 89% were male with a median age of 45 years (IQR: 41–51), whereas 42% had a history of an AIDS-defining event at trial baseline (week 0). At week 0, the median plasma HIV-1 RNA level was 4.2 $\log_{10}$ copies/mL (IQR: 3.6–4.6) and median CD4+ cell count 258 cells/mm^3 (IQR: 143–350), with 40% of patients displaying a CD4+ count <200 cells/mm^3.

At week 48, 86% [95% Confidence Interval (95% CI): 79% to 93%] of patients achieved HIV-1 RNA <50 copies/mL in the missing equal failure analysis, and 86% (95% CI: 79%-93%) in the analysis on available data. At week 96, these proportions remained high at 88% (95% CI: 82% to 94%) and 91% (95% CI: 85% to 97%), respectively.

All patients, including those experiencing virologic failure, continued raltegravir-etravirine-darunavir/ritonavir until week 96. Regarding the optimized background therapy, 87 patients received NRTIs or enfuvirtide at week 0 and 78 at week 96. Virologic success did not differ whether patients received a backbone regimen (81%) or not (85%). Moreover, baseline characteristics such as HIV-1 RNA, CD4 count or genotypic sensitivity score were not related to virologic success at week 96.

Overall, 19 (19%) patients experienced virologic failure during the trial: 12 before week 48 (8 with HIV-1 RNA ≥50 copies/mL at week 24 and 4 with a viral rebound between week 24 and week 48) and 7 between week 48 and week 96, including 2 patients with missing data considered as failure (Table 1). Among the 12 patients who experienced virologic failure before week 48, HIV-1 RNA values were detectable in 6 between week 48 and week 96. Viral amplification was obtained for 2 patients (HIV-1 RNA <100 copies/mL in the other cases). In the first of these patients (Table 1, case n = 5) whose HIV-1 RNA measurement was never below 50 copies/mL throughout the entire study, the selection of the L10F mutation was observed in protease and associated with the disappearance of the major PI resistance mutation L76V. In the second patient (Table 1, case n = 6), the selection of the I15V mutation was associated with a switch from I54T to I54V on protease. Moreover, the L74I/M integrase mutation associated with the V72I and G163R mutations observed at week 24 conferred a potential resistance to raltegravir according to the ANRS algorithm. It should be noted that the selection of mutations associated with resistance to darunavir or etravirine was previously reported in both of these patients.[5] In 5 patients with virologic failure after week 48, we demonstrated the selection of the L100I and K103N nonnucleoside reverse transcriptase inhibitor resistance mutations in 1 patient (Table 1, case n = 15; HIV-1 RNA <50 copies/mL at week 96), in addition to the minor protease resistance mutation K20M in another (Table 1, case n = 17; HIV-1 RNA = 100 copies/mL at week 96).

The mean change in HIV-1 RNA from baseline to week 96 was –2.3 $\log_{10}$ copies per mL (95% CI: −2.5 to −2.1). Median CD4+ cell counts increased from 258 cells/mm^3 (IQR: 143–350) at baseline to 360 (IQR: 240–484) at week 48 and 385 (IQR: 248–541) at week 96, with the median gain being 110 cells/mm^3 (IQR: 58–169) and 150 (IQR: 70–271), respectively. The proportion of patients with CD4+ cell count <200 cells/mm^3 decreased from 40% (95% CI: 30 to 50) at week 0 to 14% (95% CI: 7 to 21) at week 48 and week 96.

Grade 3–4 laboratory adverse events were reported in 25 patients (24%), mostly during the week 0 to week 48 study period. No biological event resulted in treatment discontinuation. Median triglycerides levels were 2.5 mmol/L at week 0 and 2.2 mmol/L at week 96. Median total cholesterol and high-density lipoprotein were 5.3 and 1 mmol/L at week 0, and 5.4 and 1.1 mmol/L at week 96, respectively. Glucose levels were 5 and 5.1 mmol/L at week 0 and week 96, respectively.

Clinical adverse events were reported in 96 patients (93%), mostly during the weeks 0–48 study period. In

TABLE 1. Virologic Failures in ANRS 139 TRIO Trial

	HIV-1 RNA Measure (Copies/mL)								
N	Week 0	Week 24	Week 32	Week 40	Week 48	Week 60	Week 72	Week 84	Week 96
Failure at Week 24 (HIV RNA measure ≥50 copies/mL), n = 8									
1	29228	ND	790	83	<40	<40	<40	<40	<40
2	5141	50	<40	<40	<40	<40	<40	<40	<20
3	11859	52	<40	70	<40	44	<40	53	<20
4	3548	60	<40	<40	<40	<40	<40	<40	<40
5	610000	1200	840	290	800	1100	610	943	487
6	69600	432	252	1212475	122	ND	37754	<40	21
7	200000	240	120	190	<40	78	48	65	<40
8	68184	60	86	<40	<40	<40	55	<40	<40
Rebound between week 24 and 48 (2 HIV-1 RNA measures ≥ 50 cp/mL), n = 4									
9	25346	<40	<40	783	86	<40	<40	<40	1121
10	8424	<40	67	105	<40	<40	<40	<40	<40
11	18200	<40	90	73	<40	<40	<40	<40	<20
12	85	<40	59	153	<40	<40	<40	<40	<40
Rebound between week 48 and 96 (2 HIV-1 RNA measures ≥50 copies/mL), n = 7									
13	6057	<40	<40	<40	52	<40	110	162	41
14	15951	<40	<40	<40	42	94	58	<40	<40
15	1398	48	73	<40	77	326	228	114	<40
16	5925	<40	<40	ND	<40	84	56	<40	<40
17	8000	<40	<40	<40	<40	<40	<40	86	100
18	2425	<40	<40	<200	<40	<40	ND	ND	ND
19	14476	<40	<40	52	<40	<40	<40	ND	ND

	Genotypic Resistance Test Results at Failure		
N	PI	NRTI and Nonnucleoside Reverse Transcriptase Inhibitor	Integrase Inhibitors
Failure at Week 24 (HIV RNA measure ≥50 copies/mL), n = 8			
1	ND	ND	ND
2	ND	ND	ND
3	Week 84: not amplified	Week 84: not amplified	Week 84: not amplified
4	ND	ND	ND
5	Week 96: selection of the L10F disappearance of the L76V	Week 96: no new mutation	Week 96: no mutation
6	Week 72: selection of I15VSwitch from I54T to I54V	Week 72: no new mutation	Week 24: V72I, G163R Week 72: V72I, L74I/M, G163R
7	Week 60: not amplified	Week 60: not amplified	Week 60: not amplified
8	Week 72: not amplified	Week 72: not amplified	Week 72: not amplified
Rebound between week 24 and 48 (2 HIV-1 RNA measures ≥ 50 cp/mL), n = 4			
9	Week 96: not amplified	Week 96: not amplified	Week 96: not amplified
10	ND	ND	ND
11	ND	ND	ND
12	ND	ND	ND
Rebound between week 48 and 96 (2 HIV-1 RNA measures ≥50 copies/mL), n = 7			
13	Week 72: no new mutation	Week 72: not amplified	Week 72: not amplified
14	Week 72: not amplified	Week 72: not amplified	Week 72: not amplified
15	Week 72: not amplified	Week 72: selection of L100I, K103N	Week 72: no mutation
16	Week 72: no new mutation	Week 72: no new mutation	Week 72: not amplified
17	Week 96: selection of the minor K20M	Week 96: no new mutation	Week 96: not amplified
18	ND	ND	ND
19	ND	ND	ND

26 patients (25%), a grade 3–4 clinical event was observed, including 4 events considered to be related to study drugs, which occurred before week 48: 1 recurrent epidermal necrolysis leading to treatment discontinuation, 1 nephrolithiasis, 1 lipodystrophia, and 1 muscular spasm.

Two patients presented a new AIDS-defining event before week 48 (HIV encephalopathy and candida esophagitis), with another patient during the week 48–week 96 period (non-Hodgkin lymphoma and tuberculosis lymphadenopathy). The incidence of AIDS events was estimated to be 1.6 per 100 person-years of follow-up (95% CI: 0.3 to 4.7).

Five cases of cancer were reported: myeloma (week 0 to week 48), non Hodgkin lymphoma, Hodgkin lymphoma, anal carcinoma, and recurrence of a Castleman disease (week 48 to week 96). Three patients presented a myocardial ischemic event, including 1 who died due to myocardial infarction syndrome after aortobifemoral bypass surgery before week 48, whether another patient exhibited a possible cerebral transitory ischemic attack. No severe renal or hepatic events were reported. The incidence of non–AIDS-related serious events was estimated to be 4.3 per 100 person-years of follow-up (95% CI: 1.9 to 8.4).

DISCUSSION

This study confirms that in treatment-experienced patients, an antiretroviral regimen containing raltegravir, etravirine, and darunavir/ritonavir showed high efficacy, with a good safety profile. Long-term efficacy in this population seemed to be as high as that reported for treatment-naive patients receiving either PI-containing regimens associated with NRTIs[6] or combinations containing new antiretroviral drugs, such as raltegravir.[7,8] In our study, virologic failures mostly occurred during the first 48 weeks after treatment initiation. Only 7 patients for whom antiretroviral treatment was efficacious at week 48 presented a failure during the extended phase: 2 with missing data but a measure of HIV-1 RNA <50 copies/mL at the last control, 4 with HIV-1 RNA levels <200 copies/mL, and 1 with 2 measurements between 200 and 400 copies/mL.

No major raltegravir resistance mutation could be detected by direct sequencing, even at a late time-point. In our study, virologic failure was rarely associated with the selection of drug resistance mutations, although a few samples were able to be analyzed due to the low level of HIV-1 RNA.

In this study, CD4+ cell count continued to increase between week 48 and week 96, and the proportion of patients with CD4+ count <200 cells/mm^3 was low at both time points. In addition, in these immunodeficient patients at risk of opportunistic diseases,[9] new AIDS-defining events were rare, with only a small proportion of patients developing AIDS-defining malignancies. Four cases of non-AIDS malignancies were reported. Given that a longer response to immunodeficiency is an important risk factor of such malignancies,[10] it is difficult to compare the study population to the general HIV population for the incidence of non-AIDS cancers.[11] However, these numbers are small, and the cases are unlikely to be related to antiretroviral drugs prescribed.

In conclusion, the treatment combination of raltegravir, etravirine, and darunavir/ritonavir was shown to be highly potent and durable in terms of efficacy and safety for treatment-experienced patients with multidrug-resistant HIV.

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APPENDIX I: ANRS 139 TRIO TRIAL GROUP

In addition to the authors, the following investigators are involved in the trial: C.H. Belfort: J.P. Faller; C.H. Perpignan: H. Aumaitre; Hôpital Gilles, Corbeil: P. Chevojon; Hôpital Saint Louis, Paris: L. Gerard, JM. Molina, D. Sereni, F. Timsit; Hôpital Avicenne, Bobigny: M. Bentata, O. Bouchaud; Hôpital Hôtel Dieu, Paris: A. Compagnucci; Hôpital Saint-Jacques, Besançon: C. Drobacheff; Hôpital Pellegrin, Bordeaux: M. Dupon, JM. Ragnaud; Hôpital Necker-Enfants Malades, Paris: JP. Viard; CH, Annecy: J. Gaillat; Hôpital Bicêtre, Paris: C. Goujard; Hôpital Lariboisière, Paris: A. Rami; Hôpital Henri Duffaut, Avignon: G. Pichancourt; Hôpital Raymond Poincaré, Garches: P. De Truchis; Hôpital Paul Brousse, Villejuif: D. Vittecoq; Hôpital Tenon, Paris: G. Pialoux; Hôpital Antoine Béclère,

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The study team also included A. M. Taburet, pharmacologist; V. Dubar, protocol pharmacist; C. Jean Marie, A. Beuscart, and N. Agher, trial clinical research assistants; S. Couffin- Cadiergues and A. Diallo, representatives of ANRS.