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Characterization of People Receiving 2-Drug Regimens (2DR) for HIV Management in Italy

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Two-Drug Regimens for HIV Management in Italy

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Abstract

Objective

To describe the clinical features and real-world treatment of people living with human immunodeficiency virus (PLHIV) using fixed-dose or free combinations of 2-drug regimens (2DR) of antiretroviral therapy (ART).

Design

Italian retrospective cohort study.

Methods

Data were extracted from PLHIV who initiated or switched to 2DR: Group 1 (fixed dose), Group 2 (free combination).

Results

Group 1 was younger and more predominantly male, and had shorter time from AIDS-defining diagnosis to 2DR-ART and from diagnosis to baseline, a lower prevalence of resistance, and fewer comorbidities than Group 2. Median baseline viral load was <50 copies/mL in both groups, but Group 1 had a higher mean due to outliers.

The most common ART classes before switching to 2DR were Integrase Strand Transfer Inhibitor (INSTI)-based (48.97%), Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based (22.73%), and Protease Inhibitor (PI)-based (16.53%). Distribution varied: Group 1: INSTI-based (53.13%), NNRTI-based (24.31%), and PI-based (15.04%); Group 2: INSTI-based (29.41%), PI-based (23.53%), and NNRTI-based (15.29%).

After switching, Group 1 was on dolutegravir/lamivudine (79,33%) and dolutegravir/rilpivirine (20,67%); Group 2 mostly on INSTI-PI (52.81%), followed by NNRTI combinations, mainly with doravirine (19.10%). Duration of ART after switching was shorter in Group 1.

Conclusion

Italian PLHIV on 2DR fixed-dose combinations were younger, virologically suppressed individuals at baseline, with a shorter lead time from diagnosis, lower prevalence of resistance and lower comorbidity rate compared to those on free combinations. These findings underscore an unmet need for 2DR fixed-dose combinations, as the free combinations were predominantly utilized for more challenging populations.

Introduction

Three-drug antiretroviral regimens (ARV) have long been the “gold standard” first-line therapy for adult people living with human immunodeficiency virus (PLHIV) [1]. However, concerns about long-term toxicities have prompted the investigation of two-drug regimens (2DR) as an alternative treatment option [2], and current EACS guidelines also recommend 2DRs [3].

Preliminary trials on early 2DR combinations for treatment-naive populations produced inconclusive outcomes due to limited sample sizes, restricted treatment options, and short durations of therapy [4]. NEAT001/ANRS143, perhaps the first true trial of dual strategy, concluded that treatment of treatment-naïve PLHIV with 400 mg raltegravir (RAL) twice daily plus 800 mg darunavir and 100 mg ritonavir (DRV/r 800/100 mg) once daily as Nucleoside Reverse Transcriptase Inhibitor (NRTI)-sparing regimen was not inferior to DRV/r 800/100 mg once daily plus tenofovir disoproxil-emtricitabine (TDF/

FTC) in a 245 mg and 200 mg fixed-dose combination (FDC) [5].

Lamivudine (3TC) has demonstrated favorable efficacy and safety, positioning itself as a candidate for combination therapy [6]. However, early studies involved the use of 3TC with ritonavir-boosted protease inhibitors (PIs), which have been associated with metabolic adverse reactions and drug interactions. These potential drawbacks may counteract benefits expected from reduced cumulative toxicity due to decreased drug exposure [7].

Phase 3 clinical trials have yielded evidence that dolutegravir (DTG) is a promising candidate as a central component in 2DRs. The GEMINI studies support DTG/3TC as a well-tolerated option in treatment-naive PLHIV [8].

The phase III SWORD trials evaluated the efficacy and safety of once-daily dolutegravir 50 mg plus rilpivirine 25 mg (DTG/RPV) versus current ART regimen (CAR), and found DTG/RPV to be not inferior, with 95% of PLHIV in both groups achieving undetectable viremia [9].

The Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) doravirine (DOR) is available both as single drug for combination and as 3-drug FDC with tenofovir disoproxil fumarate (TDF) and 3TC. Evidence for its safe and effective use is available from randomized trials [10–12], and doravirine is now among the recommended drugs for first-line ART. Doravirine has little cross resistance to other NNRTI in addition to a relatively high resistance barrier [13] and can be an option for PLHIV with extensive ART history.

Sammet et al. conducted a prospective observational study of PLHIV treated with DOR + DTG as 2DR. The main reasons for choosing DOR + DTG were drug-drug interactions (DDI) (29%), tolerability (25%), and cardiovascular risk reduction (21%). DOR + DTG proved to be a durable treatment option even in extensively pretreated individuals [14].

DOR is currently under evaluation as an FDC with islatravir [15].

In Italy, a significant proportion of PLHIV is treated with 2DR, but the factors influencing this choice are still unclear [16], as well as whether the approval of 2DR FDC leads to changes regarding patient types and treatment decisions. A better understanding of patient characteristics would help to highlight residual unmet needs in modern HIV management strategies. Consequently, this study aimed to describe the baseline patient characteristics for approved FDC and free-combination dual therapies to recognize the drivers of therapeutic decisions for 2DR.

Methods

Study design and population

We conducted a retrospective medical chart review across 10 sites in Italy From 13-May-2021 to 7-July -2022. Data from 505 adult PLHIV who initiated or switched to 2DR antiretroviral therapy (ART) within the last 5 years were collected. The ART regimen had to include dual therapy based on approved fixed-dose combinations, such as DTG/RPV and DTG/3TC or any free combination dual therapy (at least one ARV drug from NNRTI, PI or Integrase Strand Transfer Inhibitor [INSTI] class of ARV drugs). No other inclusion/exclusion criteria were applied.

Eligible PLHIV were stratified in two groups: Group 1 included PLHIV who initiated or switched to approved FDC, while Group 2 included those who initiated or switched to any free-combination dual therapy.

Outcomes

The primary outcome was the baseline patient profiles in each study group. The primary analysis included demographic data, natural history of HIV acquisition, clinical presentation, drug management before and after switching/starting 2DR, and selected concomitant non-ARV medication and comorbidities.

The secondary outcome was to describe patient profiles at baseline in subgroups of PLHIV according to previous HIV medication use at index date (treatment-naïve, switching from monotherapy to 2DR, from 2DR to 2DR, from three-drug regimen (3DR) to 2DR, and from 4+DR to 2DR). The exploratory outcome was to compare the patient profiles of these subgroups. All patient profiles were analyzed except drug management before and after switching/starting 2DR.

The study also assessed the evolution/difference in the population who switched/started 2DR over time (per year and stratification group).

Variables

Variables included demographics, history of HIV acquisition, clinical presentation, drug management before initiating/switching to 2DR, comorbidities, and concomitant non-ARV medication at baseline.

History of HIV acquisition is described as age at first AIDS-defining diagnosis, time from AIDS-defining diagnosis to start/switch to 2DR, and years of known HIV status at baseline. Clinical signs focus on CD4+ count/HIV viral load (VL) at baseline. Comorbidities include cardiovascular, lipid, CNS, and liver disorders, and diabetes mellitus.

Drug management before switching/starting 2DR at index date is categorized by ART class (NRTI, NNRTI, PI, INSTI and other). Drug management after switching/starting 2DR focuses on the ART regimen at index date, and is described as the proportion of PLHIV who switched to a 2DR therapy regimen in the last 5 years and the proportion of PLHIV using each combination.

Concomitant non-ARV medications at baseline are described for PLHIV who initiated or switched to 2DR ART.

Ethics

The study protocol was reviewed by the local Health Authority. Approvals were obtained from the Ethics Committee of participating sites. Informed consent, as appropriate per local regulations, was obtained from all participants.

Statistical analysis

All statistical analyses were performed on SAS version 9.4. All variables were analyzed descriptively. Continuous data are summarized by mean, standard deviation, median, first and third quartile, minimum and maximum. Confidence Intervals (CI) (95%) are provided for each variable in groups/subgroups with more than 5 PLHIV. The exact method in case of dichotomic variables or the Goodman's method in case of multiple categories was applied for proportions. Comparisons between stratification groups correspond to the primary analysis, and those between subgroups within stratification group to the secondary analysis.

Categorical data are presented by absolute and relative frequencies or contingency tables following the χ^2 or Fisher's exact test. Continuous data were compared using a two-sided Student's t-test or a two-sided Wilcoxon's rank-sum test. If the comparison involved more than two groups, ANOVA or the corresponding non-parametric Kruskal-Wallis test was used.

The evolution/difference in the population who switched /started 2DR over time based on the year of

index date and stratification group is summarized. Assessment of the evolution of the 2DR populations was performed using contingency table analysis with Cochran-Armitage test for trend.

Results are based on non-missing data only (i.e., missing observations were not replaced). Participants were included in each analysis based on available assessments.

Results

Study sample

A total of 505 PLHIV charts were screened and underwent data collection. Among these, 416 received approved FDC (Group 1), while 89 received a free combination (Group 2). All were valid for analysis.

Primary analysis

The primary objective was to describe the profiles of PLHIV belonging to Group 1 and to Group 2.

Demographic overview

Overall, average age was 49.9 ± 11.96 years, and most PLHIV were male (78.22%). Group 1 was younger (49.2 ± 12.07 years vs 53.3 ± 10.87 years) and more predominantly male (81.73% vs 61.80%; p-value< 0.0001). There was no significant difference in the distribution of race and ethnicity between the two groups, with the majority of PLHIV being white (89.50%) and non-Hispanic or non-Latino (83.56%) (Table 1).

History of HIV acquisition

Overall, time from first AIDS-defining diagnosis to the start/switch to 2DR was 13.8 ± 9.16 years, and years since diagnosis of HIV acquisition 13.4 ± 9.13 at the switch to 2DR. Group 1 had a shorter time from first AIDS-defining diagnosis to the start/switch to 2DR therapy (Group 1: 13.0 ± 8.60 years; Group 2: 17.9 ± 10.55 years; p-value < 0.0001) and fewer years of HIV acquisition at baseline (Group 1: 12.5 ± 8.56 years; Group 2: 17.6 ± 10.52 years; p-value< 0.0001) (Table 1).

Table 1. Demographic overview and prior AIDS defining diagnosis

	Group 1: approved fixed-dose combinations (N=416)	***Group 2: free combination dual therapy (N=89)***	***Total (N=505)***
Demographic overview			
Age at index date (years)			
Mean (SD)	49.2 (12.07)	53.3 (10.87)	49.9 (11.96)
Comparison of age:			
p-value (Wilcoxon Test)			0.0038
Sex, n (%) [95% CI]			
Male	340 (81.73) [77.68; 85.33]	55 (61.80) [50.89; 71.90]	395 (78.22) [74.36; 81.74]
Female	76 (18.27) [14.67; 22.32]	34 (38.20) [28.10; 49.11]	110 (21.78) [18.26; 25.64]
Comparison of sex:			
p-value (Chi-Square Test)			<.0001
Race, n (%) [95% CI]			

White	369 (88.70) [84.08; 92.11]	83 (93.26) [83.00; 97.51]	452 (89.50) [85.47; 92.52]
Black or African American	24 (5.77) [3.46; 9.47]	4 (4.49) [1.35; 13.96]	28 (5.54) [3.45; 8.79]
Asian	3 (0.72) [0.18; 2.81]	0 (0.00)	3 (0.59) [0.15; 2.32]
Not reported	12 (2.88) [1.40; 5.85]	1 (1.12) [0.13; 8.90]	13 (2.57) [1.28; 5.09]
Other	8 (1.92) [0.80; 4.56]	1 (1.12) [0.13; 8.90]	9 (1.78) [0.78; 4.04]
Comparison of race:			
p-value (Fisher's Exact Test)			0.9188
Ethnicity, n (%) [95% CI]			
Hispanic or Latino	40 (9.62) [6.58; 13.84]	8 (8.99) [3.88; 19.47]	48 (9.50) [6.72; 13.28]
Non-Hispanic or non-Latino	343 (82.45) [77.32; 86.62]	79 (88.76) [77.75; 94.70]	422 (83.56) [79.04; 87.27]
Not reported	28 (6.73) [4.26; 10.48]	1 (1.12) [0.14; 8.51]	29 (5.74) [3.66; 8.91]
Unknown	5 (1.20) [0.41; 3.43]	1 (1.12) [0.14; 8.51]	6 (1.19) [0.45; 3.12]
Comparison of ethnicity:			
p-value (Fisher's Exact Test)			0.1578
Prior AIDS defining diagnosis			
Age at first AIDS-defining diagnosis (years)			
Mean (SD)	36.2 (11.00)	35.4 (12.64)	36.1 (11.30)
Comparison of age at first AIDS -defining diagnosis:			
p-value (Wilcoxon Test)			0.3421
Time from AIDS-defining diagnosis to start/switch to 2DR (years)			
Mean (SD)	13.0 (8.60)	17.9 (10.55)	13.8 (9.16)
Comparison of time from AIDS-defining diagnosis to start/ switch to 2DR:			
p-value (Wilcoxon Test)			<.0001
Years of known HIV status at baseline			
Mean (SD)	12.5 (8.56)	17.6 (10.52)	13.4 (9.13)
Comparison of years of known HIV status at baseline:			
p-value (Wilcoxon Test)			<.0001
Years of known HIV status at baseline, n (%) [95% CI]			
0-5 years	98 (23.56) [18.64; 29.31]	15 (16.85) [9.03; 29.28]	113 (22.38) [17.97; 27.49]
6-10 years	101 (24.28) [19.30; 30.07]	16 (17.98) [9.84; 30.55]	117 (23.17) [18.70; 28.33]

11-15 years	89 (21.39) [16.69; 27.00]	8 (8.99) [3.78; 19.89]	97 (19.21) [15.10; 24.11]
16-20 years	55 (13.22) [9.52; 18.08]	14 (15.73) [8.23; 27.99]	69 (13.66) [10.20; 18.07]
21 years and more	73 (17.55) [13.26; 22.85]	36 (40.45) [28.17; 54.06]	109 (21.58) [17.25; 26.65]
Comparison of years of known HIV status at baseline:			
p-value (Chi-Square Test)			<.0001

Drug management before switching/starting 2DR

Overall, the most common ART used before switching to 2DR was INSTI-based (combined with NRTIs) (48.97%), with dolutegravir/lamivudine/abacavir (DTG/3TC/ABC) as the most frequent combination (21.69%), followed by NNRTI-based (22.73%), with rilpivirine/emtricitabine/tenofovir alafenamide (RPV/FTC/TAF) as the most common (11.78%), and by PI-based 3DR (16.53%), with darunavir/ cobicistat/emtricitabine/tenofovir alafenamide (DRV/c/FTC/TAF) as the most common (4.13%). Distribution varied between the two groups: Group 1 was INSTI-based (53.13%), NNRTI-based (24.31%), and PI-based (15.04%), while Group 2 was INSTI-based (29.41%), PI-based (23.53%), and NNRTI-based (15.29%).

The most frequent ARTs at baseline were DTG/3TC/ABC (25.06%), RPV/FTC/TAF (13.28%) and bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) (9.27%) in Group 1; raltegravir (RAL) (8.24%), RAL + DRV/b (7.06%), DTG/3TC/ABC (5.88%), and RPV/FTC/TAF (4.71%) in Group 2 (Table 2).

Table 2. Prior antiretroviral therapy before switching to 2DR therapy – all medications; Enrolled population

	Group 1: approved fixed-dose combinations (N=416) n (%)	**Group 2: free combination dual therapy (N=89)**	**Total (N=505) n (%)**
Number of patients with at least one Prior medications before switching to 2DR therapy	399 (95.91) [93.54; 97.60]	85 (95.51) [88.89; 98.76]	484 (95.84) [93.71; 97.41]
Prior medication category (third agent class), n (%)			
INSTI based	212 (53.13) [41.51; 64.64]	25 (29.41) [9.51; 52.87]	237 (48.97) [38.43; 59.53]
NNRTI based	97 (24.31) [14.86; 34.77]	13 (15.29) [0.97; 35.63]	110 (22.73) [14.32; 32.03]
PI based	60 (15.04) [7.42; 24.04]	20 (23.53) [5.58; 46.06]	80 (16.53) [9.22; 24.93]
ENTRY INHIBITORS (EIs)	1 (0.25) [0.00; 2.76]	2 (2.35) [0.00; 14.76]	3 (0.62) [0.00; 3.27]
INSTI-NNRTI	7 (1.75) [0.00; 5.90]	3 (3.53) [0.00; 17.18]	10 (2.07) [0.00; 5.95]
INSTI-PI	5 (1.25) [0.00; 4.97]	16 (18.82) [2.79; 40.25]	21 (4.34) [0.72; 9.45]

NNRTI-PI	4 (1.00) [0.00; 4.48]	0 (0.00)	4 (0.83) [0.00; 3.70]
PI-EIs	0 (0.00)	1 (1.18) [0.00; 12.03]	1 (0.21) [0.00; 2.28]
INSTI-NNRTI-PI	0 (0.00)	1 (1.18) [0.00; 12.03]	1 (0.21) [0.00; 2.28]
NNRTI-PI--EIs	0 (0.00)	1 (1.18) [0.00; 12.03]	1 (0.21) [0.00; 2.28]
NRTI based	13 (3.26) [0.00; 8.40]	3 (3.53) [0.00; 17.18]	16 (3.31) [0.22; 7.92]
Prior medication category/ Preferred Term *			
INSTI based			
BIC/FTC/TAF	37 (9.27) [0.00; 30.77]	2 (2.35) [0.00; 29.71]	39 (8.06) [0.00; 26.46]
DTG	1 (0.25) [0.00; 5.42]	3 (3.53) [0.00; 35.13]	4 (0.83) [0.00; 7.87]
DTG/3TC	28 (7.02) [0.00; 26.16]	0 (0.00)	28 (5.79) [0.00; 21.77]
DTG/3TC/ABC	100 (25.06) [0.00; 56.14]	5 (5.88) [0.00; 44.03]	105 (21.69) [0.00; 48.71]
DTG+FTC/TAF	3 (0.75) [0.00; 8.34]	2 (2.35) [0.00; 29.71]	5 (1.03) [0.00; 8.73]
DTG+FTC/TDF	5 (1.25) [0.00; 10.53]	1 (1.18) [0.00; 22.97]	6 (1.24) [0.00; 9.54]
EVG-c/FTC/TAF	20 (5.01) [0.00; 21.62]	2 (2.35) [0.00; 29.71]	22 (4.55) [0.00; 18.96]
EVG-c/FTC/TDF	2 (0.50) [0.00; 7.03]	0 (0.00)	2 (0.41) [0.00; 5.82]
RAL	6 (1.50) [0.00; 11.50]	7 (8.24) [0.00; 51.47]	13 (2.69) [0.00; 14.18]
RAL+3TC/ABC	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
RAL+3TC/ZDV	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
RAL+FTC/TAF	5 (1.25) [0.00; 10.53]	1 (1.18) [0.00; 22.97]	6 (1.24) [0.00; 9.54]
RAL+FTC/TDF	1 (0.25) [0.00; 5.42]	1 (1.18) [0.00; 22.97]	2 (0.41) [0.00; 5.82]
RAL+unspecified	2 (0.50) [0.00; 7.03]	1 (1.18) [0.00; 22.97]	3 (0.62) [0.00; 6.91]
NNRTI based			
DOR/3TC/TDF	3 (0.75) [0.00; 8.34]	0 (0.00)	3 (0.62) [0.00; 6.91]
DOR+FTC/TAF	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]

EFV+3TC/ABC	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
EFV+FTC/TAF	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
EFV/FTC/TDF	9 (2.26) [0.00; 14.08]	3 (3.53) [0.00; 35.13]	12 (2.48) [0.00; 13.58]
ETR	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
NVP	2 (0.50) [0.00; 7.03]	0 (0.00)	2 (0.41) [0.00; 5.82]
NVP+3TC/ABC	7 (1.75) [0.00; 12.41]	1 (1.18) [0.00; 22.97]	8 (1.65) [0.00; 11.00]
NEV+3TC+D4T	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
NEV+FTC/TAF	4 (1.00) [0.00; 9.49]	0 (0.00)	4 (0.83) [0.00; 7.87]
NEV+FTC/TDF	1 (0.25) [0.00; 5.42]	1 (1.18) [0.00; 22.97]	2 (0.41) [0.00; 5.82]
RPV	2 (0.50) [0.00; 7.03]	0 (0.00)	2 (0.41) [0.00; 5.82]
RPV+3TC/ABC	3 (0.75) [0.00; 8.34]	0 (0.00)	3 (0.62) [0.00; 6.91]
RPV/FTC/TAF	53 (13.28) [0.00; 38.12]	4 (4.71) [0.00; 39.82]	57 (11.78) [0.00; 33.29]
RPV/FTC/TDF	9 (2.26) [0.00; 14.08]	2 (2.35) [0.00; 29.71]	11 (2.27) [0.00; 12.97]
RPV+unspecified	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
PI based			
ATVb	12 (3.01) [0.00; 16.37]	2 (2.35) [0.00; 29.71]	14 (2.89) [0.00; 14.76]
ATVb+3TC	4 (1.00) [0.00; 9.49]	0 (0.00)	4 (0.83) [0.00; 7.87]
ATVb+3TC/ABC	0 (0.00)	2 (2.35) [0.00; 29.71]	2 (0.41) [0.00; 5.82]
ATZb+3TC+TDF	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
ATZb+ABC+TDF	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
ATZb+FTC/TAF	3 (0.75) [0.00; 8.34]	1 (1.18) [0.00; 22.97]	4 (0.83) [0.00; 7.87]
DRVb	12 (3.01) [0.00; 16.37]	3 (3.53) [0.00; 35.13]	15 (3.10) [0.00; 15.32]
DRVb+3TC	2 (0.50) [0.00; 7.03]	2 (2.35) [0.00; 29.71]	4 (0.83) [0.00; 7.87]
DRVb+3TC/ABC	2 (0.50) [0.00; 7.03]	2 (2.35) [0.00; 29.71]	4 (0.83) [0.00; 7.87]

DRVb+3TC/ZDV	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
DRVb/FTC/TAF	17 (4.26) [0.00; 19.75]	3 (3.53) [0.00; 35.13]	20 (4.13) [0.00; 17.97]
DRVb+FTC/TDF	2 (0.50) [0.00; 7.03]	2 (2.35) [0.00; 29.71]	4 (0.83) [0.00; 7.87]
DRVb+TDF	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
DRVb+unspecified	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
LPVb	2 (0.50) [0.00; 7.03]	1 (1.18) [0.00; 22.97]	3 (0.62) [0.00; 6.91]
SQVb+3TC/ZDV	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
ENTRY INHIBITORS			
MVC	1 (0.25) [0.00; 5.42]	2 (2.35) [0.00; 29.71]	3 (0.62) [0.00; 6.91]
INSTI-NNRTI			
DTG+NVP	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
DTG/RPV	2 (0.50) [0.00; 7.03]	1 (1.18) [0.00; 22.97]	3 (0.62) [0.00; 6.91]
RAL+3TC+NVP	2 (0.50) [0.00; 7.03]	0 (0.00)	2 (0.41) [0.00; 5.82]
RAL+3TC+RPV	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
RAL+ETR	1 (0.25) [0.00; 5.42]	1 (1.18) [0.00; 22.97]	2 (0.41) [0.00; 5.82]
RAL+RPV	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
INSTI-PI			
DRVb/FTC/TAF+DTG	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
DTG+ATVb	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
DTG/3TC/ABC+ATVb	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
DTG+ATVb	1 (0.25) [0.00; 5.42]	1 (1.18) [0.00; 22.97]	2 (0.41) [0.00; 5.82]
DTG+DRVb	3 (0.75) [0.00; 8.34]	3 (3.53) [0.00; 35.13]	6 (1.24) [0.00; 9.54]
RAL+DRVb	1 (0.25) [0.00; 5.42]	6 (7.06) [0.00; 47.89]	7 (1.45) [0.00; 10.29]
RAL+FPVb	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]

RAL+FTC/TDF+LPVb	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
RAL+LPVb	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
NNRTI-PI			
DRVb+ETR	4 (1.00) [0.00; 9.49]	0 (0.00)	4 (0.83) [0.00; 7.87]
PI-ENTRY INHIBITORS			
DRVb+MVC	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
INSTI-NNRTI-PI			
DTG+not clear combination	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
NNRTI-PI-ENTRY INHIBITORS			
DRVb/RPV/MVC	0 (0.00)	1 (1.18) [0.00; 22.97]	1 (0.21) [0.00; 4.49]
NRTI based			
3TC	1 (0.25) [0.00; 5.42]	1 (1.18) [0.00; 22.97]	2 (0.41) [0.00; 5.82]
ABC/3TC	4 (1.00) [0.00; 9.49]	1 (1.18) [0.00; 22.97]	5 (1.03) [0.00; 8.73]
ABC/3TC/ZDV	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]
TAF/FTC	2 (0.50) [0.00; 7.03]	0 (0.00)	2 (0.41) [0.00; 5.82]
TAF/FTC	4 (1.00) [0.00; 9.49]	1 (1.18) [0.00; 22.97]	5 (1.03) [0.00; 8.73]
Missing	1 (0.25) [0.00; 5.42]	0 (0.00)	1 (0.21) [0.00; 4.49]

3TC = lamivudine, ABC = abacavir, ATC = Anatomical Therapeutic Chemical, ATV = atazanavir BIC = bictegravir, CI = Confidence Interval, DOR = doravirine, DRV = darunavir, DTG = dolutegravir, EFV = efavirenz, ETR = etravirine, EVG-c = elvitegravir-cobicistat, FTC = emtricitabine, INSTI = Integrase Strand Transfer Inhibitor, LPV = lopinavir, MVC = maraviroc, NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor, NRTI = Nucleoside Reverse Transcriptase Inhibitor, NVP = nevirapine, PI=Protease Inhibitor, RAL=raltegravir, RPV=rilpivirine, SQV=saquinavir, TAF=tenofovir alafenamide, TDF=tenofovir disoproxil fumarate, WHO = World Health Organization, ZDV = zidovudine

An individual could report more than one medication Entry Inhibitors-EIs.

95% CIs have been computed applying the Student's t distribution for the mean, the Goodman's method for multinomial proportions, and the exact method in case of dichotomic variables.

Drug management after switching/starting 2DR

After switching to 2DR therapy, Group 1 PLHIV were on DTG/3TC (INSTI-NRTI) (79.33%) and DTG/RPV (INSTI-NNRTI) (20.67%) combinations. Group 2 PLHIV were predominantly on INSTI-PI combination (52.81%), followed by NNRTI combinations, mainly with DOR (19.10%). The duration of the ART regimen after switching was shorter in Group 1 compared to Group 2 (9.6 ± 10.06 months vs 28.3 ± 20.30 months; p-value=0.0020) (Table 3).

Table 3. Antiretroviral therapy regimen-all medications; Enrolled Set

	Group 1: approved fixed-dose combinations (N=416) n (%)	**Group 2: free combination dual therapy (N=89) n (%)**	**Total (N=505) n (%)**
Patients who switched to a 2DR therapy regimen in the last 5 years	416 (100.00) [99.12; 100.00]	89 (100.00) [95.94; 100.00]	505 (100.00) [99.27; 100.00]
Drug combination, n (%) [95% CI]			
INSTI-NNRTI	91 (21.88) [17.01; 27.66]	13 (14.61) [7.32; 27.03]	104 (20.59) [16.26; 25.73]
INSTI-NRTI	322 (77.40) [71.57; 82.34]	8 (8.99) [3.71; 20.22]	330 (65.35) [59.59; 70.69]
INSTI-PI	0 (0.00)	47 (52.81) [39.16; 66.05]	47 (9.31) [6.43; 13.29]
NRTI-NNRTI	0 (0.00)	7 (7.87) [3.05; 18.79]	7 (1.39) [0.53; 3.56]
NRTI-PI	2 (0.48) [0.09; 2.50]	13 (14.61) [7.32; 27.03]	15 (2.97) [1.53; 5.69]
PI-NNRTI	1 (0.24) [0.03; 2.09]	1 (1.12) [0.13; 9.21]	2 (0.40) [0.07; 2.07]
Comparison of ART combination:			
p-value (Fisher's Exact Test)			<.0001
Duration of the ART regimen, months [a]			
n	9	22	31
Mean (SD)	9.6 (10.06)	28.3 (20.30)	22.9 (19.75)
95% CI	1.8; 17.3	19.3; 37.3	15.6; 30.1
Median	3.9	24	21.1
Q1; Q3	3.7; 14.4	11.1; 41.7	3.9; 37.8
Range	0; 30	1; 72	0; 72
Comparison of duration of ART regimen:			

p-value (T-Test)			0.002
Preferred Term			
Atazanavir	0 (0.00)	3 (3.37) [0.70; 9.54]	3 (0.59) [0.12; 1.73]
Atazanavir; cobicistat	0 (0.00)	3 (3.37) [0.70; 9.54]	3 (0.59) [0.12; 1.73]
Cobicistat; darunavir	0 (0.00)	41 (46.07) [35.44; 56.96]	41 (8.12) [5.89; 10.85]
Darunavir	0 (0.00)	13 (14.61) [8.01; 23.68]	13 (2.57) [1.38; 4.36]
Dolutegravir	0 (0.00)	55 (61.80) [50.89; 71.90]	55 (10.89) [8.31; 13.94]
DTG/3TC	330 (79.33) [75.11; 83.12]	0 (0.00)	330 (65.35) [61.02; 69.50]
DTG/RPV	86 (20.67) [16.88; 24.89]	0 (0.00)	86 (17.03) [13.85; 20.60]
DOR	0 (0.00)	17 (19.10) [11.54; 28.81]	17 (3.37) [1.97; 5.34]
ETR	0 (0.00)	1 (1.12) [0.03; 6.10]	1 (0.20) [0.01; 1.10]
3TC	0 (0.00)	28 (31.46) [22.03; 42.17]	28 (5.54) [3.72; 7.91]
NVP	0 (0.00)	1 (1.12) [0.03; 6.10]	1 (0.20) [0.01; 1.10]
RAL	0 (0.00)	13 (14.61) [8.01; 23.68]	13 (2.57) [1.38; 4.36]
RPV	0 (0.00)	3 (3.37) [0.70; 9.54]	3 (0.59) [0.12; 1.73]

3TC = lamivudine, CI = Confidence Interval, DOR = doravirine, DTG = dolutegravir, ETR = etravirine, INSTI = Integrase Strand Transfer Inhibitor, NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor, NRTI = Nucleoside Reverse Transcriptase Inhibitor, NVP = nevirapine, PI=Protease Inhibitor, RAL=raltegravir, RPV=rilpivirine.
An individual could report more than one medication Entry Inhibitors-EIs.
95% CIs have been computed applying the Student's t distribution for the mean, the Goodman's method for multinomial proportions, and the exact method in case of dichotomic variables.

Clinical presentation signs

Mean HIV VL at index date was significantly different (p-value=0.0078) between the two groups, with Group 1 having a higher average than Group 2 (2161.2 ± 21272 copies/mL vs 149.8 ± 799.12 copies/mL). Nevertheless, most patients in both groups had viral load at limit of detection (19 copies/mL), as estimated by median HIV VL. The higher mean is likely due to the presence of outliers reporting higher viral loads (Figure 1).

Stratifying both Group 1 and Group 2 based on their previous use of HIV drugs at index date, for Group 1, HIV-VL was relatively lower in patients who switched from 2DR to 2DR vs 3DR to 2DR (24.3 ± 39.43 copies/mL vs 26.3 ± 121.36 copies/mL). However, the comparison was not statistically significant (p-value=0.3471). For Group 2, differences in average HIV viral load were not significant (2DR to 2DR: 23.9 ± 15.44 copies/mL vs 3DR to 2DR: 295.3 ± 1164.41 copies/mL; p=0.9835).

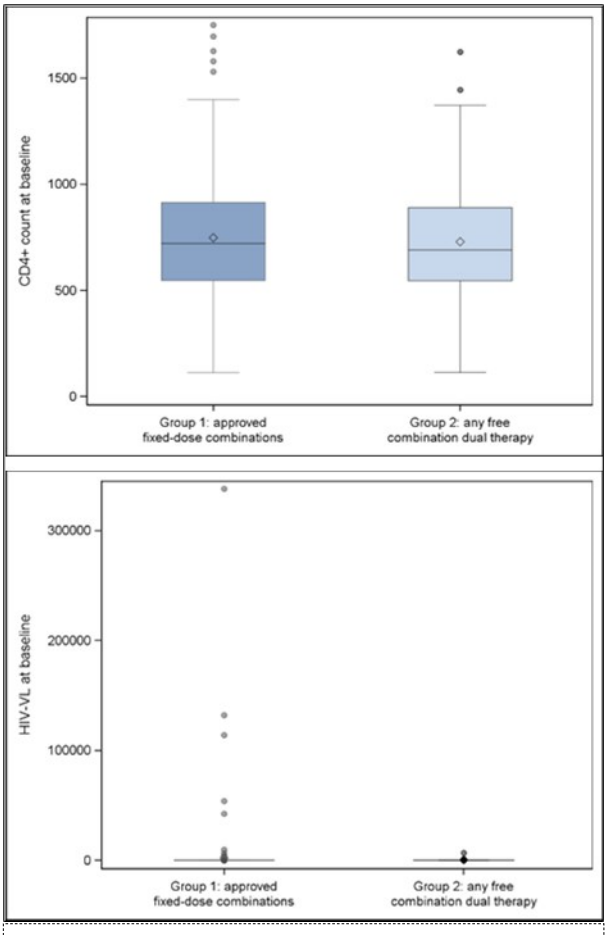

Figure 1. Box and whisker plots for clinical presentation signs (Enrolled population)

Q1=1st quartile; Q3=3rd quartile.
*The bottom and top edges of the box indicate the intra-quartile range (Q1-Q3); the diamond inside the box indicates the mean value; the line inside the box indicates the median value. Whiskers that extend from each box indicate the range of values outside of the intra-quartile range that are close enough not to be considered outliers (i.e., a distance less than or equal to 1.5*Q1-Q3 range). Dots represent outliers, i.e., observations that are more extreme than the upper and lower fences (plus-minus 1.5*Q1-Q3 range).*

Selected concomitant non-ARV medication

Approximately half of the enrolled population received non-ARV medication (48.51%). The most frequent in Group 1 were vitamins (18.99%), mainly cholecalciferol (17.55%), lipid modifying agents (18.75%), and agents acting on the renin-angiotensin system (17.55%). In Group 2, the most common were lipid modifying agents (32.58%), vitamins and specifically cholecalciferol (17.98%), and agents acting on the renin-angiotensin system (16.85%).

Selected comorbidities

Roughly half (54.65%) of the enrolled PLHIV presented at least one selected comorbidity. A lower proportion was reported for Group 1 (Group 1: 51.92%; Group 2: 67.42%; p-value=0.0077), and cardiovascular (24.28% and 30.3%, respectively) and lipid comorbidities (21.88% and 34.83%, respectively) were the most common in both groups.

Resistant mutation

Group 1 had a lower prevalence of resistance mutations compared to Group 2 (9.86% vs 14.61%), with the majority of cases showing PI resistance mutations in Group 1 (9.13%) and NRTI resistance mutations in Group 2 (13.48%).

Secondary analysis

The secondary objective was to describe the baseline patient profiles within subgroups according to previous HIV drug use at the index date. However, the analysis was limited to the subgroups who switched from 2DR or 3DR to 2DR, where patient numbers were sufficient to draw meaningful conclusions [Group 1: n=75 (2DR) and n=318 (3DR); Group 2: n=35 (2DR) and n=44 (3DR)].

In Group 1, PLHIV in the 3DR subgroup were younger (2DR: 53.3 ± 11.99 years; 3DR: 48.4±11.97 years; p-value=0.0013) and were more commonly male (2DR: 73.33%; 3DR: 84.28%; p-value=0.0259). In contrast, for Group 2 there was no statistically significant difference in age, sex, or ethnicity between the subgroups who switched from 2DR and 3DR.

In both stratification groups, time from AIDS-defining diagnosis to starting or switching to 2DR treatment was significantly shorter in PLHIV who transitioned from 3DR than from those who switched from 2DR (Group 1: 16.3 ± 9.23 years vs 12.4±8.09 years ; Group 2: 21.3 ± 9.90 years vs 16.0 ± 10.65 years), as well as years since known HIV status at baseline (Group 1: 15.7 ± 9.30 years vs 12.0 ± 8.05 years; Group 2: 20.9 ± 9.80 years vs 15.8 ± 10.66 years).

No statistically significant difference was found between the stratified groups for clinical presentation signs, the proportion of PLHIV who experienced any selected comorbidity, and the proportion who took any non-ARV medication.

Exploratory analysis

Comparing the two stratification groups in PLHIV switching from 2DR and 3DR to 2DR, males were more represented in Group 1 (2DR: 73.33%; 3DR: 268 84.28%) than in Group 2 (2DR: 54.29%; 3DR: 70.45%). Additionally, in both subgroups, time from AIDS-defining diagnosis to starting or switching to 2DR and the number of years with known HIV status at baseline were significantly lower in Group 1 [time since diagnosis: 16.3 ± 9.23 years (2DR); 12.4 ± 8.09 years (3DR); years with known HIV status: 15.7 ± 9.30 years (2DR); 12.0 ± 8.05 years (3DR)] compared to Group 2 [time since AIDS-defining diagnosis: 21.3 ± 9.90 years (2DR); 16.0 ± 10.65 years (3DR); years with known HIV status: 20.9 ± 9.80 years (2DR); 15.8 ± 10.66 years (3DR)].

At baseline, CD4+ count was not significantly different between stratification groups for PLHIV switching from 2DR to 2DR (p-value=0.6178) and from 3DR to 2DR (p-value=0.8688). HIV viral load at baseline was significantly different between stratification groups only in PLHIV switching from 3DR to 2DR (Group 1: 26.3 ± 121.36 copies/mL; Group 2: 295.3 ± 1164.41 copies/mL; p-value=0.0403). Also, the proportion of PLHIV who took any non-ARV medication was not significantly different between subgroups. The proportion of PLHIV who experienced any selected comorbidity was significantly higher in Group 2 for PLHIV switching from 2DR to 2DR (Group 1: 54.67%; Group 2: 74.29%; p-value = 0.0495).

Finally, an explorative analysis of the evolution of the 2DR population showed an increasing trend in the number of PLHIV who switched/started 2DR over time in both groups.

Discussion

This study highlights the significance of considering the baseline characteristics of PLHIV while developing HIV management strategies. To the best of our knowledge, this is the first real-world study conducted in Italy to assess the baseline profiles of PLHIV who are on 2DR FDC compared to those on 2DR free-combination therapies. Statistically significant differences were observed between the two groups with respect to age, gender, time from AIDS-defining diagnosis to start/switch to 2DR, years of known HIV status at baseline, HIV VL, ART regimen and selected comorbidities.

Many PLHIV (n=416) initiated FDC therapy (DTG/RPV or DTG/3TC), and these participants were more likely white males. This is in line with previous evidence that reported the majority of people with HIV treated with FDC DTG/3TC being male and white [17]. However, as per the report of Centre for Disease Control and Prevention (CDC), Black/African American and Hispanic/Latino communities are disproportionately affected by HIV compared to other racial/ethnic groups [18]. Group 1 PLHIV were older, with an average age of 49.2±12.07 years compared to 32.5 years in the GEMINI 1 and 2 clinical trials conducted on treatment-naïve PLHIV [19], but of similar age compared to other real-world data; 48.6 years (EUROSIDA HIV) [20] and 51 years [21].

Group 1 had significantly shorter time from AIDS-defining diagnosis to start of 2DR and fewer years of known HIV status than those in Group 2. In Group 1, the median time from AIDS-defining diagnosis to start of 2DR was 11.5 years, compared to 14 years in the LAMIDOL study [22] and 15 years in the DOLAMA study [23].

One of the significant factors that influences the HIV therapeutic choice is HIV VL at treatment initiation. In our cohort, 399 PLHIV had a median HIV VL<50 copies/mL at baseline. There was a significant difference in mean baseline HIV VL between the two groups, with Group 1 having a higher average than Group 2. From the results, it can be interpreted that the PLHIV were under viral suppression and presented a lower risk of disease progression, irrespective of the combination therapies. The efficacy and safety of DTG plus 3TC for treating PLHIV without resistance mutations were settled by the TANGO randomized trial [24]. These findings support the use of 2DR as a switch option for PLHIV with viral suppression on a 3- or 4-DR who wish to receive fewer ARTs due to treatment complexity, avoidance of potential drug-associated toxicity, risk of drug–drug interactions, or cost. Clinicians should consider viral loads at baseline for tailoring HIV management strategies to ensure optimal viral suppression and prevent the emergence of drug-resistant strains. Of note, the greater prevalence of resistant mutations in Group 2 suggests that clinical needs have not yet been fully addressed with approved 2DR FDC, and warrants investigation of potential further 2DR strategies such as DOR/ISL, which has demonstrated high potency even in the presence of drug-resistance mutations [25].

PLHIV in both cohorts were medically complex, with diagnoses of hypertension, hypercholesterolemia, dyslipidemia and vitamin D deficiency. Another study also indicated that multi-comorbidities were higher in PLHIV who switch from 2DR compared with 3DR [26].

The average duration of the ART regimen after switching differed significantly between the groups, with shorter duration in Group 1. According to the ICONA report, gender, type of treatment and time spent on HIV management were independent factors associated with discontinuation of ART regimens [27]. However, our current study did not explore the reason behind switching ART.

PLHIV who switched from 2DR were found to be significantly older, more experienced at the index date, and less likely to be male when compared to individuals on a 3DR. These findings are consistent with those reported by Ruzika et al [26].

Our study highlights that individuals who switch to 2DR may be difficult to treat, particularly if they were on free combination therapies due to the presence of resistant mutations. The need for more effective and tailored treatment options is increasingly recognized, particularly for individuals who may not respond optimally to standard triple therapy. Currently approved FDC may not adequately address the clinical complexities of various patient populations, thereby reinforcing the unmet need for more innovative therapeutic options. Ongoing clinical development of novel 2DR seeks to fill this gap. The combination of doravirine and islatravir (DOR/ISL) and bictegravir and lenacapavir (BIC/LEN) administered once daily are under investigation for their potential to provide robust virologic suppression with a favorable tolerability profile [28-29]. Furthermore, the weekly dosing option of ISL in combination with LEN is being explored to enhance patient adherence while maintaining viral suppression [30]. These advancements in 2-drug regimens will address the significant unmet needs associated with current treatment paradigms, reducing treatment burden and thereby advancing the overall management of HIV.

Although our study's retrospective data are not fully representative of the general Italian PLHIV population, it aimed to describe the baseline characteristics of PLHIV on 2DR FDC and free combination therapies, with DOR as the last NNRTI launched on the market at the time of enrollment. We assume that a similar relationship between the two comparison groups would hold in the general population as well.

This medical chart review renders the study results representative of real-world clinical practice. The study was performed in Italy, suggesting that the results may be more representative of European countries and not of the broader population and are specific to the stratification groups mentioned. The enrolment of a low percentage of women under both combination therapies suggests that the study demographics do not fully represent the Italian population of PLHIV. Data on patient adherence and virological failure with previous HIV drug use at baseline and reasons for switching to 2DR were not collected at baseline, hence the study was unable to evaluate treatment patterns based on the aforementioned variables. The majority of PLHIV had a HIV-VL<50 copies/mL, which did not allow any baseline consideration for PLHIV with very high viral loads.

Conclusion

This study was the first step in understanding the baseline profiles and medical needs of PLHIV who started 2DR in Italy. It provides a foundation for future studies to further analyze reasons for switching therapy, as well as to identify those PLHIV that may most benefit from current and future 2DR therapies. In conclusion, PLHIV in Italy on currently approved FDC 2DR therapies were younger, virologically suppressed individuals at baseline with shorter time from prior AIDS-defining diagnosis, lower prevalence of resistance, and lower comorbidities rates compared to individuals on free dual combination therapies. This highlights existing unmet needs of PLHIV with currently approved FDC, indicating a pressing need for ongoing research and the development of tailored treatment strategies that cater to the diverse clinical profiles of this population.

Ethics

The study protocol was reviewed by the local Health Authority. Approvals were obtained from the Ethics Committee of participating sites. Informed consent, as appropriate per local regulations, was ob-

tained from all participants. Data is available upon request.

All authors conceptualized, critically revised the manuscript for important intellectual content, and approved the final manuscript.

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