Efficacy and safety of dolutegravir-based regimens in advanced HIV-infected naïve patients: results from a multicenter cohort study

Barbara Rossetti[a,*], Gianmaria Baldin[b], Gaetana Sterrantino[c], Stefano Rusconi[d], Andrea De Vito[e], Andrea Giacometti[f], Roberta Gagliardini[g], Manuela Colafigli[h], Amedeo Capetti[i], Gabriella d'Ettorre[j], Luigi Celani[j], Filippo Lagi[c], Arturo Cicullo[b], Andrea De Luca[a,g,1], Simona Di Giambenedetto[b,k], Giordano Madeddu[e]

[a] Infectious Diseases Unit, Azienda Ospedaliera Universitaria Senese, Viale Bracci 16, 53100, Siena, Italy
[b] Institute of Clinical Infectious Diseases, Catholic University of Sacred Heart, Largo Agostino Gemelli, 8, 00168, Rome, Italy
[c] Department of Experimental and Clinical Medicine, University of Florence, Largo Brambilla 3, 50134, Florence, Italy
[d] Infectious Diseases Unit, DIBIC Luigi Sacco, University of Milan, Via G.B. Grassi 74, 20157, Milan, Italy
[e] Unit of Infectious Diseases, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Viale San Pietro 43, 07100, Sassari, Italy
[f] Infectious Diseases, Department of Biological Sciences and Public Health, Marche Polytechnic University, Via Conca, 71, 60200, Ancona, Italy
[g] Department of Medical Biotechnologies, University of Siena, Viale Bracci 16, 53100, Siena, Italy
[h] Infectious Dermatology and Allergology Unit, IFO S. Gallicano Institute (IRCCS), via Elio Chianesi, 53, 00144, Rome, Italy
[i] First Division of Infectious Diseases, Department of Infectious Diseases, Luigi Sacco University Hospital, Via G.B. Grassi 74, 20157, Milan, Italy
[j] Department of Infectious Diseases and Public Health, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185, Rome, Italy
[k] IRCCS Fondazione Policlinico Universitario Agostino Gemelli, Largo Agostino Gemelli, 8, 00168, Rome, Italy

ARTICLE INFO

ABSTRACT

The aims were to describe efficacy and tolerability of regimens containing dolutegravir (DTG) in advanced ART-naïve people living with HIV (PLHIV) from the clinical practice.

The frequency of Immune Reconstitution Inflammatory Syndrome (IRIS), the estimated time of discontinuation of the first ART regimen and the time to reach virological suppression in a multicenter cohort of AIDS-presenters or late-presenters with CD4 < 350/μL were assessed.

We included 272 PLHIV: 120 (44%) AIDS-presenters and 152 (56%) late-presenters. The most frequent AIDS-defining event was *Pneumocystis jirovecii* pneumonia in 41 (34%). One hundred-thirty-two PLHIV (48%) started first-line cART regimens including DTG and 140 PLHIV (52%) were treated with cART regimens without DTG. One-hundred-eighty-two (67%) individuals discontinued their first-line regimen: 109 (60%) for simplification, 32 (18%) for toxicities, 4 (2%) for drug-drug interactions, 37 (20%) for other reasons. DTG was interrupted in 19/132 (14%) PLHIV: 13 (68%) for adverse events (5 intolerance, 4 gastrointestinal disorders and 4 neurological symptoms), 2 (11%) for proactive switch and 4 (21%) for medical/individual choice. IRIS was reported in 13 (5%) AIDS-presenters without differences between arms. During a median observation time of 16 months (IQR 5–24), HIV-1 RNA < 50 copies/mL was achieved in 95/132 (72%) individuals on DTG-based regimen and in 92/140 (66%) individuals with other regimens. The 12-month estimated probability of DTG interruption was 14% (95% CI 11–17).

The results demonstrated the low risk for IRIS and the high potency, good tolerability and safety of DTG in our population of advanced naïve PLHIV.

1. Short communication

Current combination antiretroviral regimens (cART) are characterized by high viroimmunological efficacy, safety and long-term benefits in PLHIV (Di Biagio et al., 2016; Guidelines Version 9, 2019; Panel on antiretroviral g, 2019). A major concern is the late presentation of HIV infection, that refers to individuals newly presenting for HIV care with a CD4 count below 350 cells/μl or with an acquired immune deficiency syndrome (AIDS)-defining event, according to the European Late Presenter Consensus Working Group definition published in 2011 (Antinori et al., 2011). Late presentation is common (Wilton et al., 2019), reaching up to 50% of patients even in some European regions. The consequences of late presentation include lower survival probability (Celesia et al., 2013), higher morbidity, healthcare costs and risk of onward transmission to sexual partners (Li et al., 1998; Borghi et al., 2008; Late presenters working group in COHERE in EuroCoord Mocroft et al., 2015).

The integrase strand transfer inhibitors (INSTIs), raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG) and bictegravir (BIC), are recommended for first-line antiretroviral therapy in combination with two nucleos(t)ide reverse transcriptase inhibitors (NRTI) (Guidelines Version 9, 2019; Panel on antiretroviral g, 2019). DTG is a second-generation unboosted-integrase inhibitor, given once daily with limited cross resistance and a high barrier to resistance. However, limited data are available about efficacy and safety of first-line DTG use in late presenter HIV-1 infected individuals in clinical practice (Mondi et al., 2019; Bonfanti et al., 2017).

Previous studies demonstrated that the development of immune reconstitution inflammatory syndrome (IRIS) is related with lower CD4 cell counts, higher viral load at cART initiation, duration of treatment for opportunistic infections prior to cART initiation, speed of viral load decrease and CD4 cell count increase after antiretroviral therapy start (Müller et al., 2010). In addition, despite excellent safety, INSTIs have been variably associated to the development of IRIS in severely immunocompromised PLHIV receiving INSTI-based regimens as first cART (Psichogiou et al., 2017; Wijting et al., 2017; Hill AMMitchell et al., 2018; Dutertre et al., 2017).

The aims of the study were to compare frequency of IRIS defining events and to assess viro-immunological efficacy and tolerability of DTG-including regimens *vs* regimens without DTG in ART-naïve late and AIDS presenters PLHIV.

We performed a retrospective analysis in a multicenter cohort of advanced naïve PLHIV starting first-line antiretroviral regimens between 01/01/2014 and 30/12/2017 in 9 Italian clinical centers, excluding individuals that did not attend a visit after cART initiation. All PLHIV presenting for care with a CD4 count below 350 cells/μl (late presenters) or presenting with an AIDS-defining event (AIDS-presenters) regardless of the CD4 cells count were included.

Continuous variables were described using median and interquartile range (IQR, 25th; 75th percentile), categorical variables were reported as counts (%). Virological suppression, defined as HIV-1 RNA < 50 copies/mL, was evaluated after 1, 3, 6, 12 and 24 months. Median CD4 cells count and CD4/CD8 ratio changes from baseline at 1, 3, 6, 12 and 24 months were assessed using Student's t-test for paired samples.

The time of discontinuation of the first cART regimen prescribed (TD, defined as the discontinuation of any of the study drugs or the intensification of the regimen) and the time of discontinuation of the DTG were estimated by Kaplan Meier method. Censor was established at last available visit, death or loss to follow-up.

The frequency of IRIS events was investigated and univariable analysis was performed to assess the relationship of viral load strata (HIV-1 RNA < 100,000 cp/mL or ≥ 100,000 cp/mL and HIV-1 RNA < 500,000 cp/mL or ≥500,000 cp/mL), of DTG and 2 NRTIs backbones use with this outcome.

Unmasking and paradoxical IRIS events were defined by clinicians as symptoms consistent with an infectious or inflammatory condition associated with a decay of > 2 $\log_{10}$ copies/mL of HIV-RNA, not explained by a newly acquired infection, the expected clinical course of a previous infection, or side-effects.

Statistical analyses were performed using the SPSS software package (version 22, Chicago, IL, USA, IBM). The study was approved by each local Ethics Committee (protocol number of the promoter center: 5284/15) and every participant signed an informed consent before data collection.

We included 272 individuals: 120 (44%) AIDS-presenters and 152 (56%) late-presenters. Overall, 187 (69%) were males, 147 (54%) heterosexuals, 217 (80%) Caucasians. Median age was 44 years (IQR, 36–51), HIV-1 RNA $\log_{10}$ 5.2 cps/mL (4.8–5.7), CD4 median cells count 114 cell/μl (40–241) and CD4 cells count were < 200 cell/μl in 180 (66%), viral subtype was B in 89 (71%). HIV-1 RNA was > 100,000 copies/mL in 201 (80%) and > 500,000 copies/mL in 60 (24%). Twelve PLHIV (5%) were HCV coinfected and 8 (3%) HBV coinfected. One hundred-thirty-two PLHIV (48%) started first-line cART regimens including DTG and 140 PLHIV (52%) were treated with cART regimens without DTG. Twenty-three individuals (8%) started more than 3-drug cART: 8 (5%) with regimens including DTG and 15 (11%) with regimens without DTG. Three individuals (1%) started two-drugs cART including DTG: 2 were treated with DTG + darunavir (DRV) either boosted with ritonavir (r) or cobicistat (c) and 1 with DTG + rilpivirine (RPV). An INSTI-based 3-drug regimen was prescribed to 191 (70%) individuals, of which 121 (63%) including DTG, 44 (23%) EVG, 40 (21%) RAL. A PI-based 3-drug regimen was prescribed to 56 (29%) individuals, in 45 (80%) DRV/r or c and in 11 (20%) atazanavir (ATV)/r or c. One individual was treated with a 3-drug regimen including contemporary PI and INSTI (lamivudine (3TC) + RAL + DRV/r). The 2NRTIs backbone was tenofovir disoproxil fumarate (TDF) or alafenamide (TAF)/emtricitabine (FTC) in 78 (59%) individuals treated with DTG and in 132 (94%) treated without DTG, whereas abacavir (ABC)/3TC was prescribed in 49 (37%) among those treated with DTG and in 6 (4%) among those treated without DTG.

Among 120 AIDS-presenters 178 AIDS-defining events were reported (Fig. 1). The most frequent AIDS-defining event was *Pneumocystis jirovecii* pneumonia (PjP) diagnosed in 41 (34%), followed by Kaposi's sarcoma (KS) in 24 (20%) individuals, *Candida* oesophagitis and cytomegalovirus symptomatic infection both in 23 (19%) individuals.

One hundred-eighty-two (67%) individuals discontinued their first-line regimen: 109 (60%) for simplification, of whom 29/182 (16%) switched from TDF to TAF, 32 (18%) for toxicities, 4 (2%) for drug-drug interactions, 37 (20%) for other reasons. The switch from ABC/3 TC + DTG to ABC/3TC/DTG co-formulated was not considered interruption. DTG was interrupted in 19/132 (14%) individuals: 13 (68%) for reported any grade adverse events, of whom 5 for intolerance, 4 for gastrointestinal disorders and 4 for neurological symptoms, 2 (11%) for proactive switch and 4 (21%) for medical or individual choice. The 12-month estimated probability of first-line interruption was 40% (CI 95% 36–44) for any drug in regimens without DTG and 44% (CI 95% 40–48) in regimens with DTG (Log Rank p = 0.08). The 12-month estimated probability of DTG interruption was 14% (CI 95% 11–17). During a median observation time of 16 months (IQR 5–24), HIV-1 RNA < 50 copies/mL was achieved in 95/132 (72%) PLHIV on DTG-based regimen and in 92/140 (66%) PLHIV with other regimens. After DTG-based regimen initiation the proportion of individuals with HIV-1 RNA < 50 copies/mL was 36% at 1 month, 81% at 6 months, 80% at 12 months vs 17% at 1 month, 77% at 6 months, 78% at 12 months among those without DTG (Fig. 2a). Among 38 individuals with HIV-1 RNA≥ 50 copies/mL after 6 months of treatment, 14/16 of those treated with DTG and 21/22 of those not treated with DTG had HIV-1 RNA > 100,000 copies/mL at baseline. Statistically significant increases in CD4 cells count and CD4/CD8 ratio from baseline were observed at every time point (p < 0.05) for all intragroup comparisons and in both arms (Fig. 2b–c).
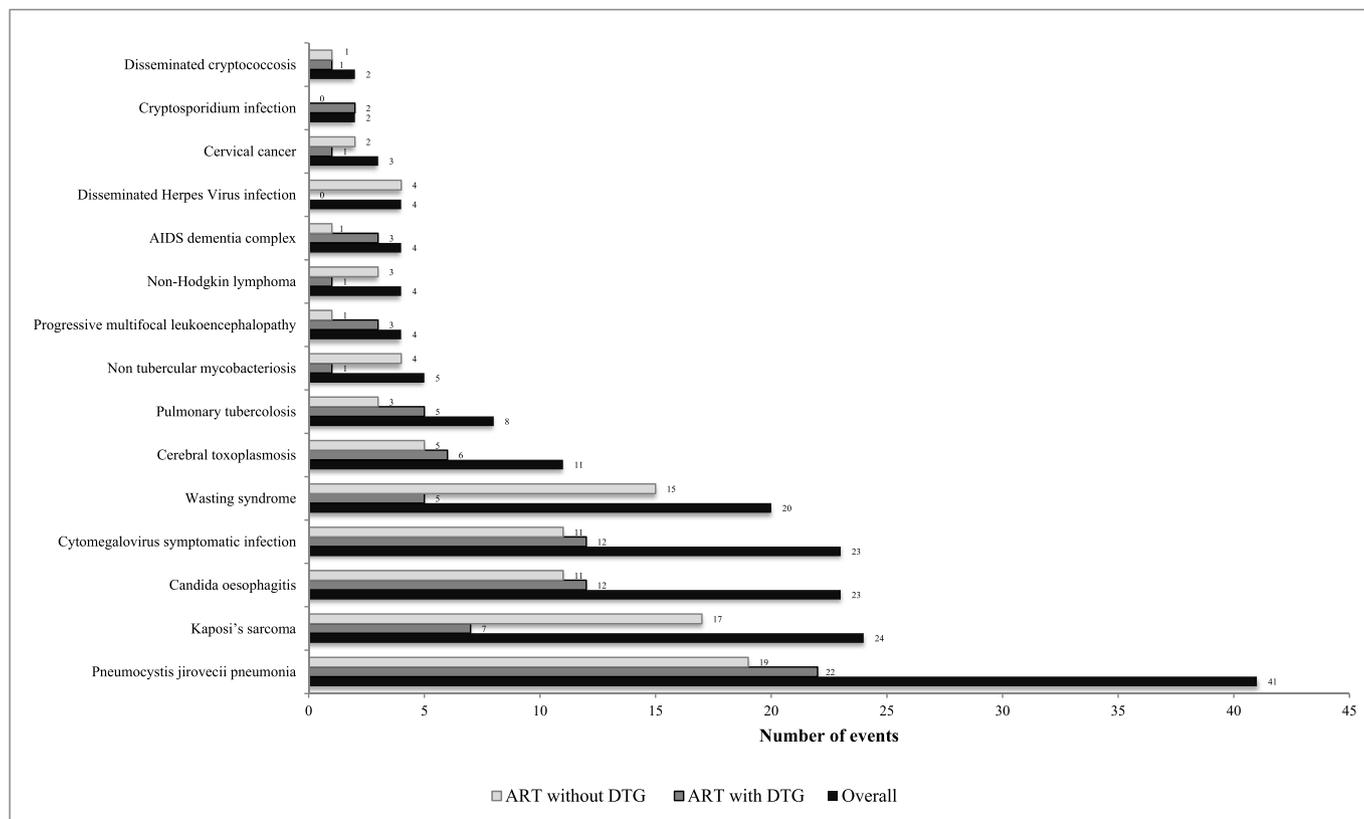
Fig. 1. AIDS-defining events according to antiretroviral regimens.

IRIS was reported in 13/272 (5%) PLHIV, all AIDS-presenters, without significant difference regarding antiretroviral therapy: 5 events (4%) occurred among patients treated with regimens including DTG and 8 (6%) among those treated with regimens without DTG. Among PLHIV on DTG-based cART, IRIS was related to KS in 2 individuals, to PjP associated to *Candida* oesophagitis and wasting syndrome or KS respectively in 2 individuals and progressive multifocal leukoencephalopathy in 1 individual. Among those on cART without DTG, IRIS was related to KS in 3 individuals, to wasting syndrome associated to Cytomegalovirus symptomatic infection and *Candida* oesophagitis in 2 individuals, to disseminated Herpes Virus infection in 1 individual, to PjP associated to wasting syndrome in 1 individual, to non-Hodgkin lymphoma associated with KS and disseminated Herpes Virus infection in 1 individual.

Univariate analysis showed no association between the development of IRIS and baseline HIV-1 RNA > 100,000 copies/mL or HIV-1 RNA > 500,000 copies/mL, DTG-including regimens, two different NRTIs backbones use (TDF or TAF/FTC *vs* ABC/3 TC), HBV or HCV coinfection.

Overall, 10 PLHIV died within 24 months after first-line cART initiation, of these 5 were on DTG regimens. The deaths were due to KS complications in 2 cases, progressive multifocal leukoencephalopathy in 1, PjP in 1 and to a non-AIDS related event in the remaining case. Furthermore, 5 PLHIV on cART without DTG died during the follow up due to PjP in 2 cases, to non-AIDS related events in 2 cases and to non-Hodgkin lymphoma in the remaining case.
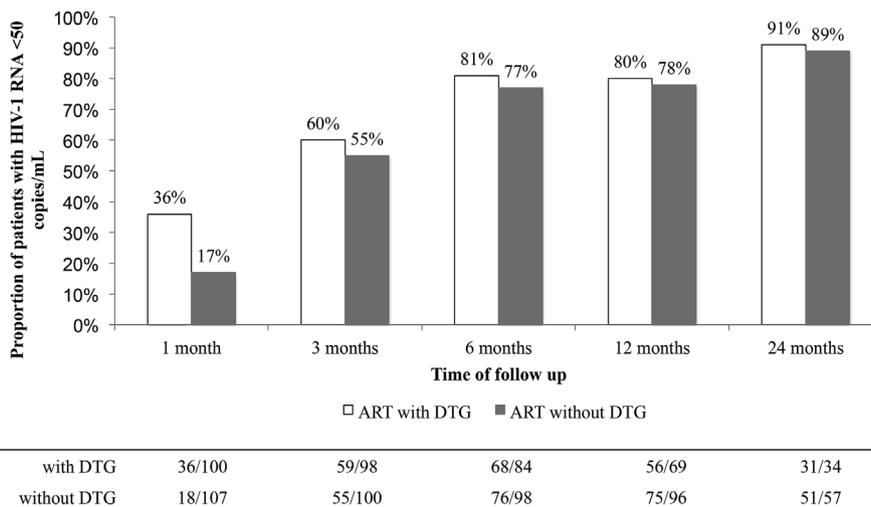

	1 month	3 months	6 months	12 months	24 months
with DTG	36/100	59/98	68/84	56/69	31/34
without DTG	18/107	55/100	76/98	75/96	51/57

Fig. 2a. Proportion of patients with virological suppression over the 12 months of follow up according to antiretroviral regimens.
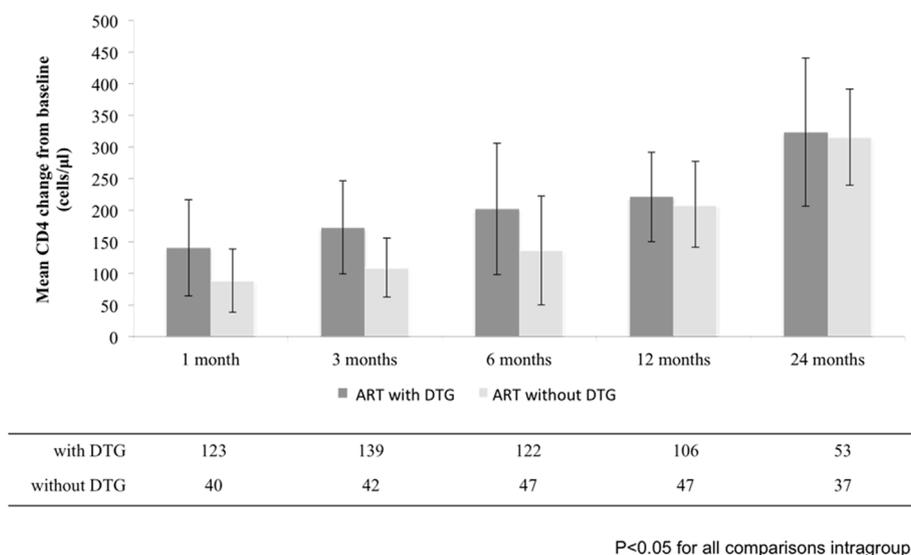
Fig. 2b. Mean CD4$^+$ cells count change from baseline according to antiretroviral regimens.
Histograms represent mean and whiskers represent 95% confidence intervals.

INSTIs have shown higher efficacy compared to other antiretroviral classes, with a favorable safety profile in trial and observational studies (Mondi et al., 2019; Bonfanti et al., 2017). In our series the cART virological efficacy was similar in regimens including DTG *vs* regimens without DTG, but DTG showed a faster viral decay in respect of the control group, as expected. In particular, patients treated with DTG achieved a HIV-1 RNA < 50 copies/mL in 36% *vs* 17% within the first month of treatment. The speed of viral decay due to the high potency of DTG could play a major role in the development of IRIS (Müller et al., 2010; Detels et al., 2001).

There is a paucity of data regarding the possible association between cART choice and the development of IRIS and they come from clinical trials in the vast majority. In our cohort study, IRIS occurred in 5% of PLHIV initiating cART and patients treated with DTG exhibited a frequency of IRIS which was comparable to those who did not receive DTG. In SAILING, a prospective trial of DTG *vs* RAL, there was an apparently slightly increased IRIS events risk in the patients on DTG who were co-infected with hepatitis B or C compared to RAL (Cahn et al., 2013).

Recently, the REALITY trial has shown that the mortality of patients with CD4 cell counts < 100 cells/μl in African countries was significantly lower in the enhanced prophylaxis group vs standard prophylaxis group at 24 and 48 weeks with higher IRIS rate in RAL recipients in both groups (Hakim et al., 2017).

Wijting et al. retrospectively evaluated 369 patients from a large cohort of participants in the ATHENA cohort and they found a significant risk for those under treatment with INSTIs (HR 2.6, 95% CI 1.6–4.4) (Wijting et al., 2017). Furthermore, Dutertre et al. evaluated 2287 participants of the Dat'AIDS cohort and found significant association of severe IRIS to the use of INSTIs (Dutertre et al., 2017) (3% *vs* 1.5% among those treated without INSTIs) and Psichogiou et al. found that INSTIs and especially DTG and EVG were significantly associated to a higher risk for IRIS emergence when compared to NNRTIs (OR 2.9, 95% CI 1.3–6.6) (Psichogiou et al., 2017).
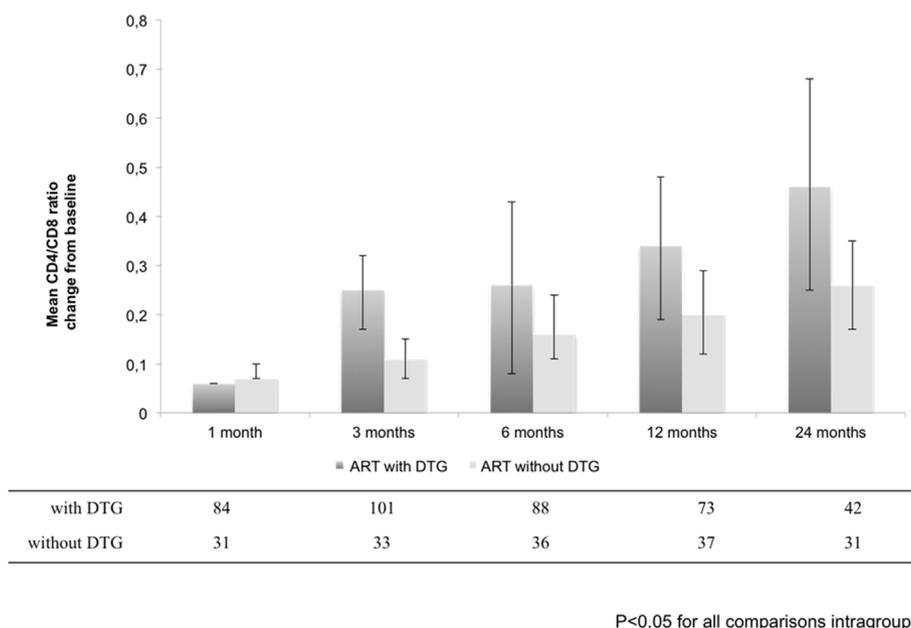

Fig. 2c. Mean CD4/CD8 ratio change from baseline according to antiretroviral regimens.
Histograms represent mean and whiskers represent 95% confidence intervals.

The main limitations of the study are its retrospective design, the clinical definition of IRIS and the unbalanced distribution in the cART arm. Due to retrospective design, some participants files had missing data. The strength of our cohort is the representativeness of the demographic of advanced naïve PLHIV in different Italian clinical centers, because AIDS-presenters, who are in increased risk for IRIS, are usually excluded from clinical trials due to their clinical conditions and thus potential IRIS events were not described.

We did not identify any association between the IRIS occurrence and other variables possibly due to the low IRIS frequency. A prospective matched cohort trial would be required in order to overcome these limitations. In parallel, the implementation of HIV testing programs appears fundamental to diagnose and treat HIV infection as early as possible, to avoid AIDS-related comorbidities and to reduce the risk of IRIS (Girardi et al., 2007).

In conclusion, our results confirm the high potency, good tolerability, and safety of DTG also in first-line treatment of advanced-naïve patients with a relatively low risk of IRIS occurrence.

References

Antinori, A., Coenen, T., Costagiola, D., et al., 2011. Late presentation of HIV infection: a consensus definition. HIV Med. 12, 61–64.

Bonfanti, P., Madeddu, G., Gulminetti, R., et al., 2017. Discontinuation of treatment and adverse events in an Italian cohort of patients on dolutegravir. AIDS 31, 455–457.

Borghi, V., Girardi, E., Bellelli, S., et al., 2008. Late presenters in an HIV surveillance system in Italy during the period 1992-2006. J. Acquir. Immune Defic. Syndr. 49, 282–286.

Cahn, P., Pozniak, A.L., Mingrone, H., et al., 2013. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, noninferiority SAILING study. Lancet 382, 700–708.

Celesia, B.M., Castronuovo, D., Pinzone, M.R., et al., 2013. Late presentation of HIV infection: predictors of delayed diagnosis and survival in Eastern Sicily. Eur. Rev. Med. Pharmacol. Sci. 17, 2218–2224.

Detels, R., Tarwater, P., Phair, J.P., et al., 2001. Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis. AIDS 15, 347–355.

Di Biagio, A., Cozzi-Lepri, A., Prinapori, R., et al., 2016. Discontinuation of initial antiretroviral therapy in clinical practice: moving toward individualized therapy. J. Acquir. Immune Defic. Syndr. 71, 263–271.

Dutertre, M., Cuzin, L., Demonchy, E., et al., 2017. Initiation of antiretroviral therapy containing integrase inhibitors increases the risk of IRIS requiring hospitalization. J. Acquir. Immune Defic. Syndr. 76, e23–e26.

Girardi, E., Sabin, C.A., d'Arminio Monforte, A., 2007. Late diagnosis of HIV infection: epidemiological features, consequences and strategies to encourage earlier testing. J. Acquir. Immune Defic. Syndr. 45 (Suppl. 1), S3–S8.

EACS Guidelines Version 9.0. http://www.eacsociety.org/files/guidelines_9.0-english.pdf Accessed 29th January 2019.

Hakim, J., Muslime, V., Szubert, A.J., et al., 2017. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. N. Engl. J. Med. 377, 233–245.

Hill AM, M., Mitchell, N., Hughes, S., et al., 2018. Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for dolutegravir versus other antiretrovirals: meta-analysis of randomized trials. Curr. Opin. HIV AIDS 13, 102–111.

Late presenters working group in COHERE in EuroCoord,Mocroft, A., Lundgren, J., Antinori, A., et al., 2015. Late presentation for HIV care across Europe: update from the collaboration of observational HIV epidemiological research Europe (COHERE) study, 2010 to 2013. Euro Surveill. 20, 47.

Li, T.S., Tubiana, R., Katlama, C., et al., 1998. Long-lasting recovery in CD4 T-cell function and viral-load reduction after highly active antiretroviral therapy in advanced HIV-1 disease. Lancet 351, 1682–1686.

Mondi, A., Cozzi-Lepri, A., Tavelli, A., et al., 2019. Effectiveness of dolutegravir-based regimens as either first-line or switch antiretroviral therapy: data from the Icona cohort. J. Int. AIDS Soc. 22 (1), e255227.

Müller, M., Wandel, S., Colebunders, R., et al., 2010. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect. Dis. 10, 251–261.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with Hiv. Department of health and human services. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf Accessed 29th January 2019.

Psichogiou, M., Basoulis, D., Tsikala-Vafea, M., et al., 2017. Integrase strand transfer inhibitors and the emergence of immune reconstitution inflammatory syndrome (IRIS). Curr. HIV Res. 15, 405–410.

Wijting, I.E.A., Rokx, C., Wit, F.W.N.M., et al., 2017. Integrase Inhibitors Are an Independent Risk Factor for IRIS: an ATHENA-Cohort Study,#731 Proceedings of the CROI 2017, Seattle, USA.

Wilton, J., Light, L., Gardner, S., et al., 2019. Late diagnosis, delayed presentation and late presentation among persons enrolled in a clinical HIV cohort in Ontario, Canada (1999-2013). HIV Med. 20, 110–120.