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

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 cell/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

RESUMEN

Objetivo. Existen combinaciones genéricas de dosis fija (FDC) de darunavir/ritonavir (DRV/r) en Argentina. Las experiencias con estas FDCs en terapia dual siguen siendo limitadas. Nuestro objetivo fue describir los resultados clínicos y virológicos en pacientes expuestos a FDC DRV/r + raltegravir (RAL) 400 mg cada 12 h en la práctica clínica.


Resultados. De 7,380 pacientes en tratamiento antirretroviral (TAR), 116 (1.5%) recibieron FDC DRV/r + RAL, siendo 58% en GC. Seis décimas recibieron DRV/r 800/100 mg (resto, 600/100 mg). La mediana (IQR) de edad y de CD4+ T-células fue: 52 (42–58) años, y 373 células/µL (202–642). Ciento nueve por ciento eran ART-experimentados con una mediana de 3 (IQR 2–5) tratamientos previos. Las razones para el cambio (GC) fueron principalmente: “RENAL” (57%), cardiovascular (54%) y osteoporóticas (14%). La mediana de exposición a DRV/r + RAL fue 18 meses. En GC, 98% y 96% tuvieron CV indetectable a 6 y 12 meses; en GV, 89% y 87% a 6 y 12 meses. Ningún paciente requirió suspensión debido a toxicidad o intolerancia.

Conclusión. En esta cohorte de pacientes experimentados en TAR, la FDC DRV/r + RAL fue eficaz y segura. Dicha terapia puede considerarse una opción para pacientes con comorbilidades y/o VIH multirresistente.

Palabras clave: Infección por VIH, terapia antirretroviral, terapia dual
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 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-naive 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.

PATIENTS AND METHODS

We performed an observational retrospective cohort study carried out in a reference private center dedicated to the care of people living with HIV based in in Buenos Aires city, Argentina, with a network all over the country. The DT regimen was chosen on routine clinical practice basis by an infectious disease’s specialist considering prior ART exposure, cumulative resistance profile, comorbidities, co-medication, history of adherence and tolerability to antiretrovirals, VL and CD4-T cell count.

The inclusion criteria were the following: HIV-infected patients older than 18 years, assisted in our institution network between January 2014 and December 2018, who have received DT with DRV/r + RAL for at least 24 weeks. Patients with evidence of resistance to DRV or RAL, active hepatitis B or pregnancy, or insufficient clinical and/or analytical information were excluded.

The information was obtained from the electronic medical records (Infhos® database). Data were retrospectively collected from the introduction of the DT until the last follow-up routine visit available within the study timeframe. Data collection included demographic and clinical variables (prior ART, clinical reason for indication, adverse events, virological and immunological response at 24 and 48 weeks after DT prescription). Individuals were classified as:

- **Switch group (SG):** suppressed patients (undetectable viral load) who switched due to toxicity or comorbidities and
- **Virologic group (VG):** HIV-infected patients with detectable viremia and infection by multidrug-resistant HIV (resistance to at least 2 drug classes)

**Statistical analysis.** For data analysis, categorical variables were described using absolute and relative frequencies and compared by χ² test or Fisher’s exact test according to expected values. Continuous variables were described using medians and interquartile ranges (IQR) and compared by t-test or Mann-Whitney test according to normality of variables. A two-sided p-value of <0.05 was considered significant.

**RESULTS**

Of 7,380 HIV-infected patients on ART in our institution, 236 (3.19%) received DT and 116 received FDC DRV + 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-
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Recombinant. 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.

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].

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<p>| Table 1 | Demographic and immunovirological profile of 116 HIV-infected patients under dual therapy (DT) with a generic fixed dose combination of DRV/r + RAL in Argentina (2014-2018). Values are number (percentages) unless otherwise stated. Switch and virologic groups are compared. |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall N=116</th>
<th>Switch group n=68</th>
<th>Virologic group n=48</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (IQR)</td>
<td>52 (42-58)</td>
<td>54.5 (49-60)</td>
<td>43 (32.5-52.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35 (30.2%)</td>
<td>18 (26%)</td>
<td>17 (35%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Male</td>
<td>81 (69.8%)</td>
<td>50 (74%)</td>
<td>31 (65%)</td>
<td></td>
</tr>
<tr>
<td>CDC category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>19 (16.4%)</td>
<td>12 (18%)</td>
<td>7 (15%)</td>
<td>0.30</td>
</tr>
<tr>
<td>B</td>
<td>44 (37.9%)</td>
<td>28 (43%)</td>
<td>15 (31%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>53 (45.7%)</td>
<td>27 (40%)</td>
<td>26 (54%)</td>
<td></td>
</tr>
<tr>
<td>Months in ART pre-DT, median (IQR)</td>
<td>144 (75-228)</td>
<td>180 (108-240)</td>
<td>120 (36-180)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of ART regimens, median (IQR)</td>
<td>3 (2-5)</td>
<td>4 (3-6)</td>
<td>2.5 (1-4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Months with viral load ≤50 copies/mL before DT, median (IQR)</td>
<td>11 (0-60)</td>
<td>48 (23-108)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of previous virologic failures, median (IQR)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>0.047</td>
</tr>
<tr>
<td>CD4+ (cell/uL) count before DT, median (IQR)</td>
<td>343 (196-646)</td>
<td>454 (338-772)</td>
<td>210 (106-407)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Viral load (copies/mL) pre DT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>64 (55.2%)</td>
<td>64 (94%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50-200</td>
<td>4 (3.4%)</td>
<td>2 (3%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>&gt;200</td>
<td>48 (41.4%)</td>
<td>2 (3%)</td>
<td>46 (96%)</td>
<td></td>
</tr>
<tr>
<td>Time in DT, months, median (IQR)</td>
<td>17 (10-25)</td>
<td>18.5 (9-25.5)</td>
<td>15.5 (10-24)</td>
<td>0.718</td>
</tr>
</tbody>
</table>

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].

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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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None to declare.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

REFERENCES


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