COMPARISON OF IMMUNOLOGICAL AND VIROLOGICAL RECOVERY OF RALTEGRAVIR, ELVITEGRAVIR AND DOLUTEGRAVIR IN HIV-1 INFECTED NAIVE PATIENTS

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ABSTRACT

Introduction*: In HIV infected patients, CD4 + T cell number indicates immunological function, but the CD4/CD8 ratio is an indicator of immune dysfunction, a prognostic marker for non-AIDS mortality, and reflects viral reservoir size in HIV patients. We aimed to investigate comparison of three integrase strand transfer inhibitors (INSTIs) with CD4+ T cell count, CD4/CD8 ratio normalization and virological suppression in HIV-1 infected patients.*

Methods*: This retrospective comparative case series study was carried out in HIV-1 positive treatment naive patients who initiated antiretroviral regime between 2016 and 2018 with raltegravir (RAL), elvitegravir/cobicistat (EVG) and dolutegravir (DTG).*

Results*: Laboratory and clinical characteristics of the patients used RAL (n=28), EVG (n=29) and DTG (n=32). Therapy response rate at 12th month in patients; did not reveal a statistically significant difference between the CD4/CD8 ratio (p=0.4345), did reveal a statistically significant difference at one percent between HIV RNA levels (p=0.0003). However, the increase of CD4+T cell count was higher in DTG than the others (p=0.003). RAL was inferior to the others about virological response at months 3rd, 6th and 12th. On the other hand, there was no statistically significant difference between EVG and DTG in virological response. The safety profile of RAL, EVG and DTG was generally the same.*

Conclusions*: In HIV infected patients, to control viral replication, which is the main cause of persistent immunological activation and inflammation is important. All three INSTIs had similar activity in CD4/CD8 ratio normalization but DTG increased the number of CD4+ T cell count and gave a high immunological response at 12th months. RAL showed inferior activity in virological suppression at 3, 6 and 12th months. Our real-life outcomes can be a guide for patients in need of immunological healing in late presenters, as well as patients who require rapid virological response.*

Keywords: *Raltegravir, Elvitegravir, Dolutegravir, HIV, CD4:CD8 ratio, Integrase inhibitors.*

DOI: 10.19193/0393-6384_2019_6_483

Received *November 30, 2018;* ***Accepted*** *February 20, 2019*

Introduction

In cases of Human Immunodeficiency Virus infection (HIV), antiviral therapy is administered to achieve optimal immunological restoration and viral suppression. Integrase strand transfer inhibitors (INSTIs) are currently the standard of care for first-line HIV therapy for most patients. Three INSTIs are currently recommended by guidelines for the first-line treatment of HIV[1-4]. INSTIs have blocked the strand transfer reaction catalyzed by HIV-1 and have been shown to potentially inhibit infection with wild-type HIV-1[5].

Raltegravir (RAL) was the first INSTI approved (US FDA, October 2007; EMA, January 2008) but its use was preferred in rescue antiretroviral therapy (ART)[6]. Elvitegravir (EVG) was latter approved with tenofovir disoproxil fumarate (FDA, August 2012; EMA, May 2013) and with tenofovir alafenamide (FDA, EMA November 2015) and dolutegravir (DTG) was approved first as a single drug (FDA, August 2013; EMA, November 2013) and subsequently as a single-tablet regimen combination with abacavir plus lamivudine (FDA, August 2014; EMA, September 2014)[7,8]. Two new INSTIs, cabotegravir and bictegravir, are currently in late-stage clinical trials[9,10]. INSTIs-based regimens have high rates of virologic suppression and often have less side effects than comparing with other ART.

They have high efficacy for the patients whose HIV RNA>100.000 copies/ml[11]. On the other hand, each has potential disadvantages; The once-daily co-formulation of unboosted RAL has recently been approved by the FDA, but requires more than one tablet, and RAL is not present in co-formulated regimens with other antiretrovirals[12]. EVG can be administered once daily as a single-tablet regimen with either tenofovir disoproxil fumarate or tenofovir alafenamide but requires boosting with cobicistat[7]. DTG is an unboosted INSTI with a high barrier to resistance and can be administered once with abacavir, which some clinicians choose to avoid in patients with high cardiovascular disease risk. However, DTG can be dosed separately with other nucleoside reverse transcriptase inhibitors[8].

In HIV-treated patients, total CD4+ T cell count is important to maintain levels above 500 cells/ mm^3 but does not always reflect the normalization of immunological function[13]. However, it has been accepted that cytotoxic CD8+ T cells are damaged and cause permanent inflammation. The studies showed that the CD4/CD8 ratio, an old biomarker is an indicator of immune dysfunction, a prognostic marker for non-AIDS mortality, and reflects viral reservoir size in HIV patients. CD4/CD8 ratio, CD4+ T cell count, and viral load are additionally important determinants of ART activity[14].

Currently, there are limited studies on comparison of RAL, EVG, DTG in real life. We therefore aimed to assess the effectiveness of three INSTIs with CD4+ T cell count, CD4/CD8 ratio normalization and virological suppression in HIV-1 infected patients over a given period.

Materals and methods

Patients

This retrospective comparative case series study was carried out in HIV-1 positive treatment naive patients who initiated combination ART between May 22, 2016 and May 30, 2018 with RAL, EVG and DTG at the clinic of HIV in Antalya-Turkey. The study involved 89 patients with HIV who were treated with RAL (n=28), EVG (n=29) and DTG (n=32). Study drugs were given with co-formulated tenofovir/emtricitabine backbone. Patients who completed 12 months of treatment were included in the study. Suitable patients were 18 years of age or older, had never received ART, and had at least 1000 copies of plasma HIV-1 RNA at a rate of at least 1000 copies per milliliter, without genotypic evidence of HIV-1 protease and screening reverse transcriptase resistance mutations.

Patients excluded from the study were any patients with co-infectious with hepatitis B and hepatitis C; pregnant women; immunosuppressive diseases; any malignancies; autoimmune diseases; concomitant illnesses (dementia, or severe psychiatric or neurological conditions); illicit drug users; incompatible to treatment and treating in less than a 12-month period.

The diagnosis of HIV/AIDS were based on clinical manifestation supported by laboratory examination. They were categorized as HIV-1 infected according to the manual of European AIDS Clinical Society Guideline[2].

Patient records were reviewed retrospectively. Follow-up visits were at weeks 2, 4, 12, 24, 36, and 48 during which plasma HIV-1 RNA levels, CD4+ T and CD8+ T cell counts, metabolic panels (including serum electrolyte levels and liver function tests), and complete blood cell counts. Study visits were at baseline, and months 1, 3, 6, and 12. Patients were considered as compliant with their therapy if they took their pills daily at the same time without interruption. Regarding side effects, any symptoms or signs that improved after cessation of treatment, or abnormal clinical or laboratory findings, were considered as adjunctive side effects.

Immunological response

CD4+ and CD8+ T cells: T lymphocytes can be functionally divided into cells that express the cluster determinant of T lymphocytes 8 (abbreviated as "CD8") while cytotoxic T cells express cluster determinant 4 (abbreviated as "CD4") and CD4 and CD8 potentiate stimulatory signals through the T cell receptor[15]. CD4+ T cell counts correlate with the immune response. In patients who achieve and maintain viral suppression, immunological response is improve progressively over years. Viral suppression is usually associated with an increase in CD4+ T cell counts of ≥50 cells/mm^3 at four to eight weeks followed by an incremental increase of 50 to 100 cells/mm^3 per year[16].

The ratio of CD4/CD8 is calculated by dividing the number of CD4+ T cells by the number of CD8+ T cells; this ratio is usually greater than 1 in immunocompetent persons[17]. In chronic infection CD8+ T cells are increased and CD4+ T cells are decreased. Although the CD4/CD8 ratio returns to normal only in the minority of patients, this rate usually increases with the onset of ART[13].

Virological response: The expectation with ART is to achieve at least a one-log (10-fold) decline in HIV-1 RNA by one to two weeks, a two log (100-fold) decline by four weeks, and a viral load near or below the level of detection by 8 to 24 weeks, regardless of previous treatment experience[1].

Laboratory analysis

Plasma samples were tested for HIV antibodies using a 4th generation anti-HIV1-2 Ab/Ag enzyme-linked immunoassay (ELISA) (Cobas E 601 Analyzer Roche Diagnostic- Mannheim, Germany) and positive results were tested once using the same ELISA assays. Positive results were confirmed by HIV1/2 Western blotting (DIA PRO, HIV-1 LIA, Diagnostic Bioprobes Srl, Italy). Plasma HIV-1 RNA detection and quantification levels were measured using real time- PCR (Abbott TagMan 2000, Illinois-Des Plaines USA) (lower limit as quantification, 10 IU/ml). CD4 and CD8+ T cell counts and percentage were measured at each study visit to assess immunological response. They were analyzed with BD Simultest™ CD4/CD8 (Becton, Dickinson and Company BD Biosciences 2350 Qume Drive San Jose, CA 95131 USA).

Statistical analysis

One-way analysis-of-variance ANOVA was conducted to compare the means of the baseline demographic and laboratory characteristics and side effects of RAL, ETV and DTG for continuous variables (age, gender, HIV RNA loads, CD4+ T cell counts, CD4/CD8 ratios). The post-hoc multiple comparison test based on Scheffe-adjusted significance levels does not reveal a statistically significant difference between the HIV RNA means for the EVG and DTG patients at 3rd and 6th month control and the same test about side effects such as myalgia does not reveal a statistically significant difference for the two groups (EVG and DTG). P-value of ≤0.05 were considered statistically significant. Statistical analyses were conducted using SPSS v.13. designed for Windows (SPSS Inc., Chicago, IL, USA).

Ethics committee approval was obtained at Health Sciences at the University Antalya and Education Research Hospital in Turkey in accordance with the principles of the 2008 Declaration of Helsinki (Registration No: 17.05.2018 10/10).

Results

Between May 22, 2016 and May 30, 2018, a total of 96 patients were investigated from the records. Subsequent seven patients were found to be ineligible due to treatment incompatibilities and discontinuations due to side effects. The final population for analysis therefore included 89 patients. Baseline demographics and disease characteristics of patients were comparable between arms. Most patients had HIV-1 subtype B (data not shown). Median age of patients was; 40.9, 40.8, 42 (p=0.9391) years and gender (Female/Male) ratios were 0.11, 0.10, 0.22 (p=0.3549) respectively. The median basal CD4+ T cell count: 416.8, 353, 376.4 cells/mm3 (p=0.6331), median basal CD4/CD8 ratio: 0.42, 044, 0.44 (p=0.9513), median basal HIV-1 RNA: 2,5+E5, 3,3+E6, 7,9+E6 copies/mL (p=0.2669) respectively. The three groups were balanced for all parameters. The baseline characteristics of patients are summarized in Table 1.

Characteristics	Integrase Strand Transfer Inhibitors			
	Raltegravir	Elvitegravir	Dolutegravir	P value
Patient, n	28	29	32	0.3675
Gender (F), n (%)	26 (93)	26 (90)	27 (84)	0.3549
Age, median years (range)	41 (19-80)	41 (22-73)	42 (21-65)	0.9391
Baseline CD4+ T cell count, median (range), SD	417 (12-1215) 291.9	353 (9-1218) 223.5	376 (8-819) 225.2	0.6331
Baseline CD4/CD8 ratio, median (range)	0.42 (0.01- 1.33)	0.44 (0.01- 1.5)	0.44 (0.03- 1.15)	0.9513
Baseline HIV-1 RNA load, median copies /mL (range)	2,5+E5 (5+E3-2.4 E6)	3,3+E5 (1.4+E3-6.6+E6)	7.9+E5 (6.5+E3-7.8+E6)	0.2669

Table 1: Baseline demographic and laboratory characteristics of the study patients.

Changes in CD4/CD8 ratio normalization and CD4+ T cell count

Comparison between treatment groups in CD4/CD8 ratio normalization showed no statistically significant difference, except in the first month of treatment, CD4/CD8 ratio of RAL was higher than other groups (Figure 1).

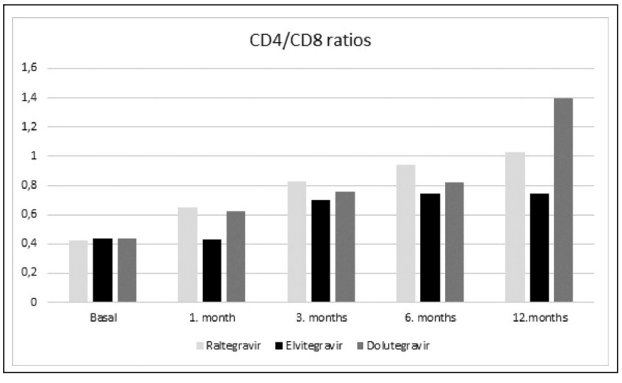

Fig. 1: The ratio of CD4/CD8 ratio between the treatment groups.

It did reveal a statistically significant difference at five percent (p=0.0456). At the 12th month of treatment, median (IQR) CD4/CD8 ratio normalization of RAL, EVG, DTG was 1.03 (0.16-2.20), 0.74, (0.19-2.13), 1.4, (0.23-2.16) respectively (p=0.4345). Although there was no statistically significant difference between the groups, RAL and DTG were found to reach normal CD4/CD8 ratio interval at 12th months. On the other hand, according to CD4+ T cell counts, there was no statistically significant difference between the RAL, EVG and DTG during the study months. (data not shown). At 12th months, CD4+ T cell counts in three groups with mean (SD) increased up 659 (269.3) cells/mm^3 for RAL, 594 (220) cells/mm^3 for EVG and 783 (376.4) cells/mm^3 for DTG at month 12 (p=0.3649). However, the change from baseline in CD4+ T cell counts was consistently greater in the DTG group than in EVG and RAL groups at 12th months (+407 cells/mm^3 vs. +241 cells/mm^3 and +242 cells/mm^3) (p=0.003). The alteration of CD4+ T cell count is showed in Figure 2.

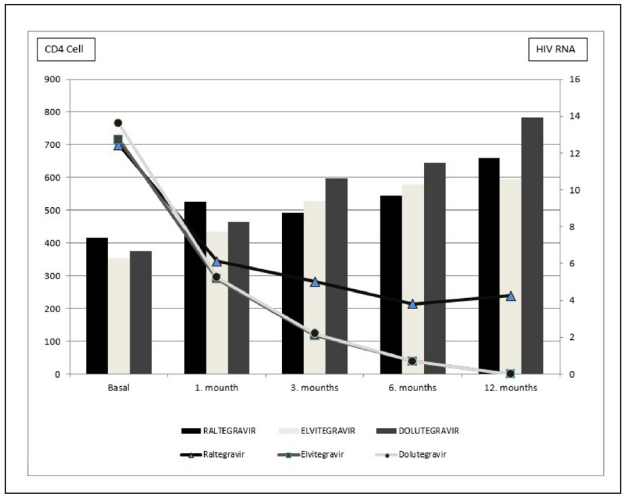

Fig. 2: CD4+ T cells and HIV-1 RNA levels in patients on antiretroviral therapy.

Virological response

At 3, 6, and 12 months, statistically significant differences in HIV-1 RNA levels were found among the groups (p=0.0412, p=0.0111, p=0.0003) (Figure 2). Decreasing of HIV-1 RNA level below undetectable levels by sensitive PCR was found higher in EVG and DTG groups than RAL group. On the other hand, there was no statistically significant difference in the reduction of HIV RNA level between EVG and DTG groups (p>0.05). When we compared the number of patients whose HIV-1 RNA levels were undetectable by sensitive PCR; at 3 months 82%, 93% and 90%; at 6 months 89%, 100% and 96%; at 12 months 92%, 100% and 100% in the RAL, EVG and DTG treatment groups, respectively. RAL was inferior to the others about virological response at months 3rd, 6th and 12th. Virological responses of the groups are shown in Figure 3.

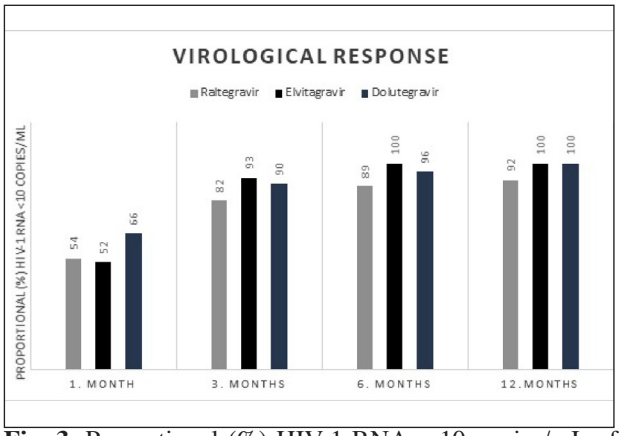

Fig. 3: Proportional (%) HIV-1 RNA < 10 copies/mL of the patients.

Safety

Discontinuations due to side effects occurred in 1 (3.5%), 0 and 1 (3.1%) patients in the respective groups (RAL, EVG, DTG). They were not included in the study group. The safety profile of RAL, EVG and DTG was generally the same. There were no statistically significant differences between the INSTIs about side effects except for myalgia that revealed a statistically significant difference at ten percent (p=0.0824) in RAL group, more than the others.

Integrase Strand Transfer Inhibitors				
Side Effects	**Raltegravir (*n*=28)**	**Elvitegravir (*n*=29)**	**Dolutegravir (*n*=32)**	***P* value**
Insomnia	2(7%)	2 (6.8%)	3 (9.3%)	0.9312
Headache	3 (10%)	2 (6.8%)	3 (9.3%)	0.8640
Dizziness	1(3.5%)	3 (10.3%)	1 (3.1%)	0.4238
Myalgia	4 (20%)	2 (13%)	ND	0.0824*
Urticer	ND	ND	ND	
Nausea	1 (5%)	ND	ND	0.3282
IRIS	ND	ND	1	0.3282
Discontinuation	1(3.5%)	ND	1(3.5%)	0.2980

Table 2: Side effects among the three integrase inhibitors.
IRIS: Immune reconstitution inflammatory syndrome
** Significant at 10 percent*
ND; not determined

The most common drug related side effect was headache; RAL (10%), EVG (6.8%), DTG (9.3%). Laboratory parameters associated with the potential side effects were not seen in all patients. Side effects among the three integrase inhibitors are shown table 2.

There was an interesting side effect about DTG in one patient (data not shown). In the first month of DTG treatment, the patient complained the loss of sense of taste and smell. After a long and detailed check, there was no reason that cause sensory loss. Whenever DTG was discontinued the patient started to taste very well but the loss of smell unfortunately was kept on until one year later. The other discontinuation due to side effect was the patient who had headache and nausea with RAL.

Discussion

Current studies regarding the INSTIs treatments efficacy between RAL, EVG and DTG in real life setting are limited. In the present study, the aim was to compare the treatment efficacy of them in real life in HIV-1 infected naive patients at months 1th, 3rd, 6th and 12th. We used the CD4+ T cell count, CD4/CD8 ratio normalization and virological suppression parameters in both the immunological and virological responses. They had similar activity in CD4/CD8 ratio normalization but DTG increased the number of CD4+ T cell count and gave a high immunological response at 12th months. RAL showed inferior activity in virological suppression at 3, 6 and 12th months.

Clinical and cohort studies analyzing the immunological effects of ART have been generally focused on CD4+ T cells; with limited data available to evaluate the effect of treatments on the CD4/CD8 ratio increase[14,17-19]. Several studies have investigated the relationship between ART regimens and CD4/CD8 ratio normalization. According to our knowledge, the ratio of CD4/CD8, especially among INSTIs, was not examined in order to investigate the efficacy of treatment. In naïve patients initiating treatment with INSTIs-based regimens, we found that there was no difference between the groups on CD4/CD8 T cell normalization rate in the first year.

However, RAL and DTG were found to reach normal CD4/CD8 ratio interval at 12th months. It is desirable to rapidly normalize the CD4/CD8 ratio of the initial regimen. In naive patients, after ART is started intense inflammation and immune activation resulting in a higher reduction of CD8+ T cells in viremic patients[20].

INSTIs have been shown a positive effect on inflammation and immunostimulatory biomarkers compared to other antiretroviral classes, potentially leading to a greater reduction of CD8+ T cells and increase of CD4+ T cells[21], except for the study by Masia M et al, INSTIs-based regimens had been shown less CD4/CD8 ratio increase than non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors therapy (PI)-based regimens[22].

Another study about CD4/CD8 ratio recovery between RAL and efavirenz was showed that RAL had faster CD4/CD8 ratio normalization compared with efavirenz[23]. CD4/CD8 ratio normalization had been shown to be an independent non-AIDS morbidity factor in HIV patients, might be low even in ART treated patients, who had negative viral load with a CD4+ T cell count above 500 cells/mm^3[24]. In this case; the selection of the first treatment regimen, especially in naive patients, is very important. It should be a regimen that increases the number of CD4+ T cells and reduces the viral load as well as normalizing the CD4/CD8 ratio more rapidly. Serrano and et al showed that RAL had reached to normalizing CD4/CD8 ratio within 593 (420-774) days (approximately 20 months) that longer duration than ours[24]. This may be due to the higher number of baseline CD4 cells count in our study (208 vs. 416 cells/mm^3). In the study comparing dolutegravir/abacavir/lamivudine and efavirenz-tenofovir/emtricitabine, there had been no statistically significant difference in the proportion of patients reaching CD4/CD8 ratio at 48th week. However, efavirenz-tenofovir/emtricitabine had showed significantly greater increases in CD4/CD8 1.0 at week 96[25]. In this case, between the INSTIs, DTG and RAL may have high advantages for in late presenter HIV-1 infected patients by providing rapid CD4/CD8 ratio normalization.

The likelihood of normalization of the CD4/CD8 ratio is also strongly related to CD4+ T cell count[26]. In the current study, a similar increase in CD4+ T cell counts was detected during the study period between three INSTIs. On the other hand, the 12th month increase in CD4+ T cell count was found to be greater in the DTG group than in the EVG and RAL groups. (+407 cells/mm^3 vs. +241 cells/mm^3 and +242 cells/mm^3). It is known that the number of CD4+ T cells increase annually by 100-150 cells/mm3 on average[16]. We saw that the increase of CD4+ T cells was high with INSTIs in one year. This situation supported previous works with INSTIs

like SPRING-2 study in which CD4+ T cell counts increased from baseline to week 48 in both DTG and RAL treatment groups by a median of 230 cells per mm^3[27]. The increase of CD4+ T cell count with INSTIs was also higher than NNRTI and PI therapy[28].

This rapid increase in CD4+ T cell counts shortens the prophylactic duration of opportunistic infections and reduces AIDS-associated morbidity and mortality. However, in late presenters treated with INSTIs may carry a greater risk to develop immune reconstitution inflammatory syndrome (IRIS) due to rapid increase in CD4+ T cell counts. It is important in resource limited countries where certain opportunistic infections are endemic. In SAILING study, increased IRIS events in patients with DTG compared to RAL in co-infected with hepatitis B or C were seen to be higher, although not statistically significant[29]. We did see IRIS in one patient that treated with DTG. did see IRIS in one patient that treated with DTG.

As virological suppression; we found that EVG and DTG had statistically significant higher virologic activity when compared to RAL, starting at 3 months. At 12 months, 29 (100%) patients in the EVG group and 32 (100%) patients in the DTG group achieved an HIV-1 RNA value of undetectable by sensitive PCR compared with 26 (92%) in the RAL group. The studies about virological response showed that in treatment-naive patients, SPRING-2 study, DTG was noninferior to RAL, in treatment-experienced patients, SAILING study, DTG was superior to RAL and in treatment-experienced patients, study 145 team, EVG was noninferior to RAL[27,29,30].

In our study, the month 12 response rates for patients, receiving study drugs in combination with backbone tenofovir/emtricitabine were found to differ from the previous studies in HIV-1 infected patients. The reason for these differences; whether our study was in real life and retrospective, the population was naive, and the number of patients studied was less than others. On the other hand, in patients treated with RAL, EVG and DTG, we did not detect antiviral resistance to INSTIs or tenofovir/emtricitabine backbone prior to treatment. In our study. HIV-1 RNA levels also dropped rapidly with DTG, EVG, and RAL in the first month. However, in the following months, viral suppression was observed higher in DTG and EVG groups than RAL group.

In the real-life setting, nine patients (10%) with INSTIs had a general side effects and ART modification was low (2%) in our study patients. Tolerance and reliability between the three INSTIs were seen in a similar manner and frequency. Similar results were found in the large cohort study by Lepik et al.[31]. We found that RAL group had more myalgia than the others. Although neuropsychiatric side effects with DTG were seen those recently reported in the studies[32,33], we did come across neuropsychiatric problems in three (9.3%) patients who treated with DTG. In the large cohort studies, the rate of discontinuation of DTG because of neuropsychiatric side effects were significantly higher than for other INSTIs[34].

In this study by Hoffmann et al., the rates of neuropsychiatric side events leading to discontinuation within 12 months was estimated to be 5.6% for DTG, but only 0.7% for EVG and 1.9% for RAL. In our study, the discontinuation rate for both DTG and RAL was 3.5% due to all side effects[34]. The explanation might be the larger number of patients included in those studies which may contribute to an overestimation of the neuropsychiatric a side effect of the drugs.

As a result; it is important to control viral replication, which is the main cause of persistent immunological activation and inflammation in HIV-1-infected patients. In this case, DTG showed a high immunologic and virological response within INSTIs groups of our study.

Conclusion

Our real-life results can be guidance for immunological recovery in late presenter HIV-1 infected patients. On the other hand, our results also support the recent update guidelines that largely recommend use of INSTIs-containing regime for naive patients.

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