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BRIEF REPORT

Outcomes of Drug Interactions Between Antiretrovirals and Co-Medications, Including Over-the-Counter Drugs: A Real-World Study

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ABSTRACT

Introduction: The objective was to characterize real-world outcomes of drug–drug interactions (DDIs) between antiretrovirals (ARVs) and other drugs, including over-the-counter medications (OTC), and treatment outcomes in clinical practice.

Methods: www.clinicalcasesDDIs.com is an open-access website for healthcare providers to consult and briefly describe real-world clinical cases on DDI with ARVs. We reviewed all the clinical cases reported to the website between March 2019 and May 2023.

Results: A total of 139 cases were reported, mostly involving ritonavir or cobicistat (boosters; 74 cases), unboosted integrase inhibitors (InSTI; 29 cases), and non-nucleoside reverse transcriptase inhibitors (NNRTI; 23 cases). Central nervous system drugs (29 cases) and cardiovascular drugs (19 cases) were the most frequently described co-medications. Notably, OTC medications were implicated in 27 cases, including mineral supplements (11 cases), her-

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bals (8 cases), weight loss drugs (4 cases), anabolic steroids (3 cases), and recreational drugs (1 case). OTC acted as the perpetrator drug in 21 cases, leading to loss of ARV efficacy in 17 instances (mineral supplements in 10 cases, weight loss drugs in 4 cases, herbals in 3 cases). Additionally, toxicity was reported in 4 out of 6 cases where OTC was considered the victim drug of the DDI (anabolic steroids in 3 cases, MDMA in 1 case).

Conclusions: Frequent unwanted outcomes resulting from DDIs between ARVs and OTC medications underscore the importance of integrating non-prescription drugs into medication reconciliation. The real-world data available through www.clinicalcasesDDIs.com serves as a valuable resource for assessing the clinical relevance of DDIs.

Keywords: HIV infection; Drug interactions; Over-the-counter medications; Real-life clinical cases

Key Summary Points

Our analysis of reported real-world cases underscores the detrimental impact of drug–drug interactions (DDIs) between antiretrovirals (ARVs) and over-the-counter medications.

It emphasizes the critical necessity for comprehensive medication reconciliation, including non-prescription drugs.

It highlights the continued clinical significance of relevant DDIs associated with boosted ARV.

It highlights the importance of reporting real-world cases of DDIs.

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INTRODUCTION

A substantial number of persons with HIV (PWH) may use combinations of drug combinations that may result in clinically relevant drug–drug interactions (DDIs) [1], potentially increasing the risk of treatment failure or undesired adverse effects from antiretroviral (ARV) or concomitant medications. The risk of DDIs is highest for ARVs requiring pharmacokinetic (PK) enhancers, such as cobicistat or ritonavir [2]. However, unboosted ARVs may also be involved in relevant DDIs. Moreover, the progressive aging of PWH and the related higher risk of polypharmacy [3] increase the likelihood of having DDIs that can lead to unwanted clinical outcomes.

In addition to medically prescribed drugs, the use of over-the-counter (OTC) medications and other substances (e.g., vitamins/mineral supplements, anabolic steroids, recreational drugs) is also common among PWH [4, 5]. OTC medications may be either victim or perpetrator of DDIs with ARVs, thereby being a potential source for clinically relevant DDIs in PWH. However, formal PK studies assessing DDIs between ARVs and OTC are scarce, and clinical cases are infrequently collected and published in peer-reviewed medical journals.

There are multiple electronic resources available for checking DDIs. However, even HIV-specific DDIs databases mostly predict the risk of developing a DDI based on the metabolic pathway of the drugs and based on the DDI studies reported in the literature or in the prescribing information. Thus, while available resources mostly report the potential risk for a DDI they rarely report outcomes of DDIs based on real-world practice. Consequently, the clinical significance of many DDIs remains uncertain. Furthermore, discrepancies on the relevance of a particular DDI may be found between different databases, further complicating the interpretation of a given potential interaction [6].

Our aim was to describe real-world outcomes of DDIs between ARVs and other drugs/products, including OTC medications, based on voluntary reports in a dedicated website.

METHODS

The website www.clinicalcasesDDIs.com is an open-access platform designed for healthcare providers to access and review concise descriptions of real-world clinical cases involving ARVs and their associated clinical harms. This resource is unique in its aim to compile clinical outcomes, share knowledge, and promptly alert prescribers to both common and emerging toxicities and adverse outcomes resulting from DDIs with HIV treatment.

The content on this platform is curated by an editorial team comprised of a multidisciplinary panel of experts in HIV medicine and clinical pharmacology from various countries, including Spain, Italy, the Netherlands, Switzerland, Serbia, the UK, Argentina, and Chile. Before being accepted, each case submitted for publication undergoes a rigorous review process, ensuring accuracy and plausibility. At least two independent panel members review and approve the cases, accompanied by editorial interpretation, classification, and commentary.

The clinical cases' descriptions encompass details of the drugs engaged in the interaction, categorized as victim and perpetrator drugs, along with their respective daily doses and duration of co-administration. Additionally, these cases present clinical details and outcomes. The outcomes are categorized as either "no unwanted outcome" or "unwanted outcome," indicating instances where toxicity or loss of efficacy of either ARV or co-medication occurred.

Data was extracted from the website dataset, and all the clinical cases reported between March 2019 and May 2023 were included in a descriptive analysis.

The study was conducted in accordance with the declaration of Helsinki. Specific data that could contribute to identify persons described in the clinical reports were deleted or modified to assure privacy of the patients. Data were obtained from an open-access platform (www.clinicalcasesDDIs.com) which is available to healthcare professionals, researchers, and patients.

RESULTS

A total of 139 cases were reported on www.clinicalcasesDDIs.com between March 2019 and May 2023. Cases were mainly reported by HIV clinicians and pharmacists. Among these cases, 99 (71%) involved men with a median age of 50 years. The most frequently implicated ARV in DDIs were those requiring ritonavir/cobicistat (boosters, as perpetrators) accounting for 74 cases, followed by unboosted integrase inhibitors (InSTI) with 29 cases, and non-nucleoside reverse transcriptase inhibitors (NNRTI) with 23 cases. Additionally, 13 cases involved other ARVs, including 8 cases with protease inhibitors (PI) as victims of the co-medication, 4 cases with TAF (tenofovir alafenamide), and 1 case with ibalizumab. Regarding the clinical outcomes, 70 out of 139 cases (50%) reported "no unwanted outcome," while "loss of efficacy" and "toxicity" were reported in 22% and in 28% of the cases, respectively (Table 1).

Among co-medications, central nervous system (CNS) drugs were the most frequently involved in DDIs, accounting for 29 cases. These included neuroleptics, antiepileptic drugs, benzodiazepines, antidepressants, and ergotamine derivatives. The reported interactions primarily occurred with boosted ARVs (19/29 cases), where the CNS drug acted as the victim drug in all instances. Outcomes varied with "no unwanted outcome" reported in 20 cases, "toxicity" in 6, and "loss of efficacy" in 3 cases.

Cardiovascular drugs were the second most commonly implicated medications (19 cases), encompassing antiplatelet and anticoagulant agents, beta-blockers, diuretics, and calcium channel antagonists. Boosted ARVs were involved in the majority of these cases (12/19). "No unwanted outcome" was noted in 8 cases, "toxicity" in 6, and "loss of efficacy" in 5 cases. As for CNS drugs, in all cases cardiovascular agents were the victim drug.

OTC medications contributed to 27 cases of DDIs (Fig. 1). These encompassed mineral supplements (11 cases), herbals (8 cases), weight loss drugs (4 cases), anabolic steroids (3 cases), and recreational drugs (1 case). Unwanted outcomes were reported in 21 (78%) cases. Of those, a loss of ARV efficacy, defined as detectable plasma HIV-RNA previously virologically suppressed individuals, was noted in 17 (63%) cases. Ten of these cases involved mineral supplements, primarily calcium and magnesium, all of which affected InSTI as victim drugs. However, one case involved coadministration with rifampicin and InSTI-resistance mutations, precluding its inclusion as more than one factor could be interfering with ART efficacy (Table 2). Weight loss drugs and herbals were implicated in 4 and in 3 cases reporting "loss of efficacy," respectively, involving PIs and NNRTI as victim drugs. Toxicity was reported in 4 out of 6 cases where OTC medications were

Table 1 Clinical cases reported to www.clinicalcasesDDIs.com from May 2019 to March 2023

	No unwanted outcome (%)	Loss of efficacy (%)	Toxicity (%)	Total
Boosted ARV	35 (47.3)	5 (6.8)	34 (45.9)	74
Unboosted InSTI	18 (62.1)	11 (37.9)	0	29
NNRTI	10 (43.5)	9 (39.1)	4 (17.4)	23
Other	7 (53.8)	5 (38.5)	1 (7.7)	13
Total	70 (50.4)	30 (21.6)	39 (28)	139

ARV antiretroviral, *InSTI* integrase inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors

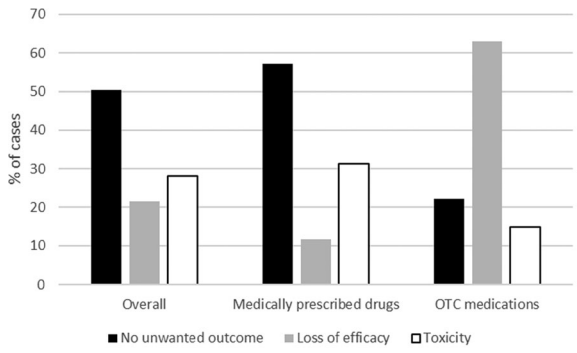

Fig. 1 Clinical outcome of reported cases

Table 2 Main characteristics of cases with loss of ARV efficacy during co-administration of InSTI with mineral supplements

ART	Victim ARV	Daily dose of victim ARV (mg)	Age (years)	Gender	OTC	Viral load (copies/mL)	Medical intervention	Final outcome
DTG/ABC/3TC	DTG	50	35	Female (pregnant)	Ca^{2+} supplements	72	Take ART 6 h after Ca^{2+} supplements	Undetectable viral load 3 weeks later
DTG/ABC/3TC	DTG	50	55	Male	Mg^{2+} supplements	110	Stop Mg^{2+} supplements	Undetectable viral load 12 weeks later
BIC/TAF/FTC	BIC	50	44	Male	Vitamin supplements including Mg^{2+}	70	Stop vitamin supplements	Undetectable viral load 8 weeks later
DTG/3TC	DTG	50	41	Male	Vitamin supplements including Mg^{2+}	80	Stop vitamin supplements	Undetectable viral load 6 weeks later
BIC/TAF/FTC	BIC	50	42	Male	Zn^{2+}, Ca^{2+}, and P supplements	56,477	Stop Zn^{2+}, Ca^{2+}, and P supplements	Undetectable viral load 4 weeks later
DTG/ABC/3TC	DTG	50	40	Female	Mg^{2+} supplements	380	Stop Mg^{2+} supplements	Undetectable viral load 12 weeks later
RAL-FTC/TDF	RAL	1200	48	Male	Mg^{2+} supplements	98	Stop Mg^{2+} supplements and repeat viral load 4 weeks later: 69 copies/mL. Then switch ART to DRV/c/FTC/TAF	Unknown
RAL-FTC/TDF	RAL	800	45	Male	White kaolin clay (containing Al^{3+} and Si^{2+})	170	Stop white kaolin clay	Undetectable viral load 12 weeks later

Table 2 continued

ART	Victim ARV	Daily dose of victim ARV (mg)	Age (years)	Gender	OTC	Viral load (copies/mL)	Medical intervention	Final outcome
RAL-FTC/TDF	RAL	1200	47	Male	Meal replacement shakes fortified with minerals and vitamins	Detectable (unknown value)	Switch RAL to DTG and separation between DTG and the meal replacements	Undetectable viral load (unknown time)

One case containing rifampicin was not included because of more than one factor interfering with ART efficacy
3TC lamivudine, *ABC* abacavir, *BIC* bictegravir, *DTG* dolutegravir, *FTC* emtricitabine, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate, *RAL* raltegravir

considered the victim of the DDI. These cases involved anabolic steroids in 3 instances and MDMA in 1 case.

DISCUSSION

DDIs become more relevant as PWH are aging, due to a higher prevalence of chronic conditions leading often to polypharmacy [7]. Moreover, the escalating popularity and accessibility of OTC medications and recreational drugs among PWH further compound this issue [8, 9]. Despite the existence of specialized HIV DDI websites (such as https://www.hiv-druginteractions.org, http://www.interaccionesvih.com, or https://www.hivmedicationguide.com) designed to assist healthcare providers in managing of DDIs, their content predominantly revolves around theoretical risks associated with DDIs. Many of DDIs, however, have never been evaluated in formal PK studies or assessed in clinical practice, leaving the clinical significance and outcomes of these interactions largely unknown. This gap in understanding is especially prominent in DDIs involving OTC medications and substances like recreational drugs, whose use is frequently undisclosed to healthcare providers.

In our study, boosted ARVs emerged as the most prevalent contributors to DDIs, accounting for 74 cases (53%) reported. This predominance can be attributed to the potent inhibition of cytochrome P450 (CYP) metabolism by ritonavir and cobicistat, which are integral components of boosting strategies [10]. The shift from boosted PI to unboosted InSTI reflects current treatment guidelines, wherein unboosted InSTI serve as first-line therapies. Unlike boosted PI, unboosted InSTI do not exert inhibition or induction effects on drug-metabolizing enzymes or transporters, rendering them favorable in terms of their DDI profile, with added advantage of achieving rapid virological suppression [11–13]. However, despite this shift, boosted PIs maintain clinical significance due to their utility in specific scenarios. They remain the preferred combination for individuals experiencing failure in pre-exposure prophylaxis (PrEP) with long-acting cabotegravir (LA

CAB) as well as for those individuals with virological failure and the subsequent selection of drug resistance mutations during therapy with LA CAB plus LA rilpivirine [14, 15]. Consequently, DDIs associated with boosted PI retain relevance in clinical practice and might potentially gain increased importance in the future.

Of significance is the involvement of OTC medications in 20% of the reported cases, notably resulting in "loss of ART efficacy" in 63% of these instances. These cases predominantly featured the combination of unboosted InSTI with mineral supplements containing divalent cations, known to interfere with intestinal absorption of InSTI by chelation in the gastrointestinal tract [16, 17]. In most of these cases, the viral load was successfully resuppressed to undetectable values, either by discontinuing the supplements or by separating their intake from ARVs (Table 2). Consequently, in managing cases of virological failure, it becomes paramount for HIV healthcare providers to meticulously review medications, including non-prescription drugs, especially mineral supplements. Equally crucial is the necessity to educate patients about potential interactions, as many individuals may not perceive minerals, herbal supplements, recreational drugs, or other OTC products as "traditional medications" and they may not be aware of possible DDIs [18].

This study may be affected by some limitations. Firstly, case reporting relied solely on self-motivation of HIV healthcare providers, potentially introducing bias in both the number and content of the reported cases. Furthermore, the majority of reports were PK-based, and drug concentrations were available in only a few of them. However, the reporting of real-world DDI data to www.clinicalcasesDDIs.com is highly encouraged as it serves as a valuable resource for assessing the clinical relevance of DDIs. This becomes particularly crucial given the occasionally theoretical and conflicting information present in available electronic databases [6, 19]. Documenting real-world cases helps bridge knowledge gaps, ultimately enhancing the quality of care for PWH. Notably, the integration of real-world cases for clinical decisions on DDIs has been recently incorporated into the EACS HIV treatment guidelines [20].

CONCLUSIONS

Our analysis of reported real-world cases underscores the detrimental impact of DDIs between ARVs and OTC medications, emphasizing the critical necessity for comprehensive medication reconciliation, including non-prescription drugs. Additionally, our analysis highlights the continued clinical significance of relevant DDIs associated with boosted ARV. Despite the emergence of newer antiretroviral drugs with more favorable DDI profiles, boosted PI remain essential in specific therapeutic scenarios.

The reporting of real-world data serves as a valuable complement to broaden our understanding of DDIs, ultimately enhancing healthcare for PWH.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest. Juan Ambrosioni has received personal fees from and participated in advisory boards for ViiV, Gilead, Janssen, and MSD; has received funding for research from ViiV, Gilead, and MSD; and has been a member of data safety monitoring boards for HIPRA and Grifols, all outside the current work. Juan Ambrosioni is an Editorial Board member of Infectious Diseases and Therapy. They were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Catia Marzolini has received speaker honoraria from ViiV, Gilead and MSD. Arkaitz Imaz has received financial compensation for lectures, consultancy work and educational activities, as well as funds for research, travel grants and non-financial support from Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, Thera Technologies and ViiV Healthcare. Adrian Curran's institution has received research grants from AbbVie, Gilead Sciences, Bristol Myers Squibb, Janssen-Cilag and ViiV Healthcare while Adrian Curran has received speaker and consultancy honoraria from Gilead Sciences, Janssen-Cilag, MSD, and ViiV Healthcare. Jesus Troya has received speaker and consultancy honoraria from Gilead Sciences, Janssen-Cilag, and MSD. Montse Tuset has received grants from Gilead, ViiV and MSD. Jose Molto has received research funding, consultancy fees and lecture sponsorships from and have served on advisory boards for various laboratories (MSD, Gilead Sciences, Viiv Healthcare, Johnson & Johnson). Natalia Anahí Díaz, Gordana Dragovic, Andrea Calcagno, Sonia Luque, Saye Khoo, David Burger, Claudia P Cortés, and Nadia Naous have no conflict of interest to declare.

Ethical Approval. The study was conducted in accordance with the declaration of Helsinki. Specific data that could contribute to identify persons described in the clinical reports were deleted or modified to assure privacy of the patients. Data were obtained from an open-access platform (www.clinicalcasesDDIs.com) which is available to healthcare professionals, researchers, and patients.

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