Efficacia e sicurezza dello switch a dolutegravir + doravirina in persone con HIV pesantemente pretrattate, con comorbidità non-infettive e HIV-RNA non rilevabile: una serie di casi.

Efficacy and safety of switching to dolutegravir plus doravirine in heavily pre-treated people living with HIV and non infectious comorbidities with undetectable HIV-RNA: a case series.

Stefano Ruiu, Alessandra Bitti, Andrea De Vito, Agnese Colpani, Beatrice Zauli, Maria Chiara Meloni, Marco Fois, Sara Bacciu , Giulia Moi, Francesca Cherchi and Giordano Madeddu

Unit of Infectious Diseases, Department of Medicine, Surgery and Pharmacology, University of Sassari, Sassari.

Autore per la corrispondenza:

Prof. Giordano Madeddu
Unit of Infectious Diseases, Department of Medicine, Surgery and Pharmacy
University of Sassari
Viale San Pietro 35,
07100 Sassari
Tel: +39 0792644529

giordano@uniss.it

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Riassunto

Le persone che vivono con l'HIV/AIDS (PWH) che hanno accesso alla terapia antiretrovirale (ART) e raggiungono la soppressione della carica virale plasmatica ora hanno un'aspettativa di vita quasi normale. Nelle linee guida attuali per il trattamento, i profili degli effetti collaterali giocano un ruolo significativo nella considerazione di farmaci specifici. Accanto al miglioramento della tollerabilità delle singole sostanze, c'è un crescente interesse nell'utilizzare regimi a due farmaci (2DR) invece delle tradizionali combinazioni a tre farmaci per ridurre la tossicità a lungo termine. L'uso dei 2DR potrebbe contribuire a minimizzare gli effetti collaterali a lungo termine rispetto alle combinazioni tradizionali a tre farmaci. Il regime dolutegravir (DTG) + doravirina (DOR) potrebbe essere particolarmente utile per i pazienti che necessitano di un regime che mantenga un'elevata efficacia virologica riducendo al contempo la tossicità complessiva e il carico farmacologico. In questa serie di casi, presentiamo tre casi clinici di PWH che sono passati a DTG + DOR.

Abstract

People living with HIV/AIDS (PWH) who have access to antiretroviral therapy (ART) and achieve suppression of plasma viral load (VL) now have an almost normal life expectancy. In current treatment guidelines, side effect profiles play a significant role in considering specific drugs. Alongside improved tolerability of individual substances, there is a growing interest in using two-drug regimens (2DR) instead of traditional three-drug combinations to reduce long-term toxicity.

The use of 2DRs may help minimize long-term side effects compared to traditional three-drug combinations. Dolutegravir (DTG) + doravirine (DOR) may be particularly useful for patients who require a regimen that maintains high virological efficacy while reducing overall toxicity and pharmacological burden. In this case series we present three clinical cases of PWH who switched to DTG + DOR.

Background

People living with HIV/AIDS (PLWH) who have access to antiretroviral therapy (ART) and achieve suppression of plasma viral load (VL) now have an almost normal life expectancy.

In current treatment guidelines, side effect profiles play a significant role in considering specific drugs. Alongside improved tolerability of individual substances, there is a growing interest in using twodrug regimens (2DR) instead of traditional three-

drug combinations to reduce long-term toxicity. Dolutegravir (DTG) is an integrase inhibitor (INSTI) known for its excellent potency, safety, and longterm tolerability in both triple and 2DR switch studies (1- 4). Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with a moderate genetic barrier and a favorable metabolic profile (5-6). The individual efficacy of both DTG and DOR suggests that combining these two molecules as part of an NRTI-sparing regimen could be a viable option. The use of 2DRs may help minimize long-term side effects compared to traditional three-drug combinations. In this context, DOR + DTG may be particularly useful for heavily pre-treated PWH who require a regimen that maintains high virological efficacy while reducing overall toxicity and pharmacological burden (7-8).

Results

In this series, we report the clinical cases of three PLWH followed up in our outpatient clinic for a long-lasting HIV infection.

The first is a 59-year-old man sent for an outpatient visit in 1989 following a positive HIV test. The first available viremia assessment revealed a viral load of 56,000 copies/ml, with a CD4 count of 410 cells/mm³.

After several ART regimens and virological falilures, in 2020 he began a treatment regimen with darunavir/cobicistat (DRV/c) 150/800 mg daily + DTG 50 mg daily, achieving good viro-immunological control. However, during the hematological and biochemical checks in October 2021, there was a progressive worsening of the lipid profile, even if atorvastatin 40 mg daily was prescribed by his general practitioner, due to the presence of an atheromasic plaque at the common carotid in a heavy smoker. His historic resistance genotype showed the presence of K65R, K103N and M184V.

As a result, DRV/c was replaced with DOR 100 mg daily, given its better metabolic safety profile and higher genetic barrier compared to other NNRTIs.

From then on, his HIV-RNA remained undetectable, accompanied by an improvement in lipid profile. At the last checkup on January 2024, virological suppression and good lipid control were confirmed (total cholesterol 145 mg/dl, triglycerides 88 mg/dl and HDL 49 mg/dl), as shown in **Figure 1**.

The second case is a 60-year-old woman, who was diagnosed with HIV in 1989. She was admitted to our ward in 2003 due to Pneumocystis jiroveci pneumonia and had a CD4 count of 55 cells/mm³. She now has arterial hypertension treated with

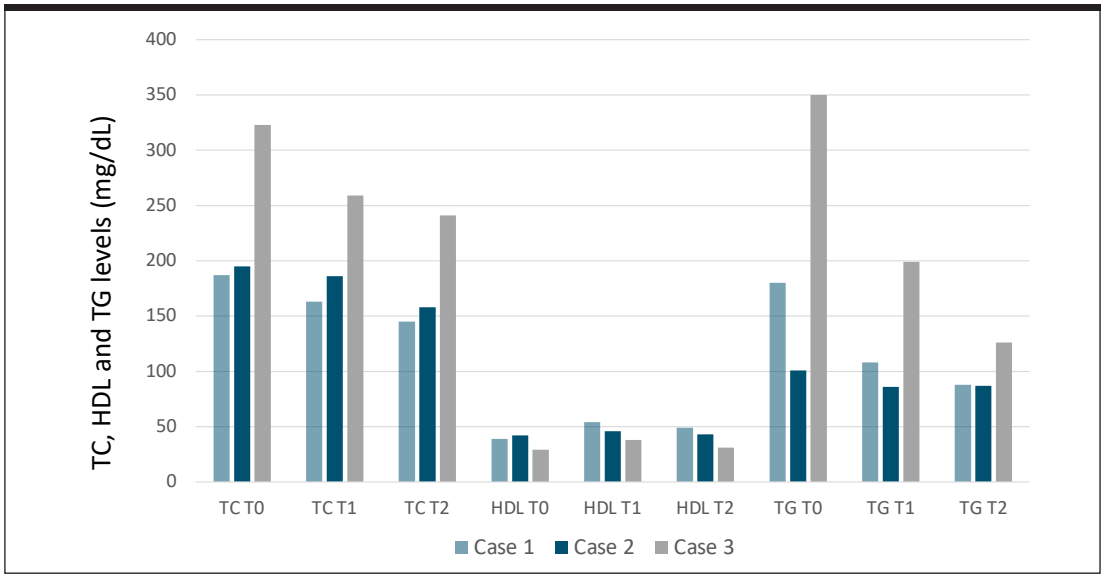

Figure 1. Changes in lipid profile during follow up in three people with HIV receiving dolutegravir + doravirine. **TC:** total cholesterol, **HDL:** high density lipoprotein, **TG:** triglycerides. **T0:** baseline value; **T1:** after one year from switch; **T2:** after two years from switch.

ramipril/hydrochlorothiazide and is a cigarette smoker. She underwent several complex antiretroviral therapy regimens due to virological failures.
In 2020, she started a dual regimen including raltegravir (RAL) 1200 mg daily + DRV/ritonavir 600 mg 100 mg twice a day, maintaining virological suppression. In May 2022, she requested a further simplification of her treatment.
After evaluating her clinical history and resistance profile (RT mutations: L74V, V90I, K103N, M184V, G190A), it was decided to simplify her therapy to DTG + DOR. Since then, she has maintained a good viro-immunological profile. At the last checkup on October 2023, virological suppression and good lipid control were confirmed (total cholesterol 158 mg/dl, triglycerides 87 mg/dl, HDL 43 mg/dl) without the need to prescribe a statin. Her last HIV-RNA was not detectable and her CD4 cell count was 924 cells/mm^3 (22%).
The last case is a 75-year-old man, with a long history of HIV infection with several admissions to our Day Hospital due to HIV infection, acute renal insufficiency on top of chronic kidney disease (with creatinine levels up to 3.56 mg/dl) and COPD.
On April 29, 2022, he underwent a therapeutic switch for simplification from a combination therapy of DRV 600 mg twice daily + RTV 100 mg twice daily + RAL 1200 mg daily to DTG+ DOR. This switch aimed to achieve better control of his lipid profile also considering that he was intolerant to statins. In the previous blood tests, his total cholesterol was 323 mg/dL, triglycerides were 350 mg/dL, and HDL cholesterol was 29 mg/dL. Subsequent tests, the ones on September 5, 2022, showed excellent control of his viro-immunological profile with an undetectable HIV-RNA and CD4 count of 1423 cells/mm^3, along with a slight improvement in lipid levels. At the last available visit on October 2023, his total cholesterol was 241 mg/dl, HDL 38 mg/dl, and triglycerides 126 mg/dl.
Furthermore, his CD4 cell count was 1202 cells/mm^3 (39,8%) and his CD4/CD8 ratio was 1.06.
Interestingly, even if receiving an INSTI, all patients lost body weight during follow-up without changing their eating habits (**Figure 2**).

Discussion

We have described three cases of PWH who switched to a dual combination of DTG + DOR in real life. All patients were heavily pre-treated, with several comorbidities, maintained their undetectable HIV-RNA, and showed an improvement in their

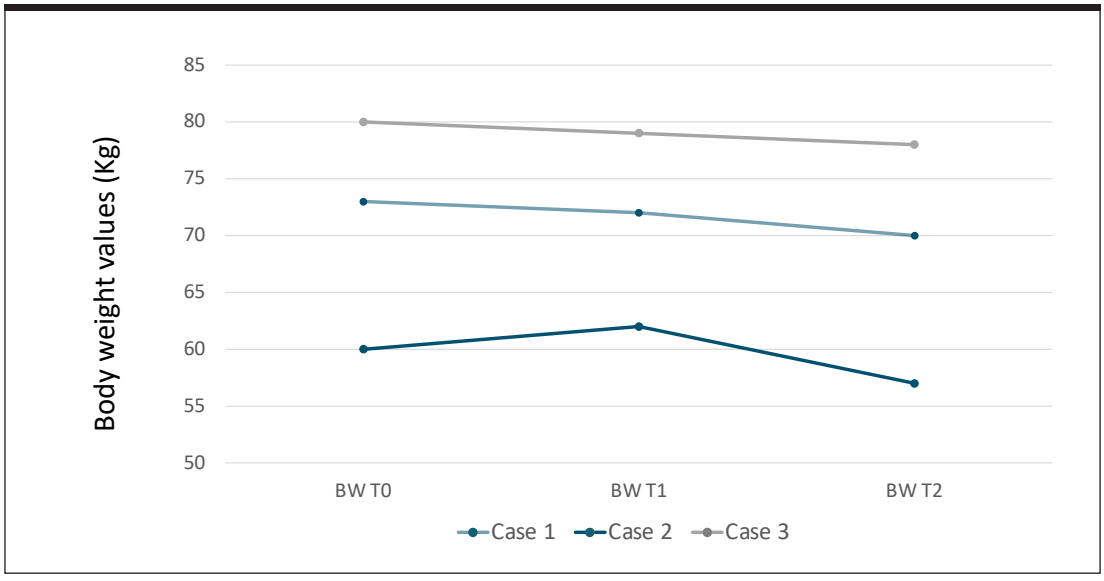

Figure 2. Changes in body weight (BW) during follow up in three people with HIV receiving dolutegravir + doravirine. **T0:** baseline value; **T1:** after one year from switch; **T2:** after two years from switch.

lipid profile. Studies regarding the role of both DTG and DOR have been published. However, real-life data on the role of DTG+DOR in maintaining virologic suppression in heavily pre-treated PWH while achieving an improvement in their lipid profile are scarce.

When considering the switch to DTG + NNRTI (rilpivirine, RPV) dual therapy in PWH with undetectable HIV-RNA, the SWORD studies have demonstrated a durable viral suppression and improvement in renal and bone biomarkers, and a neutral impact on lipid profile up to week 148 (1). Furthermore, Lagi et al showed that the efficacy and safety of DTG + RPV was confirmed in an observational cohort and was comparable to that of DTG + lamivudine (9).

Mazzitelli et al. retrospectively investigated the rationale for switching people with HIV to DOR-containing regimens in a real-life cohort. Among 132 patients, the main reasons to start DOR were prevention of toxicities (39.4%) and dyslipidemia (18.2%). DOR was combined with integrase inhibitors in 40.9% of cases, and in 25.7% of patients, DOR was prescribed without the availability of a genotypic resistance test. Twenty-four weeks after the switch to DOR-containing regimens, a significant reduction in lipids (both cholesterol and triglycerides) was observed in 52 patients for whom a follow-up assessment was available. Their data confirmed that switching to DOR-containing regimens may have a favorable impact on lipid profile and a neutral impact on weight gain. However, they acknowledged that more data are needed to support its use in patients who do not have a genotypic test available or have extensive nonnucleoside reverse-transcriptase inhibitors-associated resistance, as well as its use in a dual regimen, especially in combination with second-generation integrase inhibitors (8).

A further prospective observational study has been conducted by Maggi et al., aiming to investigate, in a real-life setting, how switching to a DOR-base regimen rather than an RPV-based regimen impacted metabolic and hepatic safety. The analysis included 551 antiretroviral ART-experienced PLWH, starting RPV-based or DOR-based ergimens with viral load < 200 copies/mL, baseline, and at least one 6-month control visit. Two hundred and ninety- five PWH in the RPV and 256 in the DOR cohort were enrolled. Total cholesterol (TC), low-density lipoprotein-C (LDL-C), and triglycerides significantly decreased in both DOR and RPV cohorts, while high-density lipoprotein-C (HDL-C) only decreased in RPV-treated people. Consistently, the TC/HDL-C ratio declined more markedly in the DOR than in the RPV cohort (6).

More recently, a prospective observational study followed PWH receiving DTG + DOR as a 2DR. Participants had extensive antiretroviral history, and the main reasons for choosing this combination were drug-drug interactions (DDI), tolerability, and cardiovascular risk reduction. DTG + DOR demonstrated durability even in extensively pretreated individuals, with most participants remaining on this regimen for an extended period (10).

In conclusion, even if further and larger studies are needed, our cases suggest that dolutegravir plus doravirine could represent a promising alternative for PWH with extensive therapeutic history and non-infectious comorbidities, balancing efficacy, safety, and long-term tolerability while minimizing the number of drugs in their regimen.

Conflict of interest

GM has received speaker fees and acted as an advisor for ViiV healthcare, MSD and Gilead sciences, all the other authors declare no conflict of interest. ■

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