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FULL PAPER

No need to modify treatment within the first month after rapid start of a tailored antiretroviral therapy: the TWODAY Study

Nicola Gianotti[1], Laura Galli[1], Michela Sampaolo[2], Riccardo Lolatto[1], Elisabetta Carini[1], Gaetana Annicchiarico[1], Alessandro Baglivi[1], Liviana Della Torre[1], Adriano Lazzarin[1], Antonella Castagna[1,3]

[1]*Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy;*
[2]*Laboratory of Microbiology and Virology, IRCCS San Raffaele Scientific Institute, Milan, Italy;*
[3]*Vita-Salute San Raffaele University, Milan, Italy*

SUMMARY

The aim of the TWODAY Study was to investigate the frequency of early treatment change after rapid start of a tailored ART regimen (a 2-drug regimen - 2DR, when clinically feasible or a 3-drug regimen - 3DR, otherwise). TWODAY was an open-label, prospective, proof-of-concept, single center study. ART-naïve patients started their first-line regimen within a few days from the first laboratory testing with a 2DR of dolutegravir (DTG) and lamivudine (3TC) if CD4+ count >200 cells/mL, HIV-RNA <500,000 copies/mL, no transmitted drug resistance to DTG or 3TC and HBsAg undetectable; otherwise, ART was started with a 3DR. The primary endpoint was the proportion of patients who needed to change ART within four week from start, for any reason. Thirty-two patients were enrolled; 19 (59.3%) were deemed eligible for a 2DR. Median time from laboratory testing to ART start was 5 days (5; 5). No regimen modification occurred within one month. In conclusion, no regimen modification was needed within the first month of treatment. Starting a 2DR within a few days after HIV diagnosis was feasible, relying upon complete results of the needed laboratory tests (including resistance testing). A 2DR can be safely proposed provided full laboratory tests are readily available.

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INTRODUCTION

The rapid start of antiretroviral therapy (ART) is currently recommended by all international guidelines, irrespective of CD4+ cell counts (WHO Guidelines Review Committee, 2018; European AIDS Clinical Society, 2021; DHHS Panel, 2022); however, in the real-life setting, the start of treatment is often delayed because of the time needed to acquire full results of laboratory tests and, in particular, of results from genotypic drug-resistance testing (GRT). One important reason for starting ART rapidly after diagnosis is that, given the results from the PARTNER-1 and PARTNER-2 studies (Rodger *et al*., 2016; Rodger *et al*., 2019), ART can be considered a means for primary prevention, since people living with HIV (PLWH) who are on a suppressive regimen (viral load <200 copies/mL for at least 6 months) do not transmit HIV through sexual intercourse. Several small studies in Western countries have proven that rapid initiation of treatment (test and treat approach) is associated with a shorter time to viral suppression (Pilcher *et al.*, 2017; Halperin *et al*., 2019; Heisler *et al*., 2019: Ruggiero *et al*., 2020; Seybolt *et al*., 2020). Therefore, a rapid ART start shortens the window of infectivity. One possibility for initiating ART very soon after HIV diagnosis (and before knowing the full results of baseline laboratory tests) is to use a three-drug regimen (3DR) with a high barrier to resistance (with a boosted-protease inhibitor or a second-generation integrase strand inhibitor, InSTIs); however, this strategy does not allow tailoring of the first-line regimen to patients' characteristics.

A two-drug regimen (2DR) of dolutegravir (DTG) and lamivudine (3TC) proved non-inferior to a conventional 3DR in two large studies, in treatment-naïve patients with baseline HIV-RNA less than 500,000 copies/mL, no resistance to DTG or 3TC, and undetectable HBsAg (Cahn *et al.*, 2020). In these studies, a lower rate of virologic success was observed among patients with baseline CD4+ count fewer than 200

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Corresponding author:
Nicola Gianotti
E-mail: nicola.gianotti@hsr.it

cells/μL. Current guidelines recommend considering starting ART with a two-drug regimen (2DR) composed of dolutegravir (DTG) and lamivudine (3TC) when HIV-RNA is less than 500,000 copies/mL, no resistance to DTG or 3TC can be documented, and HBsAg is undetectable (European AIDS Clinical Society, 2022; DHHS Panel, 2022). As a consequence, the first-line ART regimen can be tailored based on baseline patients' characteristics: people with less than 500,000 HIV-RNA copies/mL, no resistance to DTG or 3TC, undetectable HBsAg and a CD4+ count greater than 200 cells/μL can be safely started on a 2DR, while all others should preferentially be started on a 3DR. However, in order to start ART very soon after HIV diagnosis with a tailored regimen, the results of all of the above-mentioned laboratory tests must be available to the physician in a few working days. Other possible strategies include starting rapidly with a 3DR and then switching to a 2DR, when possible, according to laboratory results, as soon as they are available, or starting rapidly with a 2DR and, when deemed necessary upon laboratory results, switching to a 3DR as soon as possible (Rolle *et al.,* 2021); both these strategies entail a regimen change within few weeks from ART start.

The aim of our study was to evaluate the frequency of regimen changes for any reason during the first month of treatment with a 2DR or a 3DR, tailored on laboratory test results available within 5 days, in treatment-naïve, HIV-infected people.

MATERIALS AND METHODS

TWODAY was an open label, prospective, single center, proof-of concept, 48-week study.

The study was approved by the Ethics Committee of the San Raffaele Scientific Institute, conducted in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

Treatment-naïve, HIV-infected patients were included in the study. Individuals were not includible only if they had an active AIDS-defining condition (except Kaposi's sarcoma not requiring systemic chemotherapy), a serious illness requiring systemic treatment and/or hospitalization, concomitant use of immunosuppressive drugs, concomitant therapy with drugs that were contraindicated to use with the study drugs, absolute neutrophil count <500 cells/μL, hemoglobin <8.0 g/dL, platelet count <50,000 cells/μL, eGFR <30 mL/min/1.73 m^2 by CKD-EPI equation, alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN), Child-Pugh Class B or C liver cirrhosis, or if they were pregnant or breastfeeding.

Patients who agreed to participate in the study were tested for CD4+ cell count, HIV-RNA quantification, GRT, along with all other standard laboratory tests recommended by Italian guidelines before ART start. Those with CD4+>200 cells/μL, HIV-RNA <500,000 copies/mL, no transmitted resistance to DTG or 3TC, and undetectable HBsAg started ART with a 2DR of DTG 50 mg every 24 hours plus 3TC 300 mg every 24 hours. Patients who did not meet any of the above-mentioned criteria were initiated with a 3DR selected according to current international guidelines. Patients were evaluated at the following points in time: screening (defined as the first contact with our clinic), baseline (within two days from screening, at the beginning of therapy), week 4, week 12, week 24, week 36, week 48.

The primary study endpoint was the proportion of patients who needed to modify treatment for any reason within one month from the start.

Secondary objectives of the study were to investigate changes in HIV-RNA through the first 4 and 12 weeks of treatment, the number of patients who were virologically suppressed after 48 weeks, HIV-DNA, IL-6, and alfa-TNF changes through 48 weeks, adverse events and probabilities of treatment discontinuation because of toxicity through 48 weeks, and metabolic changes through 48 weeks.

Virologic suppression (VS) was defined as achievement of HIV-RNA <50 copies/mL during the available follow-up (median [Q1; Q3]: 11.69 [7.3; 18.34] months).

The HOMA-IR (homeostatic model assessment for insulin resistance) index was calculated as previously described (Matthews *et al*., 1985), as well as the VACS (Veterans Aging Cohort Study) index (Tate *et al*., 2013).

An adverse event (AE) was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of therapy. AEs were classified according to the Division of AIDS (DAIDS) scale, as follows: Grade 1 (Mild - symptoms causing no or minimal interference with usual social and functional activities); Grade 2 (Moderate - symptoms causing greater than minimal interference with usual social and functional activities); Grade 3 (Severe - symptoms causing inability to perform usual social and functional activities); Grade 4 (Life threatening - symptoms causing inability to perform basic self-care functions or medical or operative intervention indicated to prevent permanent impairment, persistent disability or death). A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose resulted in death or was life-threatening or required inpatient hospitalization or prolongation of existing hospitalization or resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect.

The statistical analysis of the primary endpoint considered the intention-to-treat (ITT) population as including all subjects treated with at least one dose of study medication. The proportion of individuals who discontinued the initial regimen for any reason was calculated with the corresponding two-sided 95%

confidence interval (95% CI, estimated according to the Wald method).
Continuous variables are described by median (Q1; Q3). Categorical data are reported as frequencies and proportions. Mixed linear models (MLM) with random slope and intercept for each patient were calculated to assess changes over time in immunological, metabolic, and other safety parameters. Slopes were reported with the corresponding 95% confidence interval. All analyses were conducted using SAS statistical software version 9.4 (Statistical Analyses System Inc, Cary, NC, USA).

RESULTS

Thirty-two patients were enrolled: 13 in the 2DR group, 19 in the 3DR group; patients' characteristics at baseline are illustrated in detail in *Table 1*. The median time from laboratory testing to ART start was 5 days (5; 5). The median follow-up was 11.7 (Q1; Q3: 7.3; 18.3) months (16.6 [10.9; 20.5] months in the 2DR group and 9 [5.1; 11.1] months in the 3DR group).
At baseline GRT (*Table 2*), primary mutations related to resistance to integrase inhibitors were never detected, one patient showed a mutation related to

Table 1 - *Patients' characteristics at ART start overall and according to type of initial regimen.*

Characteristics	*Overall (n=32)*	*3DR (n=13)*	*2DR (n=19)*
Age (years)	42.5 (35.6 - 48)	44.4 (40.8 - 47.1)	41.9 (31.5 - 49)
Male sex	29 (90.6%)	10 (76.9%)	19 (100%)
HIV risk factor			
Intravenous drug use	1 (3.1%)	1 (7.7%)	0 (0%)
Male who has sex with males	23 (71.9%)	8 (61.5%)	15 (79.0%)
Heterosexual	7 (21.9%)	4 (30.8%)	3 (15.8%)
Unknown	1 (3.1%)	0 (0%)	1 (5.3%)
Days to ART start from first blood drawn	5 (5 - 5)	5 (5 - 6)	5 (5 - 5)
BMI	22.4 (20.6 - 24.9)	20.5 (18.8 - 23.5)	23.4 (21.36 - 27.3)
Weight (Kg)	68.5 (61 - 76)	61 (57 - 68)	72 (64 - 80)
Height (cm)	174 (170 - 178)	173 (170 - 176)	174 (170 - 182)
Abdominal circumference (cm)	87 (80.5 - 94.5)	81 (76 - 92)	87 (83 - 97)
CD4+ T-lymphocytes (cells/µL)	337.5 (147.5 - 454.5)	62 (22 - 200)	445 (367 - 536)
CD8+ T-lymphocytes (cells/µL)	770 (528 - 1143)	531 (452 - 697.5)	882 (738 - 1298)
CD4/CD8 ratio	0.45 (0.15 - 0.61)	0.13 (0.04 - 0.36)	0.53 (0.4 - 0.65)
CD4+ T-lymphocytes (%)	20.55 (9.65 - 27.45)	5.8 (2.7 - 18.8)	25.2 (18.1 - 31.6)
CD8+ T-lymphocytes (%)	52.3 (44.4 - 60)	58.4 (52.35 - 68.75)	47.1 (42.5 - 54.5)
HIV-RNA (copies/mL)	97300 (21150 - 443500)	544000 (345000 - 2400000)	28300 (7920 - 122000)
HIV-RNA (copies/mL)			
<100000	16 (50%)	2 (15.4%)	14 (73.7%)
≥100000	16 (50%)	11 (84.6%)	5 (26.3%)
HIV-DNA (copies/10^6PBMC)	1365 (390 - 3535)	2710 (1500 - 3930)	520 (250 - 3140)
ALT (U/L)	32.5 (22 - 41)	36 (22 - 41)	25 (22 - 39)
Glucose (mg/dL)	80 (74 - 88.5)	80 (73 - 85)	80 (75 - 92)
HOMA-IR index	2.04 (1.35 - 2.89)	1.79 (1.45 - 2.32)	2.18 (1.19 - 3.6)
Total cholesterol (mg/dL)	163 (137 - 181)	156.5 (136 - 169.5)	166 (139 - 184)
Total/HDL cholesterol	3.95 (3.48 - 4.61)	4.38 (3.74 - 5.52)	3.83 (3.04 - 4.53)
HDL cholesterol (mg/dL)	40 (36 - 46)	36 (28.5 - 41)	42 (36 - 49)
LDL cholesterol (mg/dL)	107 (90 - 115)	108.5 (92 - 115)	106 (85 - 121)
Triglycerides (mg/dL)	94 (71 - 157)	117.5 (68 - 197)	90 (71 - 136)
Creatinine (mg/dL)	0.9 (0.79 - 1.02)	0.96 (0.78 - 1.11)	0.88 (0.8 - 0.99)
Hemoglobin (g/dL)	13.95 (12.9 - 15)	12.1 (10.1 - 13.6)	14.8 (13.9 - 15.1)
White blood count (cells/µL)	4.8 (3.65 - 6.25)	3.8 (2.3 - 4.4)	5.1 (4 - 6.7)
Total lymphocytes (cells/µL)	1.5 (1.1 - 2.05)	0.8 (0.5 - 1.2)	1.9 (1.4 - 2.3)
Platelets (cells/µL)	205.5 (173 - 257)	211 (153 - 231)	200 (184 - 261)
VACS index	20 (13 - 40)	40.5 (30 - 71)	14 (13 - 20)
IL-6 (pg/mL)	2.6 (2.4 - 4.1)	3.85 (2.95 - 11.7)	2.4 (2.4 - 3.3)
TNF (pg/mL)	4.9 (4.9 - 111)	4.9 (4.9 - 66.1)	4.9 (4.9 - 154.75)

Results described as median (first and third quartile) or frequency (%).
2DR: 2-drug regimen; 3DR: 3-drug regimen; BMI: body mass index; HOMA-IR: homeostatic model assessment for insulin resistance; VACS: Veterans Aging Cohort Study; IL: interleukin; TNF: tumor necrosis factor.

Table 2 - *Impact of baseline drug-resistance HIV mutations on drug susceptibility.*

Baseline drug-resistance HIV mutations	*Drugs to which HIV has reduced susceptibility*
D67N, T215S, K219E	abacavir zidovudine tenofovir
E138A	etravirine rilpivirine
V106I	doravirine etravirine nevirapine rilpivirine

resistance to thymidine analogues (D67N, T215S, K219E), and mutations related to reduced susceptibility to non-nucleoside reverse transcriptase inhibitors were detected in four patients (E138A in two cases, V106I in the other two cases).
No patient needed to modify the initial regimen within 4 weeks.

2DR group

In this group, 3 people (23%; 95% CI: 7.5%; 50.9%) discontinued treatment after study week 4, none for toxicity (all were lost to follow-up).
VS was achieved in all but one patient. The patient who did not achieve VS had an optimal drop in HIV-RNA values (from 250,000 copies/mL at baseline to 367 copies/mL at week 4), but was then lost to follow-up.
Trends and variations of CD4+ cell counts and HIV-RNA are illustrated in *Figure 1*. Median CD4+ T-lymphocytes counts were 445 (367; 536) cells/μL at baseline and 666 (522; 939) cells/μL at week 48, with a mean (95% confidence interval) increase of 16.6795 (12.1733; 21.1857) cells per month (p<0.0001). The CD4+/CD8+ ratio increased from 0.53 (0.4; 0.65) at baseline to 0.96 (0.62; 1.07) at week 48, with a mean slope of 0.017 (0.0067; 0.028) points per month (p=0.003). Changes in CD8+ T-cells were not statistically significant. Total cholesterol increased from 166 (139; 184) mg/dL at baseline to 190 (168; 206) mg/dL at week 48 (mean increase: 1.0099 [0.1408; 1.8790] mg/dL per month; p=0.025).
The VACS index was 14 (13; 20) at baseline and 0 (0; 6) at week 48, with a mean change of -1.7334 (-2.2990; -1.1677) points per month (p<0.0001).
LDL-cholesterol, HDL-cholesterol, total/HDL-cholesterol ratio, triglycerides, glucose, HOMA-IR index, weight, BMI and abdominal circumference did not change significantly throughout the study period.
No significant change was observed in HIV-DNA, TNF-alpha and in IL-6 blood concentrations.
There were no treatment-related grade 3 or grade 4 AEs; there were two serious adverse events (SAEs: one metacarpal fracture requiring hospitalization and one death from non-HIV related carcinoma), that were considered unrelated to treatment.

3DR group

In 18 patients, ART was started with the combination of bictegravir plus tenofovir alafenamide (TAF) and emtricitabine (FTC), in one with the combination of darunavir/cobicistat plus TAF and FTC.
Overall, 5 patients (26% [11.5%; 49.1%]) discontinued treatment after study week 4 due to drug interaction (1 case, 20%), inclusion in a different clinical trial (2 cases, 40%), or other reasons (2 cases, 40%). All these discontinuations occurred after study week

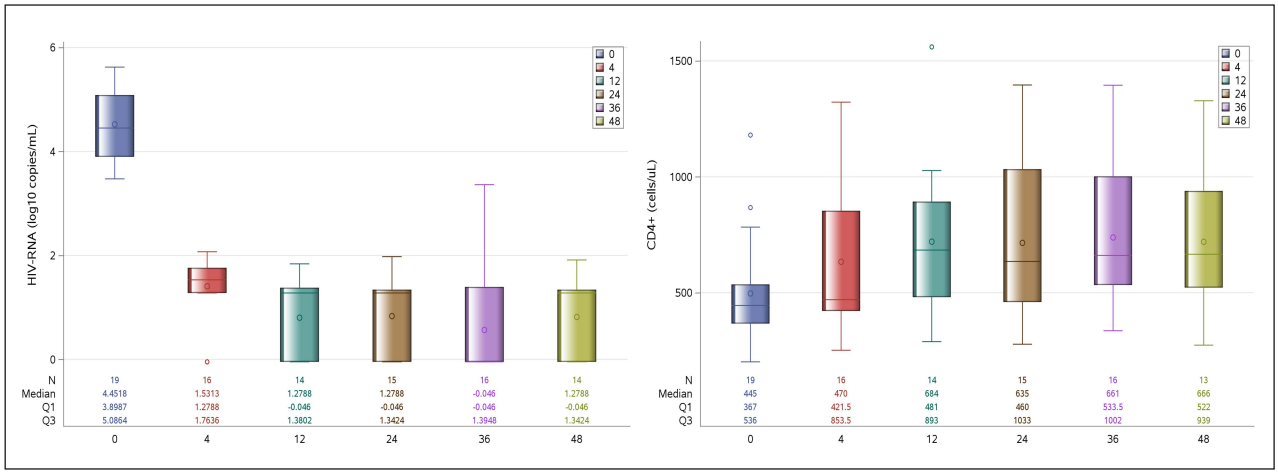

Figure 1 - *HIV-RNA and CD4+ cell counts trends during follow-up in the 2DR group.*

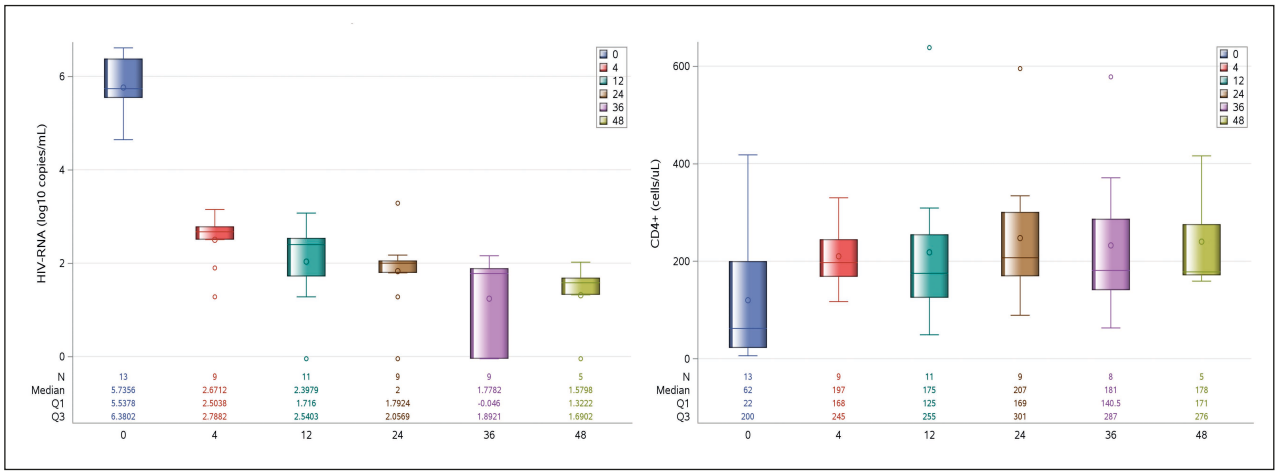

Figure 2 - *HIV-RNA and CD4+ cell counts trends during follow-up in the 3DR group.*

4. VS was reached by 12 (67%) patients at the end of follow-up. In two cases, GRT was available at virologic failure: in one case the mutation 184I was selected; mutations associated with resistance to InSTIs were not selected in either case.

Trends and variations in CD4+ cell counts and HIV-RNA are illustrated in *Figure 2*. Median CD4+ T-lymphocytes counts were 62 (22; 200) cells/μL at baseline and 178 (171; 276) cells/μL at week 48, with a mean increase of 6.1852 (1.4098; 10.9606) cells per month (p=0.016). The CD4+/CD8+ ratio increased from 0.13 (0.04; 0.36) at baseline to 0.43 (0.25; 0.9) at week 48, with a mean increase of 0.032 (0.013; 0.051) points per month (p=0.004).

The VACS index was 40.5 (30; 71) at baseline and 28 (20; 33) at week 48, with a mean change of -3.2083 (-5.5311; -0.8854) points per month (p=0.013).

Total cholesterol was 156.5 (136; 169.5) mg/dL at baseline and 190 (163; 226) mg/dL at week 48, with a mean increase of 4.8347 (3.1528; 6.5167) mg/dL per month (p=0.0001). HDL- and LDL-cholesterol increased as well: HDL-cholesterol was 36 (28.5; 41) mg/dL at baseline and 52 (40.5; 68) mg/dL at week 48 (mean increase: 1.4714 [0.7688; 2.1740] mg/dL per month; p=0.001). LDL-cholesterol was 108.5 (92; 115) mg/dL at baseline and 113.5 (99.5; 151.5) mg/dL at week 48 (mean increase: 2.4933 [0.5706; 4.4160] mg/dL per month; p=0.019). The total/HDL-cholesterol ratio, as well as weight, BMI, abdominal circumference, triglycerides, HOMA-IR index and glucose did not change significantly throughout the study period. No significant change was observed in HIV-DNA, TNF-alpha and IL-6 blood concentrations.

No drug-related grade 3 or 4 AE occurred during the study period. There was one case of non-drug-related grade 4 AE (invasive M. avium complex infection). There were also 3 SAEs: one disseminated cytomegalovirus infection, one death related to B-cell NHL, and one event of diarrhea refractory to treatment and that required hospitalization; the latter was considered non-related to treatment because of concomitant use of chemotherapy.

DISCUSSION

In this study, the rapid start of a tailored antiretroviral therapy proved to be feasible both in the 2DR group and in the 3DR group; in the first month of treatment, there was no need to change the starting regimen in either group. The results support the possibility to customize ART in treatment-naïve patients from the very beginning of therapy, entailing the option of a 2DR when clinically feasible.

Adverse events were rare in both groups; the serious adverse events reported were unrelated to treatment.

The VACS index change proved predictive of the risk of death in patients receiving at least 12 months of ART (Tate *et al*., 2013). In our study, the VACS index decreased significantly in both groups, which strongly suggests a significant restoration of health and a significant reduction in the risk of death, irrespective of the initial regimen prescribed.

There was also a significant increase in CD4+ cell counts, irrespective of the initial regimen. This rise was faster among people who started ART with a 2DR (17 cells/month in the 2DR group vs 6 cells/month in the 3DR group). The study design does not allow us to speculate and conclude that a 2DR is associated with an improved CD4+ recovery compared to a 3DR. Nevertheless, it must be underlined that patients who started on a 2DR were characterized by much higher CD4+ cell counts at baseline (445/μL in the 2DR vs 62/μL in the 3DR group). When we designed this study, we planned to avoid starting a 2DR if baseline CD4+ counts were less than 200 cells/μL; this decision was dictated by the initial results of the GEMINI studies, which showed a lower rate of virologic success among patients with less than 200

CD4+ cells/μL at baseline (Cahn *et al.*, 2020). It must, however, be emphasized that current guidelines do not limit the use of the 2DR of DTG plus 3TC as initial regimen to people with more than 200 CD4+ cells/μL at baseline (European AIDS Clinical Society, 2022; DHHS Panel, 2022).

We observed a weight gain and an increase in BMI in both groups, but these changes were not statistically significant. Indeed, data from several researches performed in the last decade suggest that these are phenomena typically observed with the ART regimens used in our study (Venter *et al.*, 2020; Buzòn-Martin *et al.,* 2020). We cannot exclude that the changes measured in our study would have resulted statistically significant with a larger sample size.

We also observed a variation in lipid profile in both groups, more relevant among patients who received a 3DR, which is consistent with data from previous studies and likely due to both a specific untoward effect of TAF (Venter *et al.*, 2019; Sapuła *et al.*, 2022) and a restoration of health phenomenon. In fact, a restoration of health phenomenon, due to ART start in a previously untreated individual, is associated with several features: alleviation of both HIV-associated inflammation and of accelerated catabolism, as well as resolution of opportunistic infections, which can result in increased adipogenesis, weight gain and rise in blood lipids (Godfrey *et al.,* 2019; Koethe *et al.*, 2020). It must also be emphasized that in the 3DR group, not only total and LDL-cholesterol increased, but also HDL-cholesterol, while the total/HDL-cholesterol ratio did not change significantly. This suggests that the impact of such changes on cardiovascular risk may be limited.

Notably, glucose metabolism was not particularly influenced in any group by the initiation and continuation of ART, considering both fasting glucose levels and in insulin resistance. However, our results could be related to the small sample size or to a short follow-up: in a recent meta-analysis, the association between altered glucose metabolism and ART was seen only in patients who had been treated for at least 18 months (Nduka *et al.,* 2017).

Importantly, resistance In STIs was not selected at failure of the initial regimen.

This study had some limitations: primarily, the above-mentioned limited sample size and the relatively short follow-up. The small sample size was due mainly to difficulty in recruiting naïve patients. The explanation may be related to epidemiological data: in fact, HIV-infection cases have dropped steadily since 2012, and in Lombardy the incidence reached its lowest point in 2020, especially in the city of Milan (Istituto Superiore di Sanità, 2022).

Secondly, the possibility to receive the genotypic resistance testing with such short notice (three working days) may not be applicable in other settings: this limits the generalizability of our results.

CONCLUSIONS

No regimen modification was needed within the first month of treatment, either in patients who started their first-line ART with a 2DR or in those who began ART with a 3DR. Starting a 2DR within a few days after HIV diagnosis was feasible, relying upon complete results of the needed laboratory tests (including drug-resistance testing). A 2DR can be safely proposed as a first-line ART regimen, provided full laboratory tests are readily available.

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