

Cross-reactivity between darunavir and trimethoprim-sulfamethoxazole in HIV-infected patients

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Objective: Both darunavir (DRV) and trimethoprim-sulfamethoxazole (TMP-SMX) carry a sulfonamide moiety and a warning for this cross-reactivity is given in the label of DRV. The aim of this study was to investigate the potential cross-reactivity between both drugs.

Design: Retrospective cohort study with a nested case-control study.

Methods: HIV-infected patients that received DRV-containing antiretroviral therapy at any time during the period of their HIV infection were included. Patients with no history of TMP-SMX use were excluded. The incidence of a DRV allergy, according to the Naranjo probability scale, was investigated in patients with an allergy to TMP-SMX compared with those without such an allergy. In order to identify possible risk factors associated with a DRV allergy among patients allergic to TMP-SMX, a nested case-control study was subsequently performed.

Results: A total of 405 patients were included, of whom 79 (17.5%) had a history of allergy to TMP-SMX. A DRV allergy was seen in four patients (5.1%) with a TMP-SMX allergy compared with four (1.2%) without a TMP-SMX allergy ($P = 0.05$). Patients with a TMP-SMX allergy were at higher risk for a DRV allergy (odds ratio 4.29; 95% confidence interval, 1.05–17.56). No additional risk factors for a DRV allergy among patients allergic to TMP-SMX were identified in the nested case-control study.

Conclusion: Although DRV allergy is uncommon, making cross-reactivity with TMP-SMX a rare clinical problem, it appears to exist more often in the background of a TMP-SMX allergy.

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Introduction

Darunavir (DRV), a frequently prescribed anti-HIV protease inhibitor in combination with the pharmacokinetic booster ritonavir (DRV/r), contains a sulfonamide moiety (SO_2NH_2) and is therefore classified as a sulfonamide nonantibacterial drug. Trimethoprim-sulfamethoxazole (TMP-SMX) is the most commonly prescribed sulfonamide antibacterial drug, especially as prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP)

in HIV-infected patients with low CD4^+ cell counts. It is thought that patients, who have had a previous allergic reaction to TMP-SMX, are at greater risk for an allergic reaction to sulfonamide-containing drugs like DRV [1].

Allergic reactions associated with sulfonamide drugs include type I through IV of the Gell and Coombs classification of hypersensitivity reactions [2]. Sulfonamide-related cutaneous drug reactions include urticaria, exanthemas, fixed drug eruptions, erythema multiforme

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and life-threatening conditions such as Stevens–Johnson syndrome and toxic epidermal necrolysis [3]. The incidence of allergic cutaneous reactions to TMP-SMX in HIV-infected patients lies between 21.5 and 39% [4–8]. The DRV registration trials reported hypersensitivity reactions up to 16%, irrespective of known TMP-SMX allergy as this was not documented [9–11]. Therefore, since the introduction of DRV in 2007 [12], multiple TMP-SMX-allergic patients must have been exposed to DRV/r-containing combination antiretroviral therapy (cART).

Two recent studies, in relatively small groups of Asian HIV-infected patients, found no association between the occurrence of DRV/r rash and TMP-SMX allergy [13,14]. Furthermore, DRV/r does not contain an arylamine group, which is believed to be a necessity for this drug hypersensitivity [15]. Although no clinical evidence of cross-reactivity exists, a warning for this potential cross-reactivity is included in the labeling of DRV based on the sulfonamide structure [1]. Therefore, the aim of this study is to investigate the potential cross-reactivity between DRV and TMP-SMX in a large number of HIV-infected patients.

Methods

Patient population and study setting

This retrospective cohort study was conducted in two large hospitals in the Netherlands: the University Medical Center Utrecht (UMCU), located in Utrecht, and the Onze Lieve Vrouwe Gasthuis, located in Amsterdam. The database of the HIV monitoring foundation (Stichting HIV monitoring, SHM) was used to select eligible patients in both centers who were in care on 1 August 2014 and were treated or previously treated with DRV/r-containing cART from June 2007 onwards. Data not included in the SHM database, for example, regarding allergies, were selected from the electronic hospital databases.

Patients were eligible for inclusion if they were aged 18 years or older, HIV-positive, had been treated with DRV/r-containing cART at any time during their HIV-infection, had at least one subsequent follow-up visit after DRV/r initiation and were still in care at the time of the analysis. Patients who participated in an experimental study and were treated with DRV/r-containing cART prior to the national availability of DRV in 2007 were included as well.

Exclusion criteria were HIV-2 infection, no record of DRV/r use after all, no history of TMP-SMX use and use of DRV/r containing cART as part of postexposure prophylaxis. In order to reliably classify patients as not allergic to TMP-SMX, exposure had to have taken place

evidenced from the electronic hospital databases. Therefore, patients with no history of TMP-SMX use were excluded.

From 2002 onwards, all HIV-infected patients in the Netherlands are, after written and oral information with subsequent consent via opting out, anonymously registered in the SHM database (procedure approved by the local ethics committee). Via a secure Internet connection, each center can access the anonymized data from its own hospital.

The following patient characteristics were extracted from the SHM database: age, sex, region of origin, and HIV-specific characteristics, such as date of the first positive HIV test, route of transmission, history of AIDS, HIV loads, CD4⁺ cell counts, hepatitis B (HBV) and hepatitis C virus (HCV) coinfection, and antiretroviral regime. Patients with current or a history of an AIDS-defining disease, based on the Centers for Disease Control and Prevention classification [16], were termed as having a history of AIDS. Patients were considered HBV or HCV coinfecting when respectively hepatitis B surface antigen or HCV antibody were once tested positive. When appropriate, data collection was done at time of DRV/r initiation.

Data collection on allergies

Information about allergies was collected from the medical records. An allergy for either TMP-SMX or DRV was defined as an allergic reaction after intake of TMP-SMX or DRV, diagnosed by a treating physician without other apparent causes. The Naranjo probability scale was used to score the likelihood of DRV being the cause of the allergic reaction [17]. The occurrence of cutaneous reactions, drug fever and anaphylaxis were considered allergic reactions to TMP-SMX or DRV. The duration of TMP-SMX therapy, reason of TMP-SMX therapy and reported allergies to other antibiotics, antiretroviral drugs or allergens were extracted. If applicable, treatment for the allergic reaction and discontinuation rates of TMP-SMX and DRV were extracted.

Data analysis

First, a retrospective cohort study was performed to investigate the incidence of DRV allergy among TMP-SMX allergic HIV-infected patients in comparison with nonallergic HIV-infected patients. Subsequently, a nested case–control study was conducted using the data from the retrospective cohort study in order to investigate the influence of HIV-related factors on the occurrence of DRV allergy. Patients with an allergy to both DRV and TMP-SMX were considered cases. Controls were defined as patients with an allergy to TMP-SMX only. For each case, four controls were matched based on age and sex. Baseline demographics and HIV-specific characteristics of the cases were compared with the controls.

Statistical significance was calculated using the χ^2 -test or Fisher's exact test for categorical variables and the Student's *t* test or Mann–Whitney *U* test for continuous variables. Statistical significance was defined as *P* values less than 0.05. All statistical analyses were performed using the Statistical Package for Social Sciences version 20.0 (IBM SPSS Statistics for Windows, New York, USA).

Results

Patient population

A total of 691 HIV-positive patients were treated with DRV/r-containing regimen within the study period, of whom 511 were in care at the Onze Lieve Vrouwe Gasthuis and 180 at the UMCU. Wanting to evaluate DRV allergy in TMP-SMX-exposed patients, those without a history of TMP-SMX exposure (*n* = 274) were excluded. Furthermore, those never starting using DRV/r-containing cART (*n* = 5), one patient with a HIV-2 infection and six without follow-up after DRV/r initiation were also excluded, leaving a total of 405 patients with known TMP-SMX exposure for analysis in this study (Fig. 1). Those latter patients without follow-up were either noncompliant, had just recently started using DRV/r-containing cART or were foreigners who only visited during their stay in the Netherlands.

An allergy to TMP-SMX was found in 79 patients (19.5%) compared with 326 patients (80.5%) without a reported TMP-SMX allergy. The allergic reaction consisted of a rash in 36 patients (45.6%), drug fever in four patients (5.1%) and a combination of both in 31 patients (39.2%). Eight patients (10.1%) were diagnosed with a TMP-SMX allergy in another hospital with only the presence of an allergy being mentioned in their medical correspondence without allergic-specific symptoms.

The baseline characteristics of both groups are summarized in Table 1 with most characteristics being similar between the two groups. The majority of patients were men with a median age of 50 years and mostly of Caucasian origin. Patients had a prolonged HIV infection with a median duration 15 and 12 years (*P* = 0.06). Patients with a TMP-SMX allergy had a longer duration of cART (median, 13 vs. 10 years, *P* = 0.05), more often a history of AIDS (69.6 vs. 50.9%, *P* = 0.003) and a lower nadir CD4⁺ cell count (50 vs. 75.5 cells/ μ L, *P* = 0.04) than patients without TMP-SMX allergy.

The median interval between TMP-SMX intake and onset of the allergic reaction was 10 days (range, 0–127 days). Reasons of TMP-SMX administration were prophylaxis (low dose) for PJP in 39 patients (49.4%), PJP treatment (therapeutic dose) in 23 patients (29.1%), another infectious disease in four patients (5%) and unknown in 13 patients (16.5%).

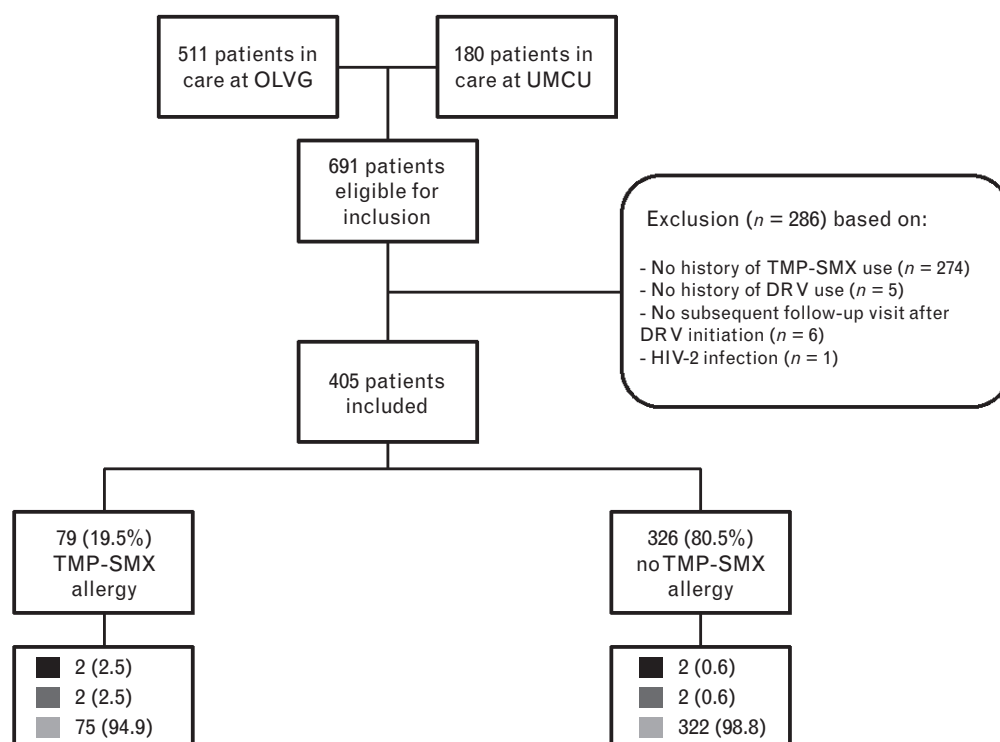


Fig. 1. Study flowchart and overview of drug allergies. DRV, darunavir; OLVG, Onze Lieve Vrouwe Gasthuis; UMCU, University Medical Center Utrecht; TMP-SMX, trimethoprim-sulfamethoxazole; ■, probable DRV allergy; ■, possible DRV allergy; ■, no DRV allergy.

Table 1. Baseline characteristics of patients with and without a trimethoprim-sulfamethoxazole allergy.

Variable	TMP-SMX allergy (n = 79)	No TMP-SMX allergy (n = 326)	P
Men, n (%)	68 (86.1)	277 (85)	0.804
Median age (years) (IQR)	51 (10)	50 (14)	0.585
Caucasian, n (%)	61 (77.2)	220 (67.5)	0.092
MSM, n (%)	53 (67.1)	202 (62)	0.397
HBV or HCV coinfectd, n (%)	39 (49.4)	176 (54)	0.460
Duration of HIV infection, median (IQR) (years)	15 (14)	12 (14)	0.064
Duration of ART, median (IQR) (years)	13 (11)	10 (13)	0.048
History of AIDS, n (%)	55 (69.6)	166 (50.9)	0.003
Undetectable HIV load at baseline, n (%)	4 (5.1)	12 (3.7)	0.748
CD4 ⁺ nadir count, median (IQR) (cells/ μ l)	50 (80)	75.5 (110)	0.036

ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; TMP-SMX, trimethoprim-sulfamethoxazole. The χ^2 test or Fisher's exact test was used for categorical data, and the Student's *t* test or Mann-Whitney *U* test was used for continuous variables. Fisher's exact test was used when >20% of cells had an expected count less than 5. Mann-Whitney *U* test was used to compare medians of variables that were not normally distributed.

Darunavir allergy

Four patients (1.0%), two in the TMP-SMX allergy and two in the no TMP-SMX allergy group, had a probable allergic reaction to DRV. The allergic reactions took place after introducing DRV to the medical regime and consisted of a rash that was seen by the treating physician and disappeared after stopping DRV administration. No other apparent causes for the allergic reaction existed, as DRV was the only new drug introduced to the medical regime. Four other patients (1.0%) also developed a rash after DRV administration: in one patient the rash disappeared spontaneously, in the remaining three patients the rash was successfully treated with antihistamines (two patients) or a combination of antihistamines and corticosteroids (one patient). In these four patients, multiple drugs from the medical regime were altered and the allergic reaction did not lead to DRV discontinuation. These patients had a possible allergic reaction to DRV according to the Naranjo probability scale [17]. The mean interval between DRV intake and onset of the allergic reaction was 10 days (standard deviation, ± 6.9 days). Taking all DRV allergies together, eight patients (2.0%) were detected. Patient characteristics of this group are depicted in Table 2.

A probable DRV allergy was found in two patients (2.5%) with a TMP-SMX allergy vs. two patients (0.6%) without a TMP-SMX allergy ($P=0.07$, Table 3 and Fig. 1). A DRV-related skin rash, thus pooling probable and possible allergies, was seen in four patients (5.1%) with a TMP-SMX allergy compared with four (1.2%) without a TMP-SMX allergy ($P=0.05$, Table 3). Patients with a TMP-SMX allergy were at higher risk for a DRV-related rash upon initiation of DRV/r-containing cART (odds ratio 4.29; 95% confidence interval, 1.05–17.56).

Subgroup with a history of AIDS

Patients with a TMP-SMX allergy had significantly lower nadir CD4⁺ cell counts (50 vs. 75.5 cells/ μ l, $P=0.04$), longer duration of cART (median, 13 vs. 10 years, $P=0.05$) and more often a history of AIDS-defining disease (69.6 vs. 50.9%, $P=0.003$) at baseline. These

factors are related, as patients with lower CD4⁺ counts receive treatment earlier and are at higher risk of developing opportunistic infections. In order to investigate the cross-reactivity between DRV and TMP-SMX in patients with a history of AIDS, two subgroups were made. No association between a DRV and TMP-SMX allergy was found in patients with a history of AIDS (5.5 vs. 0.6%, $P=0.10$), nor in patients without such history (4.2 vs. 1.9%, $P=0.43$).

Nested case-control study

Four cases with an allergy to both DRV and TMP-SMX were matched on age and sex with 16 controls with a TMP-SMX allergy only to identify potential risk factors for a DRV allergy among TMP-SMX allergic patients. Table 4 summarizes the baseline and HIV-specific characteristics of both groups. None of the investigated factors were identified as risk factors for a DRV allergy among patients with a TMP-SMX allergy.

Discussion

This retrospective cohort study showed that patients with a known TMP-SMX allergy were at greater risk for a DRV-related rash upon initiation of DRV/r-containing cART. The occurrence of a DRV-related rash led to discontinuation of DRV in only 1% of the patients, whereas none of the patients developed a potentially life-threatening allergic reaction on administration of DRV. Finally, no predicting factors for the occurrence of a DRV allergy among patients with a TMP-SMX allergy were identified.

These findings are worth noting because they contradict the results of previously published small studies in Asian patients. Nishijima *et al.* [13], and Lin *et al.* [14], found no association between TMP-SMX allergy and DRV allergy in 145 and 74 HIV-infected patients with a history of TMP-SMX use, respectively. However, higher incidences of DRV-induced rash of 5.3 [13] and 6.8% [14]

Table 2. Characteristics of patients allergic to darunavir.

DRV allergy	Symptoms	Naranjo scale [17] (score)	Total daily dosage DRV (mg)	Latency (days)	Treatment	Other allergies	HIV load CD4 ⁺ count [start]	HIV load CD4 ⁺ count [event]	ALT LDH [event]	AIDS before allergy	cART regime before allergy	Reason for switch	cART regime at time of allergy
Men, 57 years	Rash	Probable (7)	800	9	Discont.	Amoxicillin (rash)	58	72	16	No	Truvada	Blood test related	Truvada
Men, 62 years	Rash and pruritus	Probable (7)	900	9	Discont.	No	611	–	163	–	Atazanavir Ritonavir	–	DRV/r
Men, 58 years	Rash	Possible (2)	900	0	Disapp.	No	UDT	–	–	No	Truvada	Toxicity (diarrhea)	Truvada
Women, 48 years	Rash	Possible (3)	800	7	Antihist.	No	190	–	–	–	Lopinavir Ritonavir	–	DRV/r
							UDT	–	–	No	Combivir	Toxicity (hyperbilirubinemia)	Truvada
							340	–	–	–	Tenofovir Atazanavir Ritonavir	–	DRV/r
							UDT	–	25	No	Tenofovir Ritonavir	Unknown	Etravirine
							513	–	–	–	Tipranavir Ritonavir Efavirenz	–	Raltegravir Maraviroc DRV/r
DRV & TMP-SMX allergy	Symptoms - DRV - TMP-SMX Rash (both)	Naranjo scale [17] (score)	Total daily dosage DRV (mg)	Latency (days) - DRV - TMP-SMX	Treatment	Other allergies	HIV load CD4 ⁺ count [start]	HIV load CD4 ⁺ count [event]	ALT LDH [event]	AIDS before allergy	cART regime before allergy	Reason for switch	cART regime at time of allergy
Women, 51 years		Possible (3)	1200	13	Antihist.	No	193 000	–	14	No	Ritonavir	Virological failure and new drugs available	Etravirine
Men, 59 years	Rash (both)	Probable [7]	800	23	Discont.	No	332	–	703	–	Tipranavir Truvada Trizivir	–	Raltegravir DRV/r
Men, 54 years	Rash (both)	Possible (3)	1200	2	Combi.	Patches	UDT	–	–	No	Combivir	Precaution for effects of zidovudine	Abacavir
Men, 67 years	Rash + fever	Probable (6)	900	9	Antihist.	No	600	–	–	–	Lamivudine DRV/r	–	Truvada
							2410	–	–	No	Combivir	Virological failure	Etravirine
							578	406	–	–	Maraviroc	–	Maraviroc
							UDT	–	–	No	Abacavir Tenofovir Lopinavir Ritonavir	Toxicity (flatulence)	Tenofovir Abacavir DRV/r
							880	–	–	–	–	–	–

ALAT, alanine aminotransferase; antihist, antihistamines; cART, combination antiretroviral therapy; combi, combination of antihistamines and corticosteroids; disapp, disappeared spontaneously; discont, discontinued; DRV, darunavir; DRV/r, ritonavir-boosted darunavir; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; TMP-SMX, trimethoprim-sulfamethoxazole; UDT, undetectable. Laboratory values at start darunavir are labeled [start] and during darunavir allergy are labeled [event]. The column 'AIDS' depicts an AIDS-defining disease at start of darunavir. HIV load in copies/ml, CD4⁺ count in cells/μl, ALT in U/l, LDH in U/l.

Table 3. The incidence of darunavir allergy between patients with a TMP-SMX allergy and without a TMP-SMX allergy.

Variable	TMP-SMX allergy (<i>n</i> = 79)	No TMP-SMX allergy (<i>n</i> = 326)	<i>P</i> value
Probable DRV allergy, <i>n</i> (%)	2 (2.5)	2 (0.6)	0.070
Probable and possible DRV allergy, <i>n</i> (%)	4 (5.1)	4 (1.2)	0.050

DRV, darunavir; TMP-SMX, trimethoprim-sulfamethoxazole. Fisher's exact test was used because >20% of cells had an expected count less than 5.

were found in these studies compared with 2% in our study. This difference in incidence may be partly explained by the prospective study design [13] and by the different ethnicities included in these studies compared with ours [18]. Furthermore, our study is distinctive because it included a very large number of patients allergic to TMP-SMX from two large HIV-specialized hospitals in the Netherlands. Furthermore, combining data from the Dutch HIV registry with electronic hospital databases, data regarding patient or HIV-specific characteristics were rarely missing. Finally, in our study the Naranjo probability scale for drug allergy was used for a more objective classification of DRV allergies, whereas both other studies relied on the diagnosis reported in the patient chart.

Despite the large number of included patients, the number of patients allergic to DRV was small occurring in only 2% of the patients with DRV discontinuation in 1%. Therefore, DRV allergy may not be of great clinical concern among HIV-infected patients and as a result, cross-reactivity with TMP-SMX is even less of a problem. Additionally, multivariate analysis could not be performed because of the small number of DRV-allergic patients.

A limitation of our study is its retrospective design that might have caused inconsistencies in reporting information

about allergic reactions to DRV. In order to assess and support the causality of DRV in an objective manner, the Naranjo probability scale was used [17]. Using this probability scale meant that none of the allergic reactions could be classified as 'definite' because some questions of the scoring system could not be answered because of the retrospective design of this study. For example, administration of placebo or detection of DRV levels in blood lacked in all cases. This resulted in a classification of probable and possible DRV-allergic patients. When analyzing the whole cohort of DRV/r-treated HIV-infected patients irrespective of TMP-SMX exposure, a similarly low incidence of DRV-allergy of 2.5% was found, demonstrating that the reporting of allergies is not influenced by TMP-SMX exposure. Allergies were also dose independent, considering almost half of the TMP-SMX allergies occurred in patients receiving prophylactic doses (49.4%) and only two of the eight (25%) DRV-allergic patients were administered DRV 800 mg twice daily.

In conclusion, although DRV allergy was documented infrequently in our cohort, cross-reactivity with TMP-SMX was significantly observed. Importantly, DRV allergy was rarely of clinical relevance. As no potentially lethal allergic reactions were observed and most allergic reactions were treatable, it may be safe to say that

Table 4. Baseline and HIV-specific characteristics of patients allergic to trimethoprim-sulfamethoxazole and darunavir vs. patients allergic to trimethoprim-sulfamethoxazole only.

Variable	TMP-SMX allergy and DRV allergy (<i>n</i> = 4)	TMP-SMX allergy and no DRV allergy (<i>n</i> = 16)	<i>P</i> value
MSM, <i>n</i> (%)	2 (50)	9 (56.2)	1.000
HBV or HCV coinfecting, <i>n</i> (%)	2 (50)	6 (37.5)	1.000
Duration of HIV infection, median (IQR) (years)	21.5 (13)	19 (20)	0.367
History of AIDS, <i>n</i> (%)	3 (75)	14 (87.5)	0.509
Baseline HIV load, median (IQR) (copies/ml)	101 625 (133 773)	131 323.5 (250 763)	0.494
CD4 ⁺ nadir count, median (IQR) (cells/μl)	51 (55)	40 (65)	0.385
HIV load at start DRV, median (IQR) (copies/ml)	1.230 (145 303)	50 (70 773)	0.699
CD4 ⁺ count at start DRV, median (IQR) (cells/μl)	589 (417)	252 (521)	0.156
DRV dosage of 1200 mg, <i>n</i> (%)	2 (50)	4 (25)	0.549
History of other allergies, <i>n</i> (%)	2 (50)	5 (31.2)	0.587
Coadministration of			
tenofovir/emtricitabine, <i>n</i> (%)	0 (0)	4 (25)	0.999
abacavir/lamivudine, <i>n</i> (%)	1 (25)	3 (18.8)	0.930
lamivudine/zidovudine, <i>n</i> (%)	0 (0)	1 (6.2)	1.000
etravirine, <i>n</i> (%)	2 (50)	1 (6.2)	0.088
raltegravir, <i>n</i> (%)	1 (25)	7 (43.8)	0.619
maraviroc, <i>n</i> (%)	1 (25)	3 (18.8)	1.000

DRV, darunavir; IQR, interquartile range; TMP-SMX, trimethoprim-sulfamethoxazole. Fisher's exact test was used because >20% of cells had an expected count less than 5. Mann-Whitney *U* test was used to compare medians. Binary logistic regression was used to compare coadministration of the nucleoside reverse transcriptase inhibitor combinations.

DRV can be administered in patients allergic to TMP-SMX.

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Conflicts of interest

There are no conflicts of interest.

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