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Viro-immunological efficacy and tolerability of dolutegravir-based regimens compared to regimens based on other integrase strand inhibitors, protease inhibitors or non-nucleoside reverse transcriptase inhibitors in patients with acute HIV-1 infection: A multicenter retrospective cohort study

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ABSTRACT

Objectives: The aim of this study was to compare the tolerability and viro-immunological efficacy of dolutegravir-based regimens (DTG group) with regimens based on EVG, RAL, PI or NNRTI (NODTG group) in patients with acute HIV-1 infections (AHI).
Methods: All patients diagnosed with AHI and on antiretroviral therapy (ART) between January 2015 and December 2017 from five centers in Italy were included and followed-up to 30th April 2018. AHI was defined by the presence of the positive p24 antigen with negative or indeterminate western blot.
Results: Forty-three patients were enrolled: 20 in the DTG group, 23 in the NODTG group. Nine patients (20.9%; four in the DTG group, five in the NODTG group) were prescribed a four-drug regimen. In the cohort, 81.4% were Italian and 83.7% were male, with a median age of 41 years (interquartile range [IQR] 31-48). Median time between HIV diagnosis and ART initiation was 12 days (IQR 5-28). Seven patients harbored a virus with transmitted mutations at baseline (16.2%), all were in the DTG group (P=0.005). All patients had undetectable HIV-RNA at the end of follow-up except two patients, one of whom had 57 copies and one who was lost to follow-up. In Kaplan-Meier analysis, time to virological suppression was similar in the two groups (log rank: P= 0.7155). After achieving virological suppression, four patients stopped ART because of toxicity: two on DTG, two on EVG for neurological and gastrointestinal toxicity, respectively.
Conclusion: In our setting, ART in AHI is started very early. DTG showed good viro-immunological efficacy even in the presence of NRTI-transmitted mutations. DTG interruptions were rare.

1. Introduction

Acute HIV infection (AHI) is the earliest phase of HIV infection, between the appearance of HIV viremia and the first detection of antibodies [1]. Individuals who are treated during early infection may experience immunological and virological benefits [2–4]. Moreover, early HIV-1 treatment substantially reduces the risk of HIV-1 transmission [5]. Dolutegravir (DTG)-based antiretroviral therapy (ART) has been recommended as a first-line regimen in Italian guidelines since 2014 and was marketed in Italy in January 2015.

Data on patients with AHI treated with DTG-based regimens are lacking. The primary aim of this study was to compare the probability of achieving virological suppression with DTG-based regimens (DTG group) versus regimens based on other integrase

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strand inhibitors (INSTI), protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI) (NODTG group). The secondary aim was to assess the tolerability of prescribed therapies and reasons for discontinuations.

2. Material and Methods

2.1. Ethics

The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The local ethics committees of the participating clinical centers approved the study (protocol number of the promoter center, Comitato Etico Area Vasta Centro – AOU Careggi, rif 10452_oss). All participants provided written informed consent before data collection.

This was a retrospective observational cohort study in patients with very early stage infection (Fiebig II) [6]. AHI was defined by the presence of the positive p24 antigen in serum (Fourth generation EIA) associated with negative or indeterminate western blot assay. HIV-RNA RT-PCR was subsequently performed and results were positive. All patients diagnosed with AHI and on ART between January 2015 and December 2017 from five centers in Italy were observed up to 30th June 2018 or up to the time of first interruption of ART regimen. Patients were divided into two groups by the first ART regimen: patients who started dolutegravir (DTG), and patients who began any other regimen but dolutegravir (NODTG). Virological suppression was defined as two consecutive HIV-RNA <50 copies/mL. HIV RNA was measured in the plasma using Test v1.5 Roche COBAS AmpliPrep, Roche TaqMan HIV-1 Test v2.0 (Roche Diagnostics, Branchburg, NJ, USA) and Siemens Versant K PCR (Siemens Healthcare GmbH, Erlangen, Germany), with lower limits of detection of 50, 20 and 37 copies/mL, respectively. Resistance-associated mutations were assessed by TRUGENE HIV-1 genotyping assay (Siemens Healthcare GmbH, Erlangen, Germany). The frequency of any major transcriptase, protease and integrase resistance mutations was analysed according to the Stanford algorithm (Stanford HIVdb algorithm, version 8.8). Assessments of virological response to ART were performed after 4, 12, 24, 48, 60, 66 and 72 weeks of therapy.

Symptoms and signs were assessed at the first medical visit. Complete antiretroviral history, resistance tests, viro-immunological results, discontinuations, and toxicity-events were recorded. Categorical variables were analysed with X^2 Fisher's exact test and continuous variables with Wilcoxon sign rank test. Kaplan-Meier analysis was used to assess the probability of virological failure.

3. Results

Among the 45 patients with AHI diagnosis, 2 were excluded because they did not start any ART regimen during the study period; therefore, a total of 43 patients were included in the study. Median age of the patients was 41 years (IQR 31-48). Thirty-five patients (81.4%) were Italian, 36 patients (83.7%) were male and 31 patients (72.1%) were men who had sex with men (MSM). The main reasons that led to the HIV test were risk awareness (32.5%) and a flu-like syndrome (27.9%). Twenty-eight patients (65.1%) had a symptomatic infection: 18 (64.3%) had fever, 22 (78.6%) had lymphadenopathy, and 7 (25.0%) had gastrointestinal symptoms. ART was started within a median of 12 days (IQR 5-28) after the first contact with a healthcare worker. Among the 43 patients, 20 started a DTG regimen and 23 a regimen without DTG (NODTG group); 9 patients (20.9%), 4 in the DTG and 5 in the NODTG group were prescribed a four-drug regimen. Emtricitabine (FTC)+tenofovir (TDF/TAF) backbone was prescribed in 35 of 43 patients. The DTG group started DTG with FTC+TDF/TAF (n=9; 45.0%), lamivudine (3TC)+abacavir (ABC) (n=6; 30.0%), FTC+TDF+darunavir/cobicistat-ritonavir (DRV/b) (n=4; 20.0%) or DRV/b (n=1; 5.0%). Patients in the NODTG group started the following regimens: FTC+TDF+elvitegravir/cobicistat (EVG/c) (n=9; 39.1%), FTC+TDF+raltegravir (RAL) (n=4; 17.4%), FTC+TDF+rilpivirine (RPV) (n=2; 8.7%), FTC+TDF+DRV/b (n=2; 8.7%), FTC+TDF+DRV/b+RAL (n=5; 21.7%) or 3TC+ABC+DRV/b (n=1; 4.3%). Ten patients, all with the FTC+TDF/TAF backbone, started ART within 5 days: three patients started ART with a four-drug regimen (two with FTC+TDF/TAF+DRV+RAL, one with FTC+TDF/TAF+DRV+DTG), one with FTC+TDF+RAL, three with FTC+TDF+DTG and one with FTC+TDF+DRV.

Baseline characteristics and comparison between those two groups are summarized in Table 1.

Eight of the nine patients who had baseline viremia >1 000 000 copies/mL started a four-drug regimen (four on FTC+TDF +DRV/b +RAL and four on FTC+TDF + DRV/b +DTG). INSTI genotyping resistance test results were available at baseline for 13/43 (30.2%) patients. No INSTI resistance mutations were observed. Seven patients had transmitted drug resistance (TDR) at baseline (16.2%), all in the DTG group (P=0.005) (Table 2). The M184V mutation was detected in two patients; both were on 3TC+ABC+DTG and both had undetectable viral load at the end of follow-up (EOF). None of the patients with TDR at baseline started or was switched to a four-drug regimen (Table 2). Forty-one of 43 patients achieved virological success. Two of 43 patients had detectable viremia at EOF: one on 3TC+TDF+RAL was lost to follow-up after 4 months, one on 3TC+ABC+DTG had 57 copies/mL after 6 months of follow-up, and no further assessment after that. None of the patients had interrupted ART; however, 19 patients (44.2%) modified initial therapy: 15 for reducing pill burden (8 patients simplified from a 4-drug regimen to a 3-drug regimen), 4 for grade 1 toxicity (2 on DTG for neurological toxicity related to sleep disturbance and 2 on EVG for diarrhea). Details on ART modification in the TDR subset are shown in Table 2.

Kaplan-Meier analysis for the probability of achieving virological suppression during follow-up is shown in Fig. 1. Time to virological suppression was similar in the two groups (log rank: P= 0.7155), and did not differ in patients with TDR at baseline compared to patients without TDR (log rank: P=0.7119). CD4+ cells count, and CD4+/CD8+ ratio increased significantly within groups at 12, 24, 48 and 72 weeks (P<0.05 for all comparisons), but there were no statistically significant differences between the two groups.

4. Discussion

Despite the evolution in guidelines on when to start ART, there are limited data on which specific ART drugs should be initiated during AHI. This aim of this paper was to describe the characteristics and outcome of patients with AHI treated with a first therapy with or without DTG. There was no difference in the probability of achieving virological suppression in the two groups (Fig. 1). DTG showed viro-immunological efficacy compared with other regimens; DTG interruptions, mainly due to neurological toxicity, were rare and overall virological failure was uncommon [7]. Patients with AHI were predominantly young Italian MSM. That is not surprising because in Italy, HIV infection in this population has grown considerably in recent years [8].

Half the patients (50.0%) started ART within a median of 12 days (IQR 5-28) from diagnosis and in 10 patients, ART was started within 5 days. Overall, FTC+TDF/TAF backbone was prescribed in 81.4% of cases and in all 10 patients who started ART within 5 days from diagnosis. Nine patients (20.9%) were prescribed a four-drug regimen. This is common practice, although no advantage in increasing the number of drugs was demonstrated,

Table 1
Baseline characteristics of the study population.

	DTG regimens N=20	NODTG regimens N=23	*P*-value
Male n (%)	17 (85.0)	19 (82.6)	0.832
Median age, years [IQR]	33.5 [28-42]	45 [40-53]	**0.006**
Sexual contact n (%)			
• Heterosexual	4 (20.0)	8 (34.8)	0.281
• MSM	16 (80.0)	15 (65.2)	
Country of origin n (%)			
• Italy	17 (85.0)	18 (78.3)	0.573
• Romania	2 (10.0)	2 (8.7)	
• Nigeria	0 (0.0)	1 (4.4)	
• Norway	1 (5.0)	0 (0.0)	
• Portugal	0 (0.0)	1 (4.4)	
• Peru	0 (0.0)	1 (4.4)	
Reason of HIV test n (%)			
• Risk perception	8 (40.0)	6 (26.1)	0.441
• Flu-like syndrome	6 (30.0)	6 (26.1)	
• HIV-positive partner	3 (15.0)	2 (8.7)	
• Blood donation	0 (0.0)	1 (4.4)	
• Screening for other diseases	0 (0.0)	3 (13.0)	
• Unknown	3 (15.0)	5 (21.7)	
Symptomatic acute infections n (%)	14 (70.0)	14 (60.9)	0.531
HCV Ab-positive n (%)	1 (5.0)	0 (0.0)	0.278
HBsAg-positive n (%)			
• Negative	19 (95.0)	14 (60.9)	0.028
• Positive	1 (5.0)	6 (26.1)	
• Unknown	0 (0.0)	3 (13.0)	
Lue IgM positive serology n (%)	3 (15.0)	3 (13.0)	0.853
Resistance n (%)*			
• None	13 (65.0)	23 (100)	0.005
• NRTI	3 (15.0)	0 (0.0)	
• NNRTI	2 (10.0)	0 (0.0)	
• NRTI+NNRTI	1 (5.0)	0 (0.0)	
• PI	1 (5.0)	0 (0.0)	
Median CD4 cell/μL [IQR]	504 [311-710]	557 [339-717]	0.792
CD4 <350/mm^3 n (%)	6 (30)	6 (26)	0.081
Median HIV-RNA Log $_{10}$ copies/mL [IQR]	6.0 [5.4- 6.4]	5.5 [4.9-6.3]	0.173
Median days from HIV diagnosis to ART start [IQR]	10 [5-18]	22 [4-28]	0.387
Median days to achieve <50 copies/mL [IQR]	98 [58-157]	121 [60-197]	0.647
Number of drugs			
• **2**	1 (5.0)	0 (0.0)	0.554
• **3**	15 (75.0)	18 (78.3)	
• **4**	4 (20.0)	5 (21.7)	
Single Tablet Regimen n (%)	6 (30.0)	11 (47.8)	0.233

ART, antiretroviral therapy; DTG, dolutegravir; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; NODTG, non-dolutegravir; NRTI, Nucleoside/nucleotide Reverse Transcriptase Inhibitors; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitors; PI, Protease Inhibitor.

* No INSTI resistance was found in patients who had a genotyping resistance test available at baseline (13 out of 43). Not shown in the table.

Table 2
Antiretroviral therapy and transmitted resistance mutations in patients with acute HIV infection.

	Major resistance mutations	First ART	Reasons for switch	ART after switch
Patient 1	L100I K103N	3TC/ABC/DTG	-	-
Patient 2	T215S	FTC/TAF+DTG	Sleep disturbance	FTC/TDF/EVG/c
Patient 3	E138A	FTC/TDF+DTG	Simplification to STR	3TC/ABC/DTG
Patient 4	M184V K103N	3TC/ABC/DTG		-
Patient 5	M184V	3TC/ABC/DTG		-
Patient 6	T215N	FTC/TDF+DTG		-
Patient 7	M46I	FTC/TDF+DTG	Simplification to STR	3TC/ABC/DTG

ART, antiretroviral therapy; STR, single tablet regimen; 3TC, lamivudine; FTC, emtricitabine; TDF, tenofovir; EVG/c, elvitegravir/cobicistat; ABC, abacavir; DTG, dolutegravir.

even in patients with the highest viral load [9]. The first ART was frequently modified (34.9% at the second visit), probably because of the acquisition of resistance test and HLA-B*5701 results. The regimen 3TC+ABC+DTG, although recommended as first-line therapy, was not widely used in our setting (n=6, 13.9%). The reason is two-fold: first, patients with AHI need a quick intervention, but collection of the HLA-B*5701 test is cumbersome and there is a delay in acquiring the resistance test results; second, as patients in NODTG were older compared with the DTG group (*P*=0.006), ABC could not have been preferred because of its involvement in cardiovascular risk [10].

The prevalence of TDR in this cohort of AHI was 16.2% and it was primarily driven by NRTI and NNRTI resistance. This value was higher than usually reported in European cohorts [11,12], but

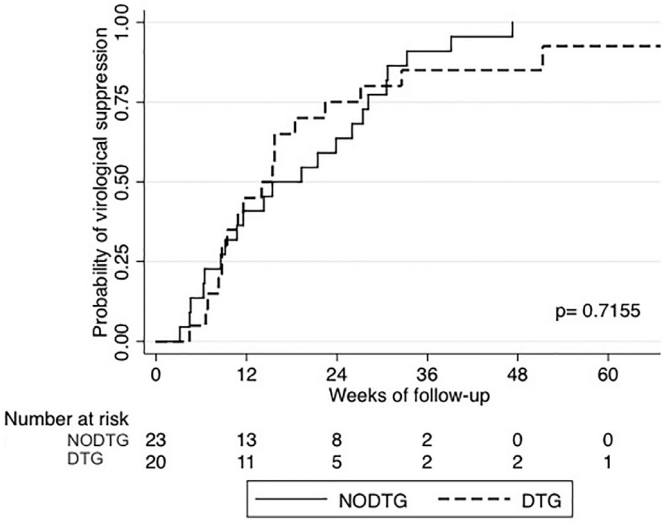

Fig. 1. Kaplan-Meier analysis for the probability of virological suppression.

was in agreement with those results showing a TDR prevalence in AHI patients as high as 20.9% [13]. Significant differences may depend on geographical area, risk group and migration timeline, but in AHI, the higher frequency of TDR may be explained by the fact that transmitted resistances have not had time to undergo any archiving process. Consequently, the execution of resistance testing to optimize ART is highly recommended in accordance with Italian Guidelines [14]. Cases with transmitted resistance for NRTI were all in the DTG group, and, interestingly, all of them achieved virological suppression. These data indicate that in highly viremic AHI patients, virological suppression can be achieved with only one fully active NRTI in the backbone, as shown in different contexts. In both the SAILING [15] and DAWNING [16] studies, groups were given regimens that primarily included only one active NRTI and high rates of viral suppression were demonstrated.

Limitations of this study are the retrospective nature and the relatively small number of patients. However, it is well known that the topic of ART in AHI is an important and difficult topic of research, mainly due to complexities in building studies with a large and homogeneous sample size. Moreover, starting ART in AHI is a clinical field where personal expertise and opinion are important. However, the strength of this current work is that patients were collected in a homogeneous and very early stage of AHI and the outcome of a therapy with DTG in AHI was described for the first time. Although no differences in prescribing between the centers were observed, a residual selection bias could not be excluded.

In conclusion, in our setting, ART in AHI is started very early, DTG showed a good viro-immunological efficacy compared with other regimens, and DTG interruptions were rare due to neurological toxicity. In AHI patients treated with DTG, mutations for one of the NRTIs in the backbone does not seem to influence the virological outcome, even in patients with very high HIV-RNA values.

Declarations

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Competing interests: A. Capetti has received fees for presentation at local congress or expert meeting from ViiV healthcare, Gilead Science, Merck Sharp & Dohme and Janssen-Cilag. S. Di Giambenedetto was a paid consultant or member of advisory boards for Gilead, ViiV healthcare, Janssen-Cilag, Merck Sharp & Dohme and Bristol-Myers Squib. Giordano Madeddu has received consultancy and/or speakers' fees from Abbott, Bristol Myers Squibb, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme and ViiV healthcare. G. Sterrantino has received funds for speaking at symposia and advisory boards on behalf of Gilead Science, Merck Sharp & Dohme, Janssen-Cilag, Abbvie and ViiV healthcare.

All other authors: none to declare.

Ethical approval: The local ethics committees of the participating clinical centers approved the study (protocol number of the promoter center, Comitato Etico Area Vasta Centro – AOU Careggi, rif 10452_oss)

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