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Original Article

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A Korean Post-Marketing Surveillance Study of Dolutegravir Single-Agent Tablets in Patients with HIV-1

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ABSTRACT

Background: The integrase strand transfer inhibitor dolutegravir has been indicated in Korea since 2014 for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in combination with other antiretroviral agents. This regulatory post-marketing surveillance (PMS) study evaluated the real-life safety and effectiveness of dolutegravir in patients with HIV-1 in clinical practice in Korea.
Materials and Methods: This open-label PMS study examined data from consecutive patients (aged ≥12 years) with HIV-1 infection receiving dolutegravir according to locally approved prescribing information; treatment-naïve and treatment-experienced patients were permitted. Data regarding patient demographics, medical history, clinical characteristics, medications (HIV-related and concomitant), and comorbidities were extracted from patient records over a 1-year treatment period. Outcomes included the safety of dolutegravir (primary endpoint) and real-life effectiveness according to the Physician Global Assessment (PGA) and the proportion of patients with plasma HIV-1 RNA count <50 copies/mL at 48 weeks.
Results: Of 147 patients treated with dolutegravir at 18 centers in Korea (August 2014 – August 2020), 139 were eligible for the safety analyses and 75 for effectiveness analyses. Patients (mean age 47 years) were mostly male (92.8%) and received dolutegravir in combination with nucleoside reverse transcriptase inhibitor (70.5%) or protease inhibitors (21.6%). Adverse events (AEs) (n = 179 in total) were mostly mild in severity, with the most common being nasopharyngitis (5.0%), dyspepsia (5.0%), pruritus (4.3%), and rash (4.3%). Of 16 adverse drug reactions (ADRs), the most frequent were rash, diarrhea, headache, insomnia, and somnolence (1.4% each). Of 2 serious ADRs, only 1 (gastroenteritis) was unexpected, and both resolved. The risk of experiencing an AE while receiving dolutegravir appeared to be especially increased in patients receiving concomitant medications for other conditions. Dolutegravir effectively suppressed HIV-1 (93.3% of patients had plasma HIV-1 RNA <50 copies/mL), and 100% of patients showed symptom improvement based on physician global assessment.
Conclusion: Results of this PMS study showed that dolutegravir administered as highly active antiretroviral therapy was well tolerated and effective in patients with HIV-1 infection.

Keywords: Anti-retroviral agents; Dolutegravir; Drug surveillance; HIV integrase inhibitor

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Funding

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Data Availability Statement

Information on GSK's data sharing commitments can be found at www.clinicalstudydatarequest.com.

Conflict of Interest

Sungshin Kwon was an employee and shareholder, Jung-Eun Cho and Eun-Bin Lee are employees of, GSK. Otherwise, no potential conflicts of interest relevant to this article was reported.

Author Contributions

Conceptualization: JEC. Data curation: SK, JEC, EBL. Formal analysis: SK, JEC, EBL. Investigation: YSK, JWS. Writing - original draft: SK, JEC, EBL. Writing - review & editing: SK, JEC, EBL, YSK, JWS.

INTRODUCTION

The estimated prevalence of human immunodeficiency virus (HIV) infection in South Korea in 2020 was 20,839 cases [1], and the prevalence is increasing [1-3]. More than 1,000 new cases are diagnosed each year [1, 2, 4, 5]. The majority of Korean HIV-infected patients are in their 30s [2, 5], with the rate of HIV infection among young adults increasing in more recent years [4]. There is also a male sex dominance; the current male to female ratio is 15.4: 1, with the male preponderance increasing over time [2, 5]. This is believed to be driven by homosexual and bisexual contact as the most common routes of infection [2, 5]. Certainly, a high-risk group for HIV infection has been identified as men who have sex with men (MSM) in Korea, attributing inconsistent use of condoms as a significant risk factor [6].

Since the introduction of the first nucleoside reverse transcriptase inhibitor (NRTI) in 1991, the number of antiretroviral agents available in Korea to treat HIV infection has increased [7]. In addition to NRTIs, other classes of antiretroviral agents, introduced sequentially in Korea, include protease inhibitors (PIs), non-nucleotide reverse transcriptase inhibitors (NNRTIs), and integrase inhibitors (IIs) [7]. The combined administration of antiretrovirals as highly active antiretroviral therapy (HAART) effectively suppresses HIV-1 replication and minimizes the risk of resistance [8]. HAART reduces HIV-related morbidity and mortality and helps to prevent transmission of the virus [9]. HAART has resulted in HIV infection becoming a chronic infection with many people living relatively long lives [8].

Dolutegravir (ViiV Healthcare UK Limited, Brentford, Middlesex, UK) is a HIV type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection [10]. It is recommended for both treatment-naïve and treatment-experienced, HIV-infected adults and adolescents (aged 12 years and older) [10]. Dolutegravir was first approved for use in Korea on August 29, 2014 [10]. Ongoing regulatory obligations include the submission of periodic reports every 6 months for 2 years after the approval date, then every year thereafter.

Thus, the aim of this post-marketing surveillance (PMS) study was to evaluate the real-life safety and effectiveness of dolutegravir in patients with HIV-1 infection in clinical practice in Korea.

MATERIALS AND METHODS

1. Study design

This was an open-label, multicenter, PMS study. Consecutive patients prescribed dolutegravir during the surveillance period were identified prospectively by participating physicians. Data were collected from patient records (electronic case report forms) and included information regarding patient demographics and clinical characteristics (*i.e.*, age, sex, body weight, pregnancy and/or breastfeeding status [in females], the date of diagnosis of HIV-1 infection diagnosis, INSTI-associated resistance), as well as the presence of any comorbidities (*e.g.*, hepatitis B or C infection, acquired immunodeficiency syndrome [AIDS], dyslipidemia, myocardial infarction, coronary artery disease, heart failure, arrhythmia), prior HIV medications, dolutegravir start/stop dates, daily dosage, dose changes (including reasons), discontinuation (including reasons), and concomitant medications (HIV-related and others). Safety data, such as adverse events (AEs), severity, causality, and dates of onset/resolution were also collected, along with effectiveness data regarding the Physician Global Assessment

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(PGA) and HIV-1 RNA count. Laboratory data, collected where available, included CD4+ T-cell count, serum creatinine, lipid profile (*i.e.*, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides), and liver chemistry (*i.e.*, alanine aminotransferase, aspartate aminotransferase, total bilirubin).

2. Ethics statement

The study conformed to ethical principles of the Declaration of Helsinki, and all patients provided written informed consent before enrolling in the study. The study protocol was approved by the Institutional Review Board (IRB) of each study center including Chungnam National University Hospital (IRB approval number: CNUH PMS2016-044).

3. Patients

Patients were eligible for inclusion in the study if they were adults and adolescents (aged ≥12 years) with HIV-1 infection and receiving dolutegravir, administered at recommended dosage according to locally approved prescribing information, in combination with other antiretroviral medications. New users of dolutegravir were also permitted. Patients with a previous history of anaphylaxis for any components of dolutegravir, or those receiving dolutegravir co-administered with dofetilide, and pilsicainide were excluded.

4. Treatment

All patients received dolutegravir according to locally approved prescribing information in combination with other antiretroviral medications. The usual recommended dose of dolutegravir was 50 mg (1 tablet) once daily for adult or adolescent patients (including those with bodyweight ≤40 kg) infected with HIV-1 without resistance to the integrase class, and 50 mg twice daily in those with resistance to the integrase class. In patients with documented or clinically suspected INSTI-associated resistance, co-administration of dolutegravir with other drugs (*e.g.*, efavirenz, nevirapine, tipranavir/ritonavir or rifampicin) was avoided.

5. Endpoints and outcome assessments

The primary endpoint of the PMS study was to monitor the safety of dolutegravir, and the secondary endpoint was to examine the real-life effectiveness of dolutegravir.

Patients with ≥1 follow-up visit after initiating dolutegravir were included in safety evaluations. Those unable to attend safety assessment visits were contacted by the physician by telephone or email. Patients lost to follow up were excluded from safety analyses. All AEs were assessed irrespective of causality, including serious AEs (SAEs)/adverse drug reactions (ADRs), and unexpected AEs/ADRs. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v22.1 terminology. SAEs/ADRs defined as events that resulted in death or life-threatening, prolonged hospitalization, disabling or incapacitating, congenital anomalies/birth defects, or were medically important conditions (*e.g.*, drug dependence, abuse, or blood dyscrasia).

Patients included in the effectiveness evaluation were those in the safety population who also had available 48-week efficacy data (± 6 weeks permitted). Effectiveness outcomes captured included PGA conducted 48 weeks after initiating dolutegravir or at discontinuation, and the proportion of patients with plasma HIV-1 RNA count <50 copies/mL at 48 weeks or at discontinuation. For PGA, the effectiveness of treatment was classified based on virologic/clinical data (*e.g.*, plasma HIV-1 RNA and/or CD4+ T-cell count) into three categories: Improved, an improvement in symptoms or maintenance effects were demonstrated; No

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change, no significant change compared with the pre-treatment status and the outcome was not deemed as a maintenance effect; and Worsening, symptoms worsened compared with the pre-treatment status. A maintenance effect was defined as when a symptom was likely to have worsened if the study drug was discontinued, or if the effect remained the same if the study drug was substituted with the prior medication.

Data regarding patient demographics and clinical characteristics were collected at enrolment to ascertain eligibility for the trial. Subsequently, therapy data as well as information regarding the effectiveness and safety endpoints were collected from real-life practice visits up to the end of surveillance (*i.e.*, 1 year of treatment) or discontinuation).

6. Statistical analyses

Although, typically, 3,000 patients are required per PMS regulation, the specific nature of the approved indications for dolutegravir and the rarity of the disease meant that the planned number of patients was adjusted to 90. The safety-evaluable population included all patients who received ≥1 dose of dolutegravir and who completed ≥1 safety assessment, while the effectiveness-evaluable population included patients in the safety-evaluable population with available 48-week effectiveness data.

Demographic data and clinical characteristics of the included patients were summarized using descriptive statistics (*i.e.*, totals, percentages, means, medians, etc.). Categorical outcomes (*i.e.*, AEs, SAEs, PGA, plasma HIV-1 RNA) were summarized as numbers and percentages, with 95% CIs calculated for percentages of patients with an AE. Continuous outcomes were summarized by the number of non-missing values, mean, standard deviation, median, minimum, and maximum values. Cases of SAEs and/or unexpected ADRs were described in detail. A subgroup analysis was conducted using the Chi-square test or Fisher's exact test to evaluate the effects of demographic and clinical factors (*i.e.*, age, sex, previous and combined HIV treatment, comorbidities) on the incidence of AEs.

RESULTS

1. Patient demographics and clinical characteristics

Over the follow-up period of August 29, 2014 to August 28, 2020, a total of 147 patients treated with dolutegravir were identified by 18 investigators in 18 centers in Korea. Of these, 139 were eligible for the safety analyses and 75 for effectiveness analyses (**Fig. 1**).

The baseline demographics and clinical characteristics of the 139 patients in the safety analysis set are shown in **Table 1**. The majority of patients were male (92.8%) and the mean (standard deviation [SD]) age was 47 (± 14.4) years. The median duration of HIV infection was 6 (range, 0 - 24) years, and 4 patients (2.9%) had INSTI-related resistance, of whom two had plasma HIV-1 RNA counts ≥50 copies/mL (48 weeks after dolutegravir administration, plasma HIV-1 RNA counts were <50 copies/mL for 3 patients [data unavailable for 1 patient]). Patients received dolutegravir mostly in combination with NRTIs (70.5%) or PIs (21.6%). The mean (SD) duration of dolutegravir treatment during the PMS was 306.0 (± 165.4) days (range, 5 - 826 days).

2. Safety analysis

1) Adverse events and serious adverse events

Among 139 patients in the safety analysis set, 179 AEs were reported in 92 (66.2%) patients

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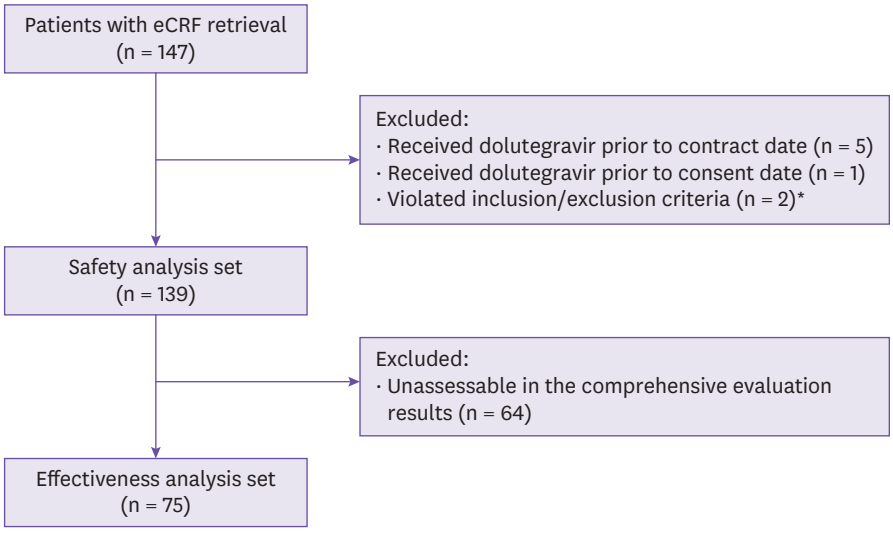

*Administration of dolutegravir twice daily despite stating no INSTI-related resistance at the first administration

Figure 1. Patient disposition.
eCRF, electronic case report form; INSTI, integrase strand transfer inhibitor.

(**Table 2**). The most common AEs by preferred term (PT) were nasopharyngitis (n = 7; 5.0%), dyspepsia (n = 7; 5.0%), pruritus (n = 6; 4.3%), and rash (n = 6; 4.3%) (**Table 2**). The majority of AEs were mild (152/179 events [84.9%]) or moderate (24/179 events [13.4%]) in severity. Among 179 events, 9 led to permanent discontinuation of dolutegravir (rash and insomnia [n = 2 each], and cellulitis, cerebral infarction, alopecia, sudden death, immune reconstitution inflammatory syndrome [n = 1 each]), and 1 led to temporary discontinuation (pyrexia); none led to dose reduction.

A total of 19 SAEs were reported in 17 patients (12.2%; **Table 2**, **Supplementary Table 1**). The most frequently reported SAEs by PT was condyloma latum and pyrexia (every 2 cases in 2 patients [1.4%]; **Table 2**); both cases of condyloma latum were of moderate severity, caused hospitalization or prolongation of hospitalization, and the patients recovered. One case of pyrexia was moderate, the other severe, both resulted in hospitalization or prolongation of hospitalization, and both patients recovered.

2) Adverse drug reactions and serious adverse drug reactions

A total of 16 ADRs, for which causality with the study drug could not be excluded, were reported in 12 (8.6%) patients. The most frequently reported ADRs by PT were rash, diarrhea, headache, insomnia, and somnolence, each reported in 2 patients (1.4%) (**Table 2**).

Overall, 2 serious ADRs were reported in 2 patients (1.4%): gastroenteritis and insomnia in 1 patient (0.7%) each. Both serious ADRs were moderate in severity and caused hospitalization or prolongation of hospitalization; both patients recovered. In the patient with gastroenteritis, no actions were taken regarding the administration of dolutegravir, whereas dolutegravir was permanently discontinued in the patient with insomnia.

3) Unexpected adverse events and severe unexpected adverse events with unexpected adverse drug reactions

A total of 120 unexpected AEs (UAEs) were reported in 74 patients (53.2%). By PT, the most

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Table 1. Characteristics of the patient population (safety analysis set)

Characteristics	N = 139
Sex, n (%)	
Male	129 (92.8)
Female	10 (7.2)
Age, mean ± SD, years	47 ± 14.4
Age categories, n (%)	
12 – 18 years	1 (0.7)
19 – 29 years	16 (11.5)
30 – 49 years	57 (41.0)
50 – 69 years	54 (38.8)
≥70 years	11 (7.9)
Weight, mean ± SD, kg (n = 127)	66.8 ± 14.5
Duration of HIV infection, years	
Median	6
Range	0 – 24
Plasma HIV-1 RNA count at baseline[a], n (%) (n=75)	
<50 copies/mL	33 (44.0)
≥50 copies/mL	33 (44.0)
Not determined	9 (12.0)
INSTI-related resistance[b], n (%)	4 (2.9)
Medical history, n (%)	
Hepatic impairment (including hepatitis B, hepatitis C)	28 (21.1)
Renal impairment (including ESRD, dialysis)	9 (6.8)
Allergy	1 (0.8)
AIDS	48 (36.1)
Dyslipidemia	36 (27.1)
Myocardial infarction	3 (2.3)
Coronary artery disease	3 (2.3)
Heart failure	1 (0.8)
Arrythmia	4 (3.0)
Other	123 (92.5)
Prior HIV-related medications[c], n (%)	
NRTIs	41 (46.6)
NNRTIs	7 (8.0)
IIs or INSTIs	59 (67.1)
PIs	29 (33.0)
Concomitant HIV-related medications[d], n (%)	
NRTIs	98 (70.5)
NNRTIs	11 (7.9)
IIs or INSTIs	7 (5.0)
PIs	30 (21.6)

[a]Data presented for the effectiveness-evaluable population (N = 75).
[b]Plasma HIV-1 RNA counts for the 4 patients were: 0, 0, 19,200 and 41,800 copies/mL. Forty-eight weeks after dolutegravir administration, counts were: 0, <40 and 20 copies/mL (data unavailable for the patient with a count of 41,800 copies/mL at baseline).
[c]Medications related to HIV treatment that were terminated before the start of dolutegravir, *i.e.*, medication end date < initial administration start date for dolutegravir.
[d]Medications related to HIV treatment that were terminated after the start of dolutegravir, *i.e.*, medication end date ≥ initial administration start date for dolutegravir, or when medication was continued.
SD, standard deviation; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; ESRD, end-stage renal disease; AIDS, acquired immune deficiency syndrome; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; II, integrase inhibitor; PI, protease inhibitor.

frequently reported UAEs were nasopharyngitis (9 events in 7 patients [5.0%]), dyspepsia (7 events in 7 patients [5.0%]), and cough (5 events in 5 patients [3.6%]).

There were 4 unexpected ADRs reported in 4 patients (2.9%). These included somnolence (2 events in 2 patients [1.4%]), and gastroenteritis and edema (each 1 event in 1 patient [0.7%]). Also, 17 unexpected SAEs were reported in 16 patients (11.5%), with 1 serious ADR (gastroenteritis) reported in 1 patient (0.7%).

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Table 2. Summary of adverse events, serious adverse events, adverse drug reactions and serious adverse drug reactions (safety analysis set, N = 139)

Summary of AEs, SAEs, ADRs, SADRs	No. of patients with AEs, n (%)	No. of events
AEs	92 (66.2)	179
Most frequent AEs[a]		
Nasopharyngitis	7 (5.0)	9
Dyspepsia	7 (5.0)	7
Pruritus	6 (4.3)	6
Rash	6 (4.3)	6
Cough	5 (3.6)	5
Diarrhea	5 (3.6)	5
Dizziness	5 (3.6)	5
Headache	5 (3.6)	5
ALT increased	4 (2.9)	4
AST increased	3 (2.2)	3
Blood creatinine increased	3 (2.2)	3
Constipation	3 (2.2)	3
Herpes zoster	3 (2.2)	3
Influenza	3 (2.2)	3
Insomnia	3 (2.2)	3
SAEs	17 (12.2)	19
Most frequent SAEs[b]		
Condyloma latum	2 (1.4)[c]	2
Pyrexia	2 (1.4)	2
ADRs	12 (8.6)	16
Most frequent ADRs[b]		
Diarrhea	2 (1.4)	2
Headache	2 (1.4)	2
Insomnia	2 (1.4)	2
Rash	2 (1.4)	2
Somnolence	2 (1.4)	2
Serious ADRs	2 (1.4)	2

All adverse events are listed according to MedDRA v22.1 preferred terms.
[a]Events occurring in ≥2% of patients.
[b]Events occurring in ≥1% of patients.
[c]Two cases of condyloma latum were reported in 2 patients. Both cases were male, aged 29 and 33 years of age, with condyloma latum of moderate severity, requiring prolonged hospitalization. Both patients recovered fully, and the SAEs were considered unrelated to dolutegravir.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event; ADR, adverse drug reaction; MedDRA, Medical dictionary for regulatory activities.

4) Deaths

There were 2 deaths reported during the study, both of which were considered unlikely to be related to dolutegravir. Sudden death was reported in a patient with edema, and cerebral infarction due to an underlying disease was reported in another patient.

5) Factors affecting the occurrence of adverse events

In the analysis of AEs by background factor, statistically significant differences in AE incidence were observed for a total of three factors including duration of HIV-1 infection (P = 0.0204), prior HIV-related medication (P = 0.0070), and concomitant non-HIV-related medication (P = 0.0134) (**Table 3**). Patient sex (P = 1.0000), age (P = 0.0676), INSTI-related resistance status (P = 1.0000), medical history (P = 1.0000), a prior history of an allergic reaction (P = 1.0000), and duration of dolutegravir treatment (P = 0.0508) did not have a statistically significant effect on the incidence of AEs.

3. Effectiveness analysis

1) Physician global assessment

Among the 75 patients in the effectiveness-evaluable population, all patients (100%) showed

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Table 3. Incidence of adverse events categorized by patient characteristics (safety analysis set, N = 139; overall, AEs reported by n = 92 [66.2%] patients)

Adverse events categorized by patient characteristics	No. of patients with AEs	
	n/N (%)	95% CI (%)[a]
Sex		
Male	85/129 (65.9)	57.0, 74.0
Female	7/10 (70.0)	34.8, 93.3
Age		
Less than 30 years	15/17 (88.2)	63.6, 98.5
30 years - 39 years	19/25 (76.0)	54.9, 90.6
40 years - 49 years	18/32 (56.3)	37.7, 73.6
50 years - 59 years	25/35 (71.4)	53.7, 85.4
60 years - 69 years	9/19 (47.4)	24.5, 71.1
70 years or more	6/11 (54.6)	23.4, 83.3
Medical history		
Hepatic impairment (including Hepatitis B, Hepatitis C)	19/28 (67.9)	47.7, 84.1
Renal impairment (including ESRD, Dialysis)	5/9 (55.6)	21.2, 86.3
Allergy (Drug induced allergy)	1/1 (100.0)	2.5, 100.0
AIDS	38/48 (79.2)	65.0, 89.5
Dyslipidemia	24/36 (66.7)	49.0, 81.4
Myocardial infarction	2/3 (66.7)	9.4, 99.2
Coronary artery disease	3/3 (100.0)	29.2, 100.0
Heart failure	1/1 (100.0)	2.5, 100.0
Arrhythmia	3/4 (75.0)	19.4, 99.4
Other	80/123 (65.0)	55.9, 73.4
Prior HIV-1-related medications		
Yes	51/88 (58.0)[b]	47.0, 68.4
No	41/51 (80.4)	66.9, 90.2
Type of HIV-1-related medication		
NRTIs	18/41 (43.9)	28.5, 60.3
NNRTIs	3/7 (42.9)	9.9, 81.6
IIs or INSTIs	38/59 (64.4)	50.9, 76.5
PIs	16/29 (55.2)	35.7, 73.6
Concomitant non-HIV-1-related medication status		
Yes	79/111 (71.2)[c]	61.8, 79.4
No	13/28 (46.4)	27.5, 66.1
Duration of HIV-1 infection		
Less than 1 year	28/32 (87.5)[d]	71.0, 96.5
1 year – 5 years	16/27 (59.3)	38.8, 77.6
5 years – 10 years	13/25 (52.0)	31.3, 72.2
10 years or more	31/51 (60.8)	46.1, 74.1

[a]Calculated by Exact method.
[b]$P < 0.007$ comparing the percentage of patients experiencing an AE between those with versus without prior HIV-1-related medication (Chi-Square test).
[c]$P < 0.0134$ comparing the percentage of patients experiencing an AE between those with versus without concomitant medication (Chi-Square test).
[d]$P < 0.0204$ comparing the percentage of patients experiencing an AE between those duration of HIV-1 infection (Chi-Square test).
AE, adverse event; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; CV, cardiovascular; ESRD, end-stage renal disease; GI, gastrointestinal; HIV-1, human immunodeficiency virus 1; II, integrase inhibitor; INSTI, integrase strand transfer inhibitor; IV, intravenous; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

an improvement in symptoms (or a maintenance effect) according to the PGA based on virologic/clinical data (**Fig.-2**).

2) Plasma HIV-1 RNA

Overall, the majority of patients (70/75 [93.3%]) had <50 copies/mL, and 5/75 (6.7%) had ≥50 copies/mL (**Fig. 2**).

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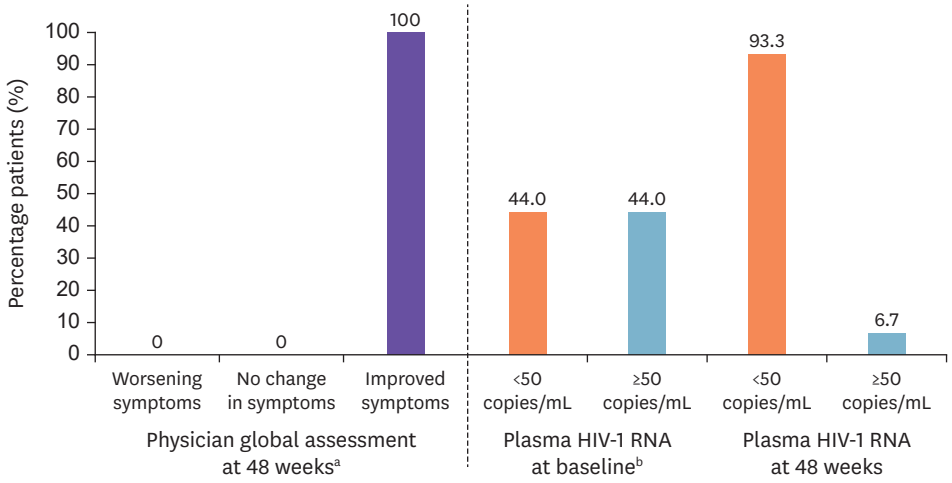

Figure 2. Effectiveness analysis (effectiveness-evaluable population; N = 75).
[a]Defined based on virologic/clinical data (*e.g.*, plasma HIV-1 RNA and/or CD4+ T-cell count) as: Worsening: Symptoms worsened compared with the pre-treatment status; No change: No significant change compared with the pre-treatment status and the outcome was not deemed as a maintenance effect; and Improved: An improvement in symptoms or maintenance effects. A maintenance effect was defined as when a symptom was likely to have worsened if the study drug was discontinued, or if the effect remained the same if the study drug was substituted with the prior medication.
[b]Data unavailable for n = 9 patients; percentage values shown are calculated with N = 75 as the denominator.
HIV-1, human immunodeficiency virus 1.

DISCUSSION

Results of this PMS study confirm that dolutegravir, administered as HAART, is safe and effective in Korean patients in real-life practice. Dolutegravir was well tolerated with a low incidence of AEs, the majority of which were mild; however, the risk of experiencing an AE while receiving dolutegravir appeared to be especially increased in patients receiving concomitant medications for other conditions. In addition, dolutegravir effectively suppressed HIV-1 and all patients showed symptom improvement based on physician global assessment. In line with previous reports that dolutegravir has a high barrier against the emergence of drug resistance [11], there was no evidence of resistance observed in the current study.

These data are consistent with those from other studies demonstrating the safety and effectiveness of dolutegravir in Asian patients with HIV-1 infection. An interim report from a Japanese PMS study, conducted from April 2014 - August 2020, showed an overall incidence of ADRs of 24.7% (565/2,292 patients) among 2,292 patients with HIV-1 treated with dolutegravir single-agent tablets (n = 1,784) or as a combination tablet with abacavir sulfate (n = 820) [12]. Interestingly, the incidence of serious ADRs in that study (n = 147, 6.4%) was higher compared with serious ADRs reported in our study (n = 2, 1.4%). We postulate that this could be due to different patient characteristics amongst the safety analysis set in terms of proportions of patients with pretreatment presence of comorbidities (including psychiatric disorders), liver disorder, renal disorders, and prior antiretroviral therapy. AEs/ADRs reported in the current study are consistent with AEs reported in international clinical trials of dolutegravir, with nausea, diarrhea, headache, and insomnia as common treatment-related AEs [13-18]. While pharmacovigilance data suggest an increased risk of depression and suicide as a class-effect of INSTIs [19], no cases of depression or suicide were reported in the current study.

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Although typical of PMS studies, a limitation of the current study was its open-label design and the lack of a control group. Also, effectiveness data for dolutegravir were only available for half of the 139 patients comprising the safety analysis set. Other limitations were that the time to onset of AEs/ADRs was not evaluated, and specific known risks of dolutegravir (*e.g.*, change in body weight) were not assessed. In addition, body weight gain, and metabolic changes are required monitored considering that there have been several recent reports of related factors [20].

In conclusion, in this open-label PMS study, dolutegravir administered as HAART was well tolerated and effective in patients with HIV-1 infection. Of 2 serious ADRs reported over the 6-year post-marketing period, only 1 (gastroenteritis) was unexpected, and both resolved.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Detailed information for the n=19 serious adverse events that were reported during the study period (safety analysis set, N = 139; overall, SAEs reported by n = 17 [12.2%] patients)

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