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SHORT COMMUNICATION

Therapeutic failure reported with HIV long-acting injectables: An analysis of the FDA Adverse Event Reporting System from 2021 to 2024

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Abstract

Objectives: We examined adverse event (AE) reports relating to cabotegravir/rilpivirine (CAB/RPV) in the US FDA Adverse Event Reporting System (FAERS), focusing on therapeutic failure (TF) and non-therapeutic failure (NTF) outcomes.

Methods: FAERS is a database of AE and medication error reports from post-marketing surveillance. The study was granted exempt approval by the Binghamton University Institutional Review Board. We queried reports for CAB/RPV in the FAERS system from 1 January 2021 to 31 March 2024. TFs were defined as involving any of the following terms: viral load increased, virological failure, pathogen resistance, blood HIV RNA increased, treatment failure, drug ineffective, viral mutation identified, viraemia, and therapy non-responder. The top 20 most common AEs were also identified. Means, standard deviations, and percentages were used to characterize the sample.

Results: The study cohort consisted of 2605 reports. The reported sex of the study cohort was 50% male ($n = 1295$), 19% female ($n = 505$), and 31% unspecified ($n = 805$), with a mean ± standard deviation (SD) age of 46.9 ± 12.4 years ($n = 378$). The top three most reported AEs were TFs, product dose omissions, and injection site pain, with 377 (14.5%), 354 (13.6%), and 331 (12.7%) cases, respectively. The mean ± SD weight of people with a report of TF versus NTF was 101.8 ± 33.4 kg and 87.7 ± 26.7 kg, respectively ($p = 0.0175$).

Conclusion: Our findings suggest that healthcare professionals should have a heightened awareness of potential challenges with CAB/RPV administration, including TFs and dose omissions in real-world settings.

KEYWORDS

adverse events, cabotegravir/rilpivirine, HIV, long-acting injectable, treatment failure

INTRODUCTION

HIV affects an estimated 1.2 million individuals in the USA [1]. Left untreated, this virus can progress to AIDS [2]. Presently, a cure for HIV remains elusive. However, people living with HIV who adhere to effective antiretroviral (ARV) treatment experience reduced HIV-related morbidity and mortality across all stages of HIV infection as well as a diminished risk of transmission [2]. Attaining viral suppression necessitates the use of combination ARV regimens comprising two or more drug classes [3]. High adherence rates are necessary to maintain viral suppression and reduce the risk of resistance [4, 5].

In January 2021, Cabenuva® (cabotegravir/rilpivirine [CAB/RPV]) became the first long-acting injectable (LAI) treatment for people with HIV approved by the US Food and Drug Administration (FDA) [6]. CAB/RPV has been approved for individuals living with HIV who are aged 12 ≥years, weigh at least 35 kg, and have maintained virological suppression for a minimum of 3 months. The medication is administered as two intramuscular injections by a healthcare professional every 1 to 2 months [7]. CAB/RPV underwent fast-track and priority review because of the unmet medical need for long-acting HIV treatment and its demonstrated increased efficacy and adherence [6]. As more people with HIV transition from oral therapeutic regimens to injectable CAB/RPV, real-world evidence regarding the clinical effectiveness and safety of this novel therapy is emerging.

The use of CAB/RPV treatment as a replacement for daily oral medication in people living with HIV may have notable benefits, including the eradication of a person's daily ARV pill burden while maintaining viral suppression with as few as six injection appointments per year [7]. However, reports have documented the potential for virological failure when switching from oral therapy to LAI CAB/RPV [8, 9]. A specific concern was raised by a pooled analysis of randomized controlled trials (ATLAS, ATLAS-2 M, and FLAIR) involving CAB/RPV, which identified elevated body mass index (BMI) as a variable associated with TF [10]. In contrast, a subgroup analysis of the SOLAR trial stratified by baseline BMI (<30 and ≥30 kg/m^2) did not reveal a significant difference in the rate of TF [11]. Ongoing post-marketing surveillance of this new injectable therapy is warranted to explore the adverse event (AE) profile in real-world settings, including cases of TF. The present study seeks to expand upon our understanding of virological failure involving injectable CAB/RPV through a novel examination of the FDA Adverse Event Reporting System (FAERS) database by comparing the reporting rank of this event with other AEs and investigating for associated factors. To our knowledge, this is the first pharmacovigilance study of the FAERS database to explore AEs, focusing on TFs of CAB/RPV.

MATERIALS AND METHODS

Procedures

FAERS is a database containing reports of AEs and medication errors from post-marketing surveillance, voluntarily reported by healthcare professionals and patients [12]. FAERS is maintained in a public-access dashboard. Reports are coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology [13]. All reports are de-identified. The study was granted exempt approval by the Binghamton University Institutional Review Board.

We queried 7 336 160 total reports in the FAERS system from 1 January 2021 to 31 March 2024, using the search term "cabotegravir\rilpivirine", which revealed 2607 total reports. Two reports were excluded because the patients were aged <18 years, resulting in 2605 cases for the total study cohort. Reports were downloaded into a Microsoft Excel file with each case represented by a unique identification number. Cases were sorted and coded as either TF or non-therapeutic failure (NTF) outcomes. TFs were defined by any of the following component terms: "viral load increased", "virological failure", "pathogen resistance", "blood HIV RNA increased", "treatment failure", "drug ineffective", "viral mutation identified", "viraemia", and "therapy non-responder". The component terms that were selected are categorized in the MedDRA terminology system under the preferred term class "lack of efficacy/effect", whereas the HIV-specific term "blood HIV RNA increased" was selected as a potential sign of TF, consistent with other case reports. We collected data on reported age (converted to years), sex, weight (converted to kg), reporter type, and AE outcomes. We also evaluated cases for reported product errors, product quality issues, product dose omission issues, and off-label uses.

Statistics

Descriptive statistics, including means, standard deviations, and percentages, were calculated to characterize the sample. We created a list of the top 20 most common AE reports. The mean reported weight of people between the TF and NTF groups was compared with a two-sided *t* test. Categorical variables such as sex and reporter type were compared with a chi-squared test. The alpha level for significance was 0.05.

RESULTS

The study cohort consisted of 2605 CAB/RPV AE reports. Nearly half of the reports involved males (1295; 49.7%), followed by females (505; 19.4%) and unspecified sex (805; 30.9%) as shown in Table 1. Age and weight were specified in 378 (14.5%) and 181 (6.9%) reports, with a mean ± SD of 46.9 ± 12.4 years and 89.7 ± 28.1 kg, respectively. Most AE reports were submitted by healthcare professionals (2121; 81.4%).

The top 20 most common AEs reported for CAB/RPV are shown in descending order in Figure 1. "Product dose omission" (354; 13.6%), "injection site pain" (331; 12.7%), and "viral load increased" (263; 10.1%) were the three most common AEs. Use and administration issues were also frequently reported. The most common co-reported adverse reactions with product dose omission included "inappropriate schedule of product administration", "product complaint", "aggression", "psychotic disorder", "substance use", and "product storage error". The most

TABLE 1 Characteristics of the study cohort.

Characteristics	TF reports $N = 377$	NTF reports $N = 2228$	Total reports $N = 2605$	p-value[a]
Sex				0.9542
Male	186 (49.3)	1109 (49.8)	1295 (49.7)	
Female	72 (19.1)	433 (19.4)	505 (19.4)	
Not specified	119 (31.6)	686 (30.8)	805 (30.9)	
Age (years)	44.8 ± 12.7	47.3 ± 12.3	46.9 ± 12.4	0.1490
No. reported	61	317	378	
Weight (kg)	101.8 ± 33.4	87.7 ± 26.7	89.7 ± 28.1	**0.0175**
No. reported	26	155	181	
Reporter type				**<0.0001**
Healthcare professional	350 (92.8)	1771 (79.5)	2121 (81.4)	
Consumer	26 (6.9)	452 (20.3)	478 (18.3)	
Not specified	1 (0.27)	5 (0.22)	6 (0.23)	

Abbreviations: NTF, non-therapeutic failure, TF, therapeutic failure.
Data are presented as n (%) or mean ± standard deviation unless otherwise indicated.
[a]p-value comparing each characteristic between TF vs. NTF groups.

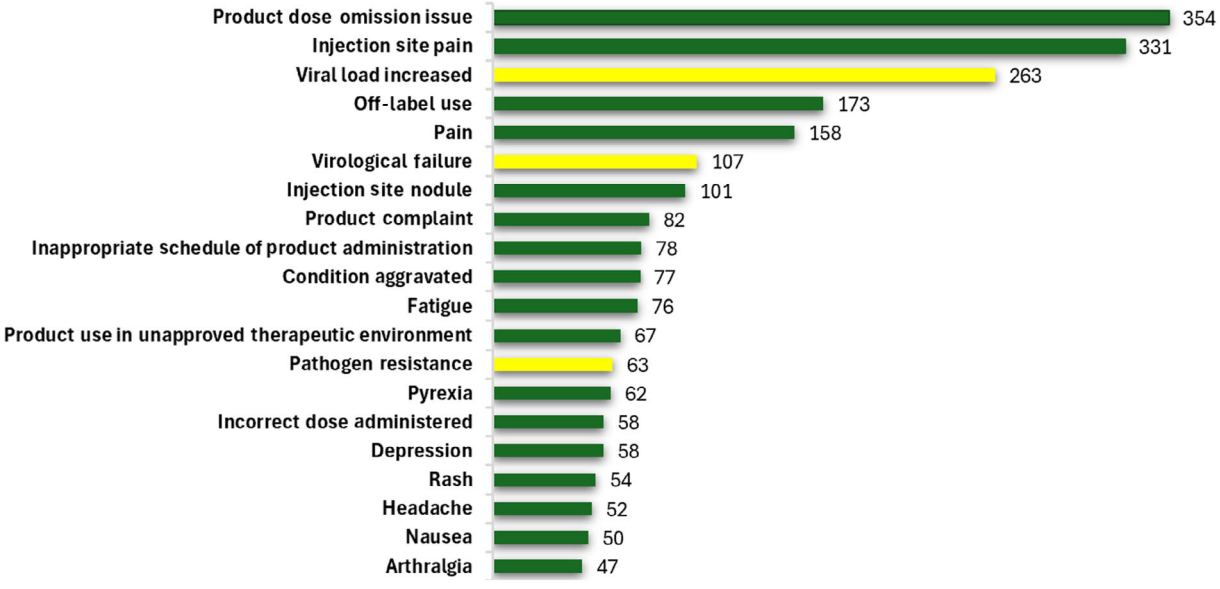

FIGURE 1 Top 20 cabotegravir/rilpivirine adverse event reports by reaction in descending order*.

common co-reported adverse reactions with TF included "product use in unapproved therapeutic environment", "off-label use", and "condition aggravated".

A total of 377 (14.5%) unduplicated cases were categorized as TF and included the component outcomes of "viral load increased" (263), "virological failure" (107), "pathogen resistance" (63), "blood HIV RNA increased" (52), "treatment failure" (42), "drug ineffective" (40), "viral mutation identified" (36), "viraemia" (19), and "therapy non-responder" (1). As shown in Table 1, there was no significant difference ($p = 0.9542$) in reported sex between TF and NTF groups, with 49.3% and 49.8% males, respectively. Age was also not significantly different ($p = 0.149$) between TF and NTF groups, with a mean ± SD of 44.8 ± 12.7 and 47.3 ± 12.3 years, respectively. A significantly higher proportion of TF cases (92.8%) than NTF cases (79.5%) were reported by healthcare professionals ($p < 0.001$). As shown in Table 1, reported weight was significantly higher ($p = 0.0175$) in the TF group than in the NTF group, with a mean ± SD of 101.8 ± 33.4 and 87.7 ± 26.7 kg, respectively.

DISCUSSION

Our analysis of 2605 FAERS reports for CAB/RPV revealed that "TF" and "product dose omission" were two of the most common AE reports in the database. The real-world AE profile for CAB/RPV was consistent with controlled trials in that both settings included reports of injection site reactions, pain, fatigue, and headache [14–16]. However, the notably high ranking of TF and dose omission reports in post-marketing surveillance was an unexpected finding of our study given the high rates of adherence and treatment success across three randomized controlled trials of CAB/RPV [14–16].

TFs and product dose omission reports appeared to be co-related to a variety of factors and may illustrate that the administration of LAIs for people with HIV in routine clinical settings are more complex than in controlled trial settings. One of the most frequent co-reported reactions with both TF and dose omissions included "administration errors". The FDA prescribing information for CAB/RPV contains a recommendation that providers may consider using a longer 2″ length needle for intramuscular injections in people with BMI >30 kg/m^2 in order to reach sufficient depth into the muscle tissue and avoid inadvertent administration of the drug into adipose tissue [7]. However, educational materials targeting medical professionals, such as the *Dosing and Administration Guide* from the manufacturer, do not mention needle size selection based on body weight [17]. This drug is only packaged with a 1.5″ length needle, and longer needles may not be readily available at all clinical practice sites [7, 17].

Although guidelines for managing treatment-experienced people with HIV cite strong evidence to support the use of LAI therapy, concerns have been raised about the generalizability of safety and efficacy data for CAB/RPV in real-world settings with diverse populations [3]. Case reports of TF after switching to long-acting CAB/RPV have been documented [8, 9]. Low drug levels of CAB, RPV, or both antivirals may have contributed to the occurrence of TF in these cases [9]. Population pharmacokinetic studies indicated that the absorption of CAB was lower in females, decreased with increasing BMI, and decreased with shorter needle length, whereas none of these factors were found for RPV [18, 19]. A recent real-world study of 725 drug levels obtained from 186 people with HIV showed large inter-individual variability in CAB/RPV concentrations and lower CAB concentrations than reported in randomized controlled trials [20]. However, the lower CAB concentrations noted in these real-world data were not associated with virological failure [20]. Another real-world study involving a cohort of 72 virologically suppressed people with HIV-1 switching to long-acting CAB/RPV revealed a significant association between low CAB trough concentrations at 1 and 3 months after the first injection and individuals who had either no oral lead-in therapy or with high BMI [21]. In contrast to real-world data, pooled data from FLAIR, ATLAS, and ATLAS-2 M revealed that BMI category as a cut point of 30 kg/m^2 was not associated with elevated trough levels of CAB/RPV or virological failure [22].

In the reports in our study that included weight, we also found a significant association between higher weight and reporting of TF. However, weight was reported in a minority of cases, and BMI was not available. Our study adds to the growing body of evidence regarding the potential for TF with LAI CAB/RPV. Our findings emphasize the importance of pharmacovigilance studies to identify potential risk factors for TF in people with HIV who are treated with LAI CAB/RPV beyond those already reported. Further investigation in real-world settings may be warranted to explore optimal dosing, administration, and monitoring for CAB/RPV in certain populations, including those with elevated BMI.

Strengths of our study include multiple years of reports from a national database in which nearly all cases of TF were submitted by healthcare professionals. The FAERS database is populated by voluntary report submissions, which may result in under-reporting, particularly of non-severe AEs [23]. Another limitation is that reports in the FAERS database may be incomplete, with omissions such as weight. Potential confounding factors such as prior HIV treatment regimens, concomitant medications, underlying

medical conditions, and demographics also exist and can affect the interpretation of these AEs. Although each AE report in FAERS involves a unique person, suspect drug, and reaction, with a unique case number for tracking, it is possible that a person may have multiple reports in the database related to two or more suspect drugs and/or two or more reactions. Moreover, this is a cohort study, which is not designed to detect causality. Further research is needed to confirm the results of this investigation.

CONCLUSIONS

Using a national adverse event database, an association between higher body weight and TF with CAB/RPV was observed. In addition, product dose omission was a frequently reported AE, which suggests that the administration of CAB/RPV in real-world practice is more complex than in controlled trial settings. Our study results add to a growing body of evidence that healthcare providers should have a heightened awareness of potential challenges with CAB/RPV administration in diverse settings and populations.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, analysis, and writing (original draft and reviewing) – KLM, DLC, JFC, AMC, KED, SSS. Supervision – KLM. Final editing – KLM and DLC. Guarantor – KLM. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest declared.

DATA AVAILABILITY STATEMENT

Data supporting the results reported in the article can be found on the FDA FAERS public dashboard. https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

ETHICS APPROVAL STATEMENT

The study was approved by the Binghamton University Institutional Review Board. IRB ID# STUDY00005007, May 9, 2024.

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