

Original Article



Safety and Effectiveness Analysis of Kivexa® (lamivudine/abacavir sulfate) in Human Immunodeficiency Virus Infected Korean Patients

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ABSTRACT

Background: Lamivudine and abacavir sulfate are widely used nucleoside/tide reverse transcriptase inhibitors (NRTI) backbone agents, which are recommended in major international treatment guidelines. The fixed-dose combination of lamivudine and abacavir sulfate has been developed to contribute to low pill burden of antiretroviral therapy (ART) regimen and patient adherence. A mandatory post-marketing surveillance was conducted in Korea to monitor the safety of Kivexa (lamivudine 300 mg/abacavir 600 mg).

Materials and Methods: An open label, multi-center, non-interventional post-marketing surveillance was conducted to monitor the safety of Kivexa from July 2011 to July 2017 in 23 hospitals in Korea. Subjects over 12 years old taking Kivexa per prescribing information were enrolled. The primary outcome was defined as the occurrence of any adverse events during the study period. Secondary outcomes included the occurrence of adverse drug reaction, the occurrence of serious adverse events and the effectiveness of Kivexa.

Results: A total of 600 patients from 23 hospitals were enrolled within the 6 years of study. The total observation period was 1,004 person-years. Three hundred and ten patients reported 674 adverse events. The incidence of upper respiratory infection (65 cases, 10.9%) was the highest, followed by diarrhea (20 cases, 3.3%), and nausea (18 cases, 3.0%). 109 subjects reported 71 events of adverse drug reactions, and the most common reaction was nausea in 2.33% of the subjects. Thirty-one subjects reported serious adverse events, none of them were considered drug related. From the total of 600 subjects, excluding 48 subjects who were 'effectiveness unassessable' by investigators, 552 patients were eligible for the subjective effectiveness analysis. 459 (83.2%) were evaluated as 'improved'. Proportion of subjects

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Conflict of Interest

Heawon Ann and Yil-Seob Lee are employees of GlaxoSmithKline Korea.

Author Contributions

Conceptualization: YSL, HA. Funding acquisition: YSL, HA. Investigation: YSK, SIJ, SHL, CSL, JSL, WSC, YHC, SWK. Supervision: YSL, SWK. Writing - original draft: HA, YSL. Writing - review & editing: HA, YSK, SIJ, SHL, CSL, JSL, WSC, YHC, SWK.

whose human immunodeficiency virus-RNA is <50 copies/ml was 61.2% (309/505) at the beginning of observation and increased to 91.9% (464/505) at the end of study period.

Conclusions: The post-marketing surveillance showed the safety of Kivexa in HIV-1 patients in Korea. Ischemic cardiovascular events and hypersensitivity associated with Kivexa were few. There was no significant new safety information. This data may be helpful in implementing Kivexa and lamivudine/abacavir sulfate containing drugs in Korea.

Keywords: Safety; Anti-retroviral; Cofomulate of lamivudine and abacavir

INTRODUCTION

Kivexa is a fixed-dose combination tablet containing 600 mg of abacavir sulfate (ABC) and 300 mg of lamivudine (3TC), which is approved for treatment of human immunodeficiency virus (HIV) infection. Lamivudine and abacavir, the components of Kivexa, are recommended in international and local guidelines and widely used since their approval in 1995 and 1998 worldwide [1-3]. Triple combination treatment, as known as highly active antiretroviral therapy (HAART), has been long established as the standard treatment for HIV, using two nucleoside/tide reverse transcriptase inhibitors plus one other agent from a protease inhibitor (PI) or a non-nucleoside/tide reverse transcriptase inhibitor (NNRTI) class. Since then, the dual nucleoside combination of ABC and 3TC demonstrated antiretroviral efficacy when used with one other antiretroviral agents [4-6]. Kivexa has been developed as a fixed-dose combination to improve patients' convenience and improve adherence.

Kivexa was approved in Korea in 2011. We conducted a post-marketing surveillance study to evaluate safety and effectiveness of Kivexa from the real world setting.

MATERIALS AND METHODS

1. Study design and population

An open label, multi-center, non-interventional post-marketing surveillance was conducted to monitor safety and effectiveness of Kivexa from July 2011 to July 2017 in 23 hospitals in Korea. Patients with confirmed HIV infection taking Kivexa according to prescribing information were included. Subjects who commenced Kivexa before the study period were also included and the observation started on the day of consent. Patients who have contraindication to the component of Kivexa such as moderate to severe hepatic impairment (Child-pugh class B or C), renal insufficiency (eGFR <50 mL/min/1.73 m²) or confirmed HLA-B*5701 carriers were excluded. Primary outcome was defined as the occurrence of any adverse events during the study period. Secondary outcomes included the occurrence of adverse drug reactions, the occurrence of serious adverse events and the effectiveness of Kivexa. Effectiveness was measured by the changes of proportion of subjects with plasma HIV-1 RNA less than 50 copies/ml throughout the study period. Regarding the non-interventional study design, a subjective assessment of 'clinical improvement' was also included for subjects with observation period greater than 24 weeks. A total of 780 subjects were planned to be enrolled with consideration of an estimated 20% drop out rate, to provide 600 evaluable subjects for the primary analysis. This study was approved by the Institutional Review Board of each participating hospitals.

2. Definitions

Based on WHO-ART 092 [7], an adverse event (AE) was defined as any untoward medical occurrence in a subject temporally associated with the use of a Kivexa, regardless of relation to the medicinal product. Serious adverse event (SAE) was defined as any untoward medical occurrence that with any dose that; 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalization or prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, or 5) is a congenital anomaly/birth defect. An adverse drug reaction (ADR) was defined as all noxious and unintended responses related to Kivexa administration. Physicians classified the causality into 6 category; “certain”, “probable/likely”, “possible”, “unlikely”, “conditional/unclassified,” and “unassessable/unclassifiable” by WHO-UMC causality categories [8]. If the causality between Kivexa and AEs are considered “certain”, “probable/likely”, “possible” “conditional/unclassified,” and “unassessable/unclassifiable,” AEs were classified as ADRs. ADRs that are not stated in Korean prescribing information were classified as unexpected ADR.

3. Demographic and clinical data

Each physician decided patient visit schedules based on their routine practices. At the initial visit, demographic information (including subject's sex, age, weight, and pregnancy), medical history (including result of HLA-B*5701 test, allergy history, renal impairment, hepatic impairment, other concomitant diseases, duration on Kivexa, time since HIV diagnosis and HIV treatment history), concomitant medications, laboratory values including viral load, CD4+ cell counts (if any) were recorded. Because of the non-interventional design of the study, not all the subjects had their HIV-1 RNA viral load and CD4+ T cell counts every visit. Physicians were guided to record any treatment-emergent adverse events during the follow up visits. Any results of HIV RNA viral load and CD4+T cell counts as a part of standard of care within the study period were collected for analysis. At 48-week visit, the effectiveness of Kivexa was subjectively evaluated as “improved”, “no change”, “worsened” or “not assessed” by the investigator's medical judgment.

4. Statistical analysis

Continuous variables were expressed as the mean±standard deviation and discrete variables are expressed as the frequency and rate. Once all AEs were classified by preferred terms and system-organ classes, the frequency and percentage of each AE were calculated. Statistical calculation was carried out using SAS version 9.0 (SAS Institute Inc, Cary, NC, USA).

RESULTS

1. Characteristics of study participants

Among 640 enrollments, a total of 600 patients were included in safety analysis within the 6 years of post-marketing surveillance, excluding 40 subjects with protocol deviation (**Fig. 1**). Total observation period was 1,003.8 person-years. 551 subjects (91.8%) were male. Age was 47.2 ± 12.4 and 54 (9.0%) subjects were over 65 years old. 19.7% of participants were diagnosed with HIV infection within a year at the study entry. 312 subjects were naïve to abacavir. Four of the participants reported pregnancy during observation period. 19 subjects with a human leukocyte antigen (HLA)-B*5701 test was all negative. During the screening, there were no patients positive for HLA-B*5701. Patients on Kivexa plus a PI, NNRTI and integrase strand transfer inhibitor (INI) were 58.3%, 25.2% and 13.8%, respectively. Six of the participants had renal impairments (chronic kidney disease stage 2 to 3), 18 subjects had hepatic impairment with hepatic impairment score of Child-Pugh class A (**Table 1**).

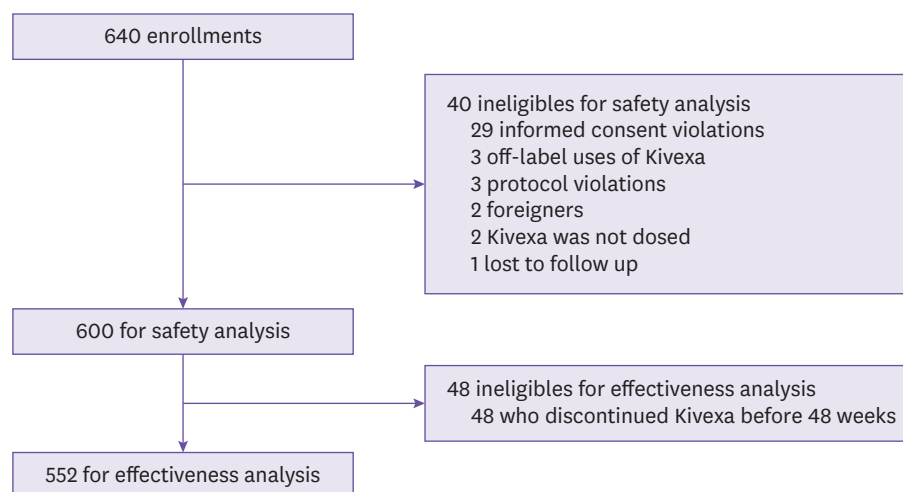


Figure 1. Trial profile.

Table 1. Baseline characteristics of study participants

Characteristics	Number (%)
Total (n, %)	600 (100.0%)
Gender (Male, n, %)	551 (91.8%)
Age (years, mean \pm SD)	47.2 \pm 12.4
Less than 19 years (n, %)	2 (0.3%)
19–65 years	544 (90.7%)
Over 65 years	54 (9.0%)
Time since HIV diagnosis (n, %)	
Less than 1 year	118 (19.7%)
1–4 years	243 (40.5%)
4–10 years	166 (27.7%)
Over 10 years	66 (11.0%)
Abacavir naïve	312 (52.0%)
Pregnancy	4 (0.7%)
Have been tested of HLA-B*5701 status	19 (3.2%)
Observation duration of Kivexa administration	
Less than 12 months	35 (5.8%)
13–23 months	13 (2.2%)
24 months and more	552 (92.0%)
ART regimen at study registration	
Kivexa + PI	347 (58.3%)
Kivexa + NNRTI	150 (25.2%)
Kivexa + INI	82 (13.8%)
Kivexa + others	16 (2.7%)
Any concomitant diseases	
Renal impairment (CKD stage 2 and 3)	6 (1.0%)
Hepatic impairment (Child-pugh class A)	18 (3.0%)
Hypertension	97 (16.2%)
Diabetes mellitus	56 (9.3%)
Dyslipidemia	148 (24.7%)
History of angina	4 (0.7%)
Concomitant drug use	
Antihypertensive drugs	87 (14.5%)
Lipid lowering drugs	126 (21.0%)
Glucose lowering drugs including insulin	36 (6.0%)

n, number; SD, standard deviation; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; PI, protease inhibitor; NNRTI, non-nucleoside/tide reverse transcriptase inhibitor; INI, integrase inhibitor; CKD, chronic kidney disease.

Table 2. Adverse drug reaction and reported in >1 subjects and its expectedness

	Number of Cases	%	Expectedness ^a
Nausea	14	2.3%	Yes
Gastrointestinal distress	9	1.5%	Yes
Vomiting	6	1.0%	Yes
Rash	6	1.0%	Yes
Hypertriglyceridemia	6	1.0%	Yes
Diarrhea	5	0.8%	Yes
Dizziness	5	0.8%	No
Headache	4	0.7%	Yes
Fatigue	4	0.7%	Yes
Pruritis	3	0.5%	No
Anorexia	3	0.5%	Yes
Dyslipidemia	3	0.5%	No
Heartburn	2	0.3%	No
Paraesthesia	2	0.3%	Yes
Dermatitis, seborrheic	2	0.3%	No
Myalgia	2	0.3%	Yes
Fever	2	0.3%	Yes

^aExpectedness is based on Korean prescribing information.

2. Safety and Tolerability

Three hundred and ten subjects reported 674 adverse events. The incidence of upper respiratory infection (10.83%, 65/600) was the most common, followed by diarrhea (3.33%, 20/600) and nausea (3.00%, 18/600). A total of 109 cases with adverse drug reactions were reported by 71 subjects. Nausea (2.33%, 14/600) was the most common, followed by vomiting (1.00%, 6/600), diarrhea and dizziness (0.8%, 5/600 each) (**Table 2**). The incidence of adverse events according to the class of co-administered antiretroviral agents is shown in **Table 3**.

Thirty-one cases of serious adverse event were reported from 25 subjects. None of the cases were considered as Kivexa related based on physician's medical judgement. A 59 years old male hospitalized with unstable angina. He was diagnosed with HIV infection 8 years before, had been taking Kivexa with darunavir (400 mg, twice a day) and norvir (100 mg, once a day) at the time of unstable angina for over three years. No underlying disease but spinal stenosis reported, and he was smoker. The investigator reported the event was not associated with Kivexa administration, and the patient continued Kivexa (**Table 4**).

To the query to assess whether the adverse event is related to hypersensitivity or allergic reaction, 15 subjects were suggested as possible allergic reactions. All 15 subjects were tested and did not have HLA-B*5701. Details of cases and clinical outcomes are listed in **Table 5**. None of the suggested allergic cases met the criteria for serious adverse event.

Four of the 49 female subjects became pregnant during the study period. One of the two subjects who were pregnant at the time of enrollment reported tongue pain (mild, resolved, causality unassessable), and one subject of the two who became pregnant during the

Table 3. The incidence of adverse events according to the class of co-administered antiretroviral agents

	Incidence	95% CI	P-value ^a
Non-nucleoside reverse transcriptase Inhibitor	42.8% (68/159)	35.0–50.9%	0.0088
Protease inhibitor	52.7% (193/366)	47.5–57.9%	0.5136
Integrase inhibitor	68.9% (62/90)	58.3–78.2%	0.0004

Subjects who switched antiretroviral regimen while on Kivexa were included both antiretroviral groups, resulting in a total number of subjects that exceed 600. Incidence: number of subjects who reported adverse events/number of subjects who were on each class of antiretroviral agent at the time of adverse event CI, confidence interval. 95% CI was calculated by Exact Method.

^aChi-square test p-value for the occurrence of adverse events according to the use of each antiretroviral agents.

Table 4. Clinical characteristics of cases with serious adverse events

No.	Sex/Age	Adverse events	Outcome	Drug cessation	Association with Kivexa ^a
1	F/70	Pelvic fracture	Resolved with sequelae	No	Unlikely
2	M/46	Worsened hemorrhoid	Resolved	No	Unlikely
3	F/69	Dementia	Resolved	No	Unlikely
4	M/27	Neutropenic	Resolved	No	Unlikely
5	M/40	Viral infection	Resolved	No	Unlikely
6	M/23	Septic shock	Death	No	Unlikely
7	M/51	Diarrhea	Resolved	No	Unlikely
8	M/43	Malignant lymphoma, intussusception	Unresolved	No	Unlikely
9	M/59	Unstable angina	Resolved	No	Unlikely
10	M/39	Cellulitis	Resolved	No	Unlikely
11	M/41	Convulsion	Resolved with sequelae	No	Unlikely
12	M/23	Anal disorder	Resolved	No	Unlikely
13	M/58	Bladder stone	Resolved	No	Unlikely
14	M/71	Aspergillosis, viral infection	Resolved	No	Unlikely
15	M/54	Leg fracture	Resolved	No	Unlikely
16	M/38	Arm fracture	Resolved	No	Unlikely
17	M/56	Traffic accident	Resolved	No	Unlikely
18	M/40	Aspiration pneumonia, loss of consciousness, cognitive impairment	Unresolved	No	Unlikely
19	M/43	Pneumonia aggravation	Death	No	Unlikely
20	M/47	Admission for sugar control	Resolved	No	Unlikely
21	M/62	General weakness	Resolved	No	Unlikely
22	M/52	Dizziness	Resolved	No	Unlikely
23	M/41	Colitis, pancreatitis, arthralgia	Resolved	No	Unlikely
24	M/48	Paroxysmal atrial fibrillation	Resolved	No	Unlikely
25	M/50	Acute appendicitis	Resolved	No	Unlikely

observation period reported hypertriglyceridemia (mild, unresolved, causality possible), heartburn (mild, resolved, causality unlikely), and vomiting (mild, resolved, causality unlikely). There were no adverse birth outcomes.

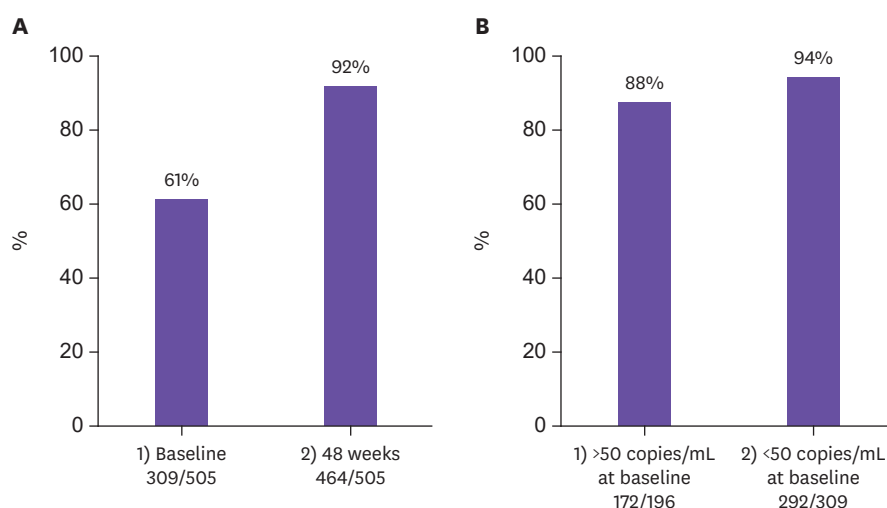
3. Effectiveness

Among 600 patients with safety evaluation, 552 subjects were assessed for 48 week effectiveness. Forty-eight subjects were excluded because their observation period was less than 48 weeks.

Table 5. Clinical characteristics of cases with suggested hypersensitivity or allergic reaction

No.	Sex/Age	Symptoms	Severity	Treatment duration	Outcome	Causality	Drug cessation
1	M/33	Diarrhea	Mild	14 days	Resolved	Possible	No
2	M/35	Nausea	Mild	0 day	Resolved	Probable	No
3	M/50	Rash	Mild	52 days	Resolved	Possible	Yes
4	M/65	Hypertriglyceridemia	Moderate	10 months	Not resolved	Possible	Yes
5	M/70	Edema	Mild	56 days	Resolved	Possible	Yes
6	M/47	Dyslipidemia	Mild	10 months	Resolved	Possible	No
7	M/57	Pruritic rash	Mild	3 months	Resolved	Possible	Yes
8	F/32	Nausea	Mild	14 days	Resolved	Possible	No
9	M/48	Nausea, vomiting, headache, febrile sensation, giddiness	Moderate	48 days	Resolved	Probable	Yes
10	M/43	Skin eruption	Moderate	33 days	Resolved	Possible	No
11	M/49	Skin burning sensation	Mild	12 days	Resolved	Possible	No
12	M/51	Alopecia	Mild	28 days	Resolved	Possible	Yes
13	F/39	Pruritic rash	Moderate	0 day	Resolved	Probable	Yes
14	M/35	Vomiting	Mild	1.5 years	Resolved	Possible	No
15	M/49	Nausea	Mild	1 year	Resolved	Possible	No

F, female; M, male.



No. of the patients				
Subjects with HIV RNA <50 copies/mL	309	464	172	292
Total	505	505	196	309

Figure 2. Proportion of subjects with human immunodeficiency virus (HIV) RNA <50 copies/mL at baseline and 48 weeks of Kivexa treatment.

A. 1) at baseline, 2) at 48 weeks after Kivexa treatment.

B. Proportion of subjects who achieved HIV RNA <50 copies/mL at 48 weeks 1) in subjects with HIV RNA >50 copies/mL at baseline, 2) in subjects with HIV RNA <50 copies/mL at baseline.

By subjective medical judgement of the investigator, 459 (83.2%) were evaluated as 'improved', 91 (16.5%) were 'no change', and 2 (0.4%) were 'worsened'. HIV RNA results of baseline and 48 weeks of observation period were collected from 505 subjects. From 196 subjects with HIV RNA >50 copies/mL at the beginning of observation, 172 (87.8%) were fully suppressed to under 50 copies/mL at 48 week. Of 309 patients with HIV RNA <50 copies/mL at baseline, 292 (94.5%) stayed suppressed through 48 weeks of Kivexa administration (**Fig. 2**). CD4+T cell count increased from 442.1 ± 262.3 cells/mm³ at baseline to 580.6 ± 258.7 cells/mm³ at 48 weeks of follow up from patients with a baseline and week 48 observation ($P < 0.0001$) (**Fig. 3**).

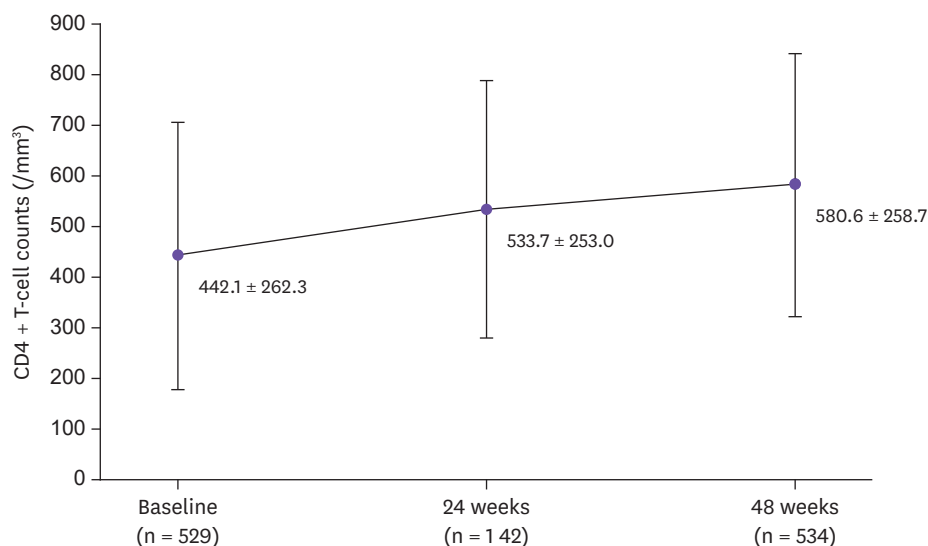


Figure 3. Change in CD4 + T-cell counts in study subjects.

DISCUSSION

This post marketing surveillance (PMS) has been conducted to observe the safety of Kivexa in clinical setting as a requirement of Korean regulatory authority.

We observed a total of 1,004 person-years with 600 subjects for 6 years, from 2011 to 2017. The high proportion of male subjects (90%) and the proportion of elderly subjects over 65 years old (9.0%) is somewhat reflective of the HIV population in Korea [9, 10]. Over a half of the subjects took Kivexa with PI, which also reflects high usage of PI in Korea, compared to other Asian countries [11, 12]. Since INIs were introduced from 2010 in Korea, subjects that used Kivexa with INIs began to be enrolled later, and thus have lower representation in the study population (**Table 1**).

Kivexa generally showed good tolerability, yet there were adverse events associated with Kivexa administration. The three most common adverse drug reactions were nausea, gastrointestinal distress, and vomiting. This observation was different from the previous 3TC and Ziagen PMS reports where diarrhea was observed as the most common adverse events (4.72%, 1.8%, respectively), however the gastrointestinal trouble accounted were similar [13]. When list up all the adverse events that reported from over 1 subject, there were no events related to cardiac events.

Subjects taking NNRTI with Kivexa reported less AE than those taking PI and INI, and those receiving INI with Kivexa reported more AE than those receiving NNRTI and PI (**Table 3**). This incidence comparison has limitations because it did not take into account the causality with Kivexa, and each class includes couple of different antiretroviral agents.

A total of 25 subjects experienced serious adverse events. Among them, one 59 years old male reported unstable angina. He had no underlying disease related to cardiovascular risk factors but had a history of spinal stenosis. Since the association between abacavir and ischemic heart is still inconclusive [14-17], the occurrence of ischemic heart disease was subject for close observation. The investigator evaluated the unstable angina case unrelated to the study drug, and there was no further other cardiac event was reported. Thus, in this Ziagen PMS report, there were no drug-related ischemic heart disease observed with the administration abacavir in Korea [13].

Investigators were asked to evaluate any adverse event related to allergic reactions or suspected hypersensitivity, 15 adverse events 15 cases were suggested as possible allergic reactions (**Table 5**). A 48 years old male presented nausea, vomiting, headache, febrile sensation and giddiness on his 48th day of Kivexa administration. He did not have a previous HLA-B*5701 test. The investigator reported this might be related to Kivexa, and the patient's symptoms resolved after he stopped Kivexa. The series of symptoms and resolution of symptoms after Kivexa cessation suggest this as a possible case of abacavir hypersensitivity. Abacavir hypersensitivity reaction can occur in 5–8% of patients and can be lead to serious toxicity without appropriate and timely management [18, 19]. It is well documented that abacavir hypersensitivity is strongly associated with HLA-B*5701 allele, thus HLA-B*5701 test before commencing abacavir containing regimens are recommended. However, the prevalence of HLA-B*5701 is quite low in Asian population (0–1%) compared with those of other ethnicities (3–4.98%) [20-23]. One report evaluated the prevalence of HLA-B*5701 allele among the Korean HIV patients, however there were no subjects in study with a positive

HLA-B*5701. The authors suggested that it might be more cost-effective to closely monitor the occurrence of hypersensitivity compared to testing for all the Korean HIV population [21]. Although the responsible company constantly communicates the necessity of HLA-B*5701 test and the risk of ABC hypersensitivity, the testing rate for HLA-B*5701 of this study was very low, which reflects the clinical significance of HLA-B*5701 testing in real world in Korea.

In the effectiveness analysis, we observed positive virologic and immunologic improvement with Kivexa contained regimen with an increasing of proportion of subjects with HIV RNA below 50 copies/mL and an increasing mean CD4+T-cell counts. Kivexa was administrated with either PI, NNRTI or INI in most cases, and thus it was not feasible to assess the effectiveness of Kivexa own. And with the design of post-marketing surveillance, we could not analyze the cases with virologic failure.

This study has several limitations. Firstly, with the design of non-interventional surveillance, we could not obtain the information beyond the information that investigator collected and presented. As we could not follow up with the serial HIV RNA level or CD4+ T cell count with ongoing treatment, the consistency of effectiveness analysis including HIV RNA and CD4+T cell counts could not be attained. We also could not collect actual laboratory result such as serum creatinine, or vital sign such as body temperature and patients' adherence. Secondly, to include enough subjects to report in restricted surveillance period, subjects who have already commenced Kivexa before the study period were included along with Kivexa naïve patients, which might be a reason for some loss of acute adverse events. Finally, a sample size of 600 patients may not be large enough to detect rare adverse events.

In conclusion, we present the result of surveillance of Kivexa use in Korean HIV-positive population. Kivexa was generally well tolerated and the incidence of adverse drug reaction was substantially low. There were no cardiovascular adverse events related to Kivexa in this population and ABC hypersensitivity was rare. Similar to the PMS results of other antiretroviral agents, the safety results must be interpreted comprehensively since Kivexa was administrated other antiretrovirals. The results were similar to the PMS results of single components of Kivexa, and there was no significant new safety information [13]. Kivexa is still widely used by itself as a backbone, and its components abacavir and lamivudine is also available as a fixed dosed combination tablet with dolutegravir in Korea. This data may be helpful to understand the safety profile of lamivudine/abacavir containing regimens in Korea.

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