Dual therapy with raltegravir plus a fixed dose combination of darunavir/ritonavir in people living with HIV in Argentina

Fernanda Rombini
Diego M. Cecchini
Jamile Ballivian
Mara Huberman
Analía Urueña
Isabel Cassetti

Helios Salud, Buenos Aires, Argentina

ABSTRACT

Objective. There are generic fixed-dose combinations (FDCs) of ritonavir-boosted darunavir (DRV/r) available in Argentina. Experiences with these FDCs in dual therapy remain limited in clinical practice. We aimed to describe clinical and virologic outcomes in patients exposed to FDC DRV/r + raltegravir (RAL) 400 mg every 12 h in a real-life setting.

Patients and methods. Retrospective analysis of electronic medical records of HIV-infected patients under FDC DRV/r + RAL in an HIV clinic in Argentina (2014-2018). Individuals were classified as "switch group" (SG, undetectable viral load [VL] with any toxicity/comorbidity) and "virologic group" (VG, detectable viremia and infection by multidrug-resistant HIV).

Results. Of 7,380 patients on ART, 116 (1.5%) received FDC DRV/r + RAL, being 58% in SG. Sixty percent received DRV/r 800/100 mg dose (rest, 600/100 mg). The median (IQR) age and CD4+ T-cell count were: 52 (42–58) years, and 373 cells/µL (202–642). Ninety-eight percent were ART-experienced with a median of 3 (IQR 2–5) prior treatments. Main reasons for switch (SG) were renal (57%), cardiovascular (54%) and bone (14%) comorbidities. Median exposure to DRV/r + RAL was 18 months. Among patients in SG, 98% and 96% had undetectable VL at 6 and 12 months; in the VG, 89% and 87% had undetectable VL at 6 and 12 months. No patient required suspension due to toxicity/intolerance.

Conclusion. In this cohort of mostly experienced HIV-infected patients, FDC DRV/r + RAL was effective and safe. Such therapy may be considered an option for patients with comorbid conditions and/or with multidrug-resistant HIV.

Keywords: HIV infection, antiretroviral therapy, dual therapy
INTRODUCTION

Until recently, HIV treatment guidelines recommended triple antiretroviral therapy (ART) based on combining a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone with a third agent, such as a ritonavir-boosted protease inhibitor (bPI), an integrase inhibitor (INSTI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) [1–3]. However, toxicities associated with long-term use of NRTIs have led to the assessment of dual therapy approaches that do not include this drug class [4]. Cohort studies describe an increased prevalence of comorbidities associated with natural aging, including renal, cardiovascular, metabolic disorders such as diabetes, dyslipidaemia and osteoporosis, among others [5–7]. These comorbid conditions appear in people living with HIV at younger ages than non-infected controls [6-8]. Drug-related adverse events associated with the long-term use of NRTIs, as other antiretrovirals, may contribute to these comorbidities [9].

Some studies have suggested a possible improvement of NRTI-related adverse events after switching to NRTI-sparing regimens. These regimens could potentially achieve and maintain viral suppression and immunologic control, reduce costs, while avoiding long term toxicities. It can also be an alternative for patients under failing regimens (eg. patients with resistance to NRTI and other drug classes) [1-4].

In Argentina, DRV/r 800/100 and 600/100 mg generic fixed-dose combinations (FDC) are available and recommended (with a NRTI backbone) for naive or experienced patients in local guidelines [3,10]. The FDC considerably reduces the pill burden of this bPI, allowing better tolerability. Despite this FDC showed efficacy and low prevalence of adverse events in a randomized control trial in naive patients [11], there are no publications considering its effectiveness and safety in routine clinical practice.

Raltegravir (RAL) was the first available INSTI, approved for use in Argentina in 2008 and, until recently, the most widely used drug of this family. It leads to potent viral suppression while maintaining a favorable adverse effect profile and minimal drug interactions. Its effectiveness to rapidly control HIV viral load (VL) has been demonstrated in antiretroviral-naïve and experienced patients. However, its low genetic barrier precludes its use in patients with drug resistance mutations unless associated with accompanying drugs with higher genetic barrier, such as bPIs [12-14].

Experience with DRV/r + RAL dual therapy has been limited in clinical practice with no publications considering the use of a generic FDC of DRV/r. Addressing this information will contribute to guide use of ART in certain HIV-infected populations, we aimed to describe indications, efficacy and safety of a generic FDC of DRV/r + RAL 400 mg BID in real-life patients.

RESULTS

Of 7,380 HIV-infected patients on ART in our institution, 236 (3.19%) received DT and 116 received FDC DRV/r + RAL. This DT regimen was the most frequently prescribed and accounted for 1.57% of our total population. Considering demographics, 69.8% were male and the median of age was 52 years (IQR 42-59). The majority of patients were experienced in ART (98%) with a median time of exposure of 144 months (IQR 75-228). Considering group classification, 68 (58%) individuals corresponded to SG and 48 (42%) to VG.

Clinical and immunovirological profile and time on dual therapy are shown in table 1. Patients in SG were older (t = 5.1029; p<0.001), had higher CD4 T-cell count prior to DT (t = 4.7071; p<0.001), and had been exposed longer (t = 7.8199; p<0.001) to more ART regimens (z = 8.791; p<0.001) than those in the VG. Both groups had a median of 2 prior virologic failures, with patients in VG with additional ongoing failure at DT indication. Regarding prior ART: 88.8% of the patients were re-
ceving triple therapy, being the most frequent the association of 2 INTI + bPi or NNRTI (detail shown in table 2).

Main reasons for prescription of DT in SG were renal (57%), cardiovascular (54%) and bone (14%) comorbidities, while in the VG the indication was exclusively as rescue therapy in the context of infection by multidrug resistant HIV. Regarding dosage used, 69 (59%) and 18 (37.5%) received FDC DRV/r 800/100 mg QD in the SG and VG, respectively (rest, 600/100 mg BID).

High prevalence of virologic suppression was observed at 24 and 48 weeks in both groups (table 3), with a trend to higher rates in SG. In 6 cases (4 from de VG and 2 from the SG) with VL >200 c/ml at 48 weeks, a resistance test was performed, showing emerging resistance to RAL (N155 pathway) in one patient from the VG. No patient developed resistance to DRV/r.

No discontinuations of DT due to adverse events (toxicity or intolerance) were observed. Considering mortality, one individual (1.47%) in the SG group died of non-HIV related cause (septic shock in a diabetic patient with chronic renal disease).

**DISCUSSION**

Effective ART is the most important intervention in terms of improving quality of life and survival in HIV-infected population. This therapy should involve combinations of drugs recommended by current guidelines, mostly based on two NRTIs plus a third drug, which may vary according to regional policies: INSTI, NNRTI, or a bPI [1-3]. Despite current drugs are safe and with minimal tolerance issues, certain proportion of patients may require an individualized approach due to either comorbidities or resistance that precludes the use of NRTIs and other drug classes [4,9,15].

As far as we know, in this study we provide the largest experience in DT based in the use of DRV/r + RAL in a real-life setting using exclusively a generic FDC of the bPi. Our population represents ART-experienced patients in two complex clinical scenarios: those with comorbidities that required a NRTI-sparing regimen to prevent/minimize mainly renal and cardiovascular adverse events, and patients with limited therapeutic options due to multidrug-resistant HIV. Despite other INSTIs (elvitegravir, dolutegravir) were approved for use in Argentina during the period of the study, access was limited until recently and no experience in dual therapy in clinical practice could be documented. Of, note elvitegravir (with cobicistat booster) is only available as triple drug combination and not as independent medication. Bictegravir was approved in 2019 in Argentina and is available only as part of a coformulation with tenofovir alafenamide and emtricitabine.
patients in SG had also history of virologic failure that didn’t impact sustaining virologic suppression with this DT strategy. Prevalence of adverse events and tolerance issues leading to discontinuation of this two-drug combination was null, providing empirical evidence of the safety of this strategy in complex populations.

Our results are consistent with other studies concerning the efficacy and tolerability of DRV/r + RAL in treatment-experienced patients. Maddeau et al, described an overall 9% probability of virologic failure at 24 months in experienced patients switched to RAL + DRV/r in the ICONA Foundation Study [16]. Jablonowska et al, in a cohort of 109 experienced patients described no discontinuations of this DT due to virologic failure, and low rates of adverse events, being simplification strategies the main reason for stopping this regimen [17,18]. Nishijima et al, on behalf of the SPARE study team, described 100% suppression rates at week 48 in patients switched to this DT due to prevention of TDF renal toxicity [19].

Despite our study has limitations inherent to its retrospective and descriptive nature that may limit the generalization of the results, our cohort provides evidence of the efficacy and safety of a generic FDC of DRV/r + RAL in a pretreated population, supporting this DT as an option for selected individuals with comorbid conditions or drug resistance.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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2. E.A.C.S. European Guidelines for the treatment of people living with HIV (PLWH) in Europe. Guidelines. 2019. Available at https://

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Table 2

| ARV family prior to DT | % subjects |
|------------------------|------------|
| N = 116                |            |
| 2 NRTIs                | 1 (1.0%)   |
| 3 NRTIs                | 1 (1.0%)   |
| 3 NRTIs + NNRTI        | 1 (1.0%)   |
| 4 NRTIs + NNRTI        | 1 (1.0%)   |
| 2 NRTIs + ANTCCR5      | 1 (1.0%)   |
| NRTI + ANTCCR5 + bPI + INSTI | 1 (1.0%) |
| 2 NRTIs + bPI + ANTCCR5| 1 (1.0%)   |
| NNRTI + bPI + INSTI    | 1 (1.0%)   |
| NRTI + NNRTI + bPI     | 1 (1.0%)   |
| 2 NRTIs + INSTI        | 2 (1.9%)   |
| NNRTI + bPI            | 2 (1.9%)   |
| NRTI + bPI + INSTI     | 2 (1.9%)   |
| 2 NRTIs + NNRTI + bPI  | 3 (2.9%)   |
| ANTCCR5 + bPI          | 3 (2.9%)   |
| 3 NRTIs + bPI          | 9 (8.7%)   |
| bPI + INSTI            | 10 (8.9%)  |
| 2 NRTIs + bPI          | 29 (27.9%) |
| 2 NRTIs + NNRTI        | 35 (33.7%) |

DT: dual therapy; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; bPI: ritonavir boosted protease inhibitor; INSTI: integrase strand transfer inhibitor; ANTCCR5: CCR5 antagonist.

Table 3

| Variable | Overall | Switch group | Virologic group | p-value |
|----------|---------|--------------|-----------------|---------|
| Viral load at 24 weeks (n = 116) |         |              |                 |         |
| <50      | 110 (94.8%) | 67 (99%)     | 43 (90%)        | 0.08    |
| >200     | 6 (5.2%)   | 1 (1%)       | 5 (10%)         |         |
| Viral load at 48 weeks (n = 112) |         |              |                 |         |
| <50      | 103 (91.9%) | 63 (97%)     | 40 (85%)        | 0.054   |
| 50-200   | 2 (1.7%)   | 0 (0%)       | 2 (4%)          |         |
| >200     | 7 (6.2%)   | 2 (3%)       | 5 (11%)         |         |

Considering efficacy, overall high rates of virologic suppression were observed in both groups, with a trend to higher suppression rates in the SG at 48 weeks. This difference may be potentially attributable to more frequent of adherence issues, higher burden of drug resistance in the VG, and to the fact that no patient in this group had virologic suppression prior to DT initiation. Of note, in addition to comorbid conditions,
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