Original article

Prevalence of comedications and effect of potential drug–drug interactions in the Swiss HIV Cohort Study

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Background: Potential drug–drug interactions (PDDIs) might expand with new combination antiretroviral therapies (ART) and polypharmacy related to increasing age and comorbidities. We investigated the prevalence of comedications and PDDIs within a large HIV cohort, and their effect on ART efficacy and tolerability.

Methods: All medications were prospectively recorded in 1,497 ART-treated patients and screened for PDDIs using a customized version of the Liverpool drug interactions database.

Results: Overall, 68% (1,013/1,497) of patients had a comedication and 40% (599/1,497) had ≥1 PDDI. Among patients with comedication, 2% (21/1,013) had red-flag interactions (contraindicated) and 59% (597/1,013) had orange-flag interactions (potential dose adjustment and/or close monitoring required). The latter involved mainly central nervous system drugs (49%), cardiovascular drugs (34%) and methadone (19%). In the multivariate analysis, factors associated with having a comedication were advanced age, female gender, obesity and HCV infection. Independent risk factors for PDDIs were regimens combining protease inhibitors and non-nucleoside reverse transcriptase inhibitors (odds ratio [OR] 3.06, 95% confidence interval [CI] 1.44–6.48), ≥2 comedications (OR 1.89, 95% CI 1.32–2.70), current illicit drug use (OR 2.00, 95% CI 1.29–3.10) and patients with HCV infection (OR 1.74, 95% CI 1.19–2.56). Viral response was similar in patients with and without PDDIs (84.5% versus 86.4%; *P*=0.386). During follow-up, ART was modified in 134 patients with comedication regardless of the presence of PDDIs (*P*=0.524).

Conclusions: PDDIs increase with complex ART and comorbidities. No adverse effect was noted on ART efficacy or tolerability; however, most PDDIs affected comedication but were manageable through dose adjustment or monitoring.

Introduction

Antiretroviral therapy (ART) has significantly reduced morbidity and mortality, thus improving long-term survival in HIV-infected individuals [1,2]. As a result, patients are more exposed to age-, disease- or treatment-related morbidities leading to polypharmacy and, consequently, to potential drug–drug interactions (PDDIs) [3]. Antiretroviral (ARV) agents are among the therapeutic agents with the highest potential for drug–drug interactions. Both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are extensively metabolized by the cytochrome P450 (CYP450) enzymes, and can inhibit and/or induce different CYP450 isoenzymes [4]. In addition, PDDIs with ARV agents can occur through other metabolic pathways or mechanisms, including drug transporters [5], glucuronidation enzymes [6], nuclear receptor activation [7] and pH-dependent

drug absorption [8]. The risk for PDDIs can be further exacerbated by the use of over-the-counter drugs, herbal therapies and social/recreational drugs, which might not be reported to the physician [9]. Incomplete medication history also occurs because HIV-infected individuals might receive prescription drugs for other conditions from different healthcare providers [10].

Drug interactions might be associated with a substantial risk for toxicity, decreased efficacy and subsequent emergence of drug resistance; therefore, the prevention, identification and management of drug interactions are crucial for patient care. The clinical effect of dose adjustments to manage ARV drug interactions was evaluated within the Ontario HIV Cohort Study and, interestingly, was associated with a larger reduction in HIV viral load as compared with unadjusted treatments [11]. Previous studies have indicated that PDDIs in HIV therapy are common, ranging from 23–41% [12–15]; however, those studies were performed retrospectively by medical chart or pharmacy record reviews, and thus might have underestimated the prevalence of PDDIs as the complete medication history is not always thoroughly documented [9,10]. Furthermore, some of these studies were carried out with relatively small patient populations, and thus might reflect neither general prescribing patterns nor provide a complete description of PDDIs related to HIV therapy.

We prospectively investigated the prevalence of drug interactions associated with ARV agents among the participants of the Swiss HIV Cohort Study (SHCS). We then informed clinicians about PDDIs and analysed the medical management of deleterious interactions. Furthermore, we assessed risk factors for drug interactions and explored the association between PDDIs and viral suppression, as well as ART modification in the follow-up investigation.

Methods

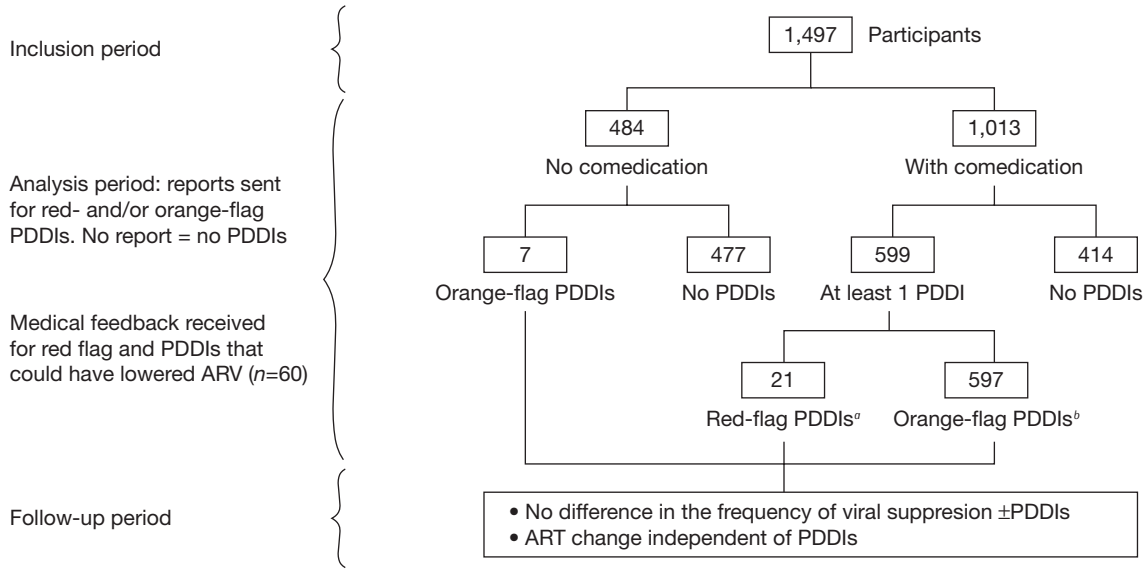
Study population

This study included ART-treated patients from the SHCS, a nationwide prospective cohort study enrolling HIV-infected individuals aged ≥16 years, who were followed-up in HIV clinics or specialized HIV practices [16]. Socio-demographic characteristics, data on the clinical course, coinfection with HBV and HCV, ART, comedications (prophylaxis and treatment of opportunistic infections or cardiovascular drugs), reasons for ART modification (for example, viral failure, toxicity, patient's decision and physician's decision), immunological and viral parameters were collected on standardized forms at enrolment into the study and every 6 months thereafter (follow-up visits). The study was approved by the local ethical review boards and written informed consent was obtained from all participants.

Study design

All ART-treated patients scheduled for a follow-up visit from April 2008 to January 2009 were prospectively included in this study (Figure 1). In addition to the regular clinical assessment, information on current medication was obtained by patient self-report and medical prescription history. The drugs documented included ART, comedications used for opportunistic infections and concurrent diseases, as well as medications used for symptomatic relief, herbals and recreational drugs. The complete treatment was subsequently screened for PDDIs using a customized version of the University of Liverpool drug interaction database [17] and, additionally, by two experts in HIV pharmacology. The Liverpool drug interaction database features interactive charts for assessing the risk of drug interactions between HIV–HIV drugs and HIV–non-HIV drugs. These charts categorized the severity of an interaction by using flags: a red flag for drugs that should not be coadministered as they might lead to serious adverse events or profoundly impair ART efficacy, an orange flag indicates a potential interaction that might require dosage modification or close monitoring to minimize clinical consequences and a green flag represents no known or anticipated interaction. Information on drug interactions for the medications not listed in the database was obtained from prescribing information, published studies or predicted on the basis of the metabolic pathway. These new data were subsequently implemented in the Liverpool database, for example, recent data have shown that ginkgo (*Ginkgo biloba*) and hops (*Humulus lupulus*) induce CYP450 expression via pregnane X receptor activation [18,19]. PDDIs were independently validated by two experts (CM and SG) in HIV pharmacology according to the definitions described below and subsequently reported to the clinicians. The report provided a summary of the PDDIs as well as a recommendation for the management of PDDIs (efficacy or toxicity monitoring or dose adjustment). In order to investigate the adherence to our recommendations, medical feedback was requested for deleterious drug interactions, for example, red-flag interactions and orange-flag interactions that could have lowered the ARV drug level. Clinicians were asked in a structured questionnaire whether the drug causing the drug interaction was changed, or to provide a reason for not modifying the treatment (including, absence of side effects, viral load not affected, target ARV level documented by therapeutic drug monitoring, no alternative treatment available and drug interaction considered as irrelevant). The virological and immunological outcomes, as well as the rate of treatment discontinuation because of viral failure or drug tolerability, were assessed after 6–12 months using the SHCS database.

Figure 1. Study design and prevalence of the identified PDDIs



[a]A red flag indicates drugs that should not be coadministered as they might lead to serious adverse events or profoundly impair antiretroviral therapy (ART) efficacy. [b]An orange flag indicates a potential interaction that might require dosage modification or close monitoring to minimize clinical consequences. ARV, antiretroviral; PDDIs, potential drug–drug interactions.

Definitions

Potentially clinically relevant drug interactions were considered as drug interactions requiring dose adjustment or contraindicated drug combinations according to the US Prescribing Information and/or the European Summary of Product Characteristics [20,21]. Drug interactions were not counted as clinically significant if the appropriate dose adaptation had already been performed (for example, reduced dose of didanosine with tenofovir disoproxil fumarate [TDF] or atorvastatin in the presence of a boosted PI), if the change in pharmacokinetic parameters was <25%, if the interaction was reported as clinically irrelevant or if the level of evidence was judged as very low by the expert in HIV pharmacology. Finally, for the determination of the number of PDDIs, ritonavir was not counted as a separate ARV when prescribed as a boosting agent. Viral suppression was defined as an HIV viral load <50 copies/ml at the time of comedication assessment and after 6–12 months of follow-up.

Statistical analyses

Basic socio-demographic characteristics, CD4+ T-cell count, HIV viral load, ART regimens and comedication were compared using the χ^2 test or Fisher's exact test for categorical variables, and the Mann–Whitney U test for continuous variables. Logistic regression was used to investigate factors associated with having a comedication and, in these patients, predictors of PDDIs. All analyses were performed using Stata software version 9.2 (Stata Corp., College Station, TX, USA) for Windows.

Results

Study population and their medications

Medical prescriptions were analysed for 1,497 ART-treated patients (median age 46 years, interquartile range [IQR] 40–52; 67% male and 81% White). Current illicit drug use was reported by 264 individuals, of whom 51 were currently injecting drug users. Coinfection with HBV and HCV was found in 5% and 26% of the study population, respectively. The median CD4+ T-cell count was 505 cells/mm^3 (IQR 357–689) and viral suppression (<50 copies/ml) was noted in 85% of the whole study population, and in 87% of 978 patients receiving ART for at least 6 months. Overall, ART regimens were mainly PI- (46%) or NNRTI-based (38%) with TDF plus emtricitabine as the nucleoside reverse transcriptase inhibitor (NRTI; 45%) backbone. The most frequently administered PIs were boosted lopinavir (LPV; 26%) and boosted atazanavir (ATV; 22%), whereas efavirenz (EFV; 33%) was the most prescribed NNRTI.

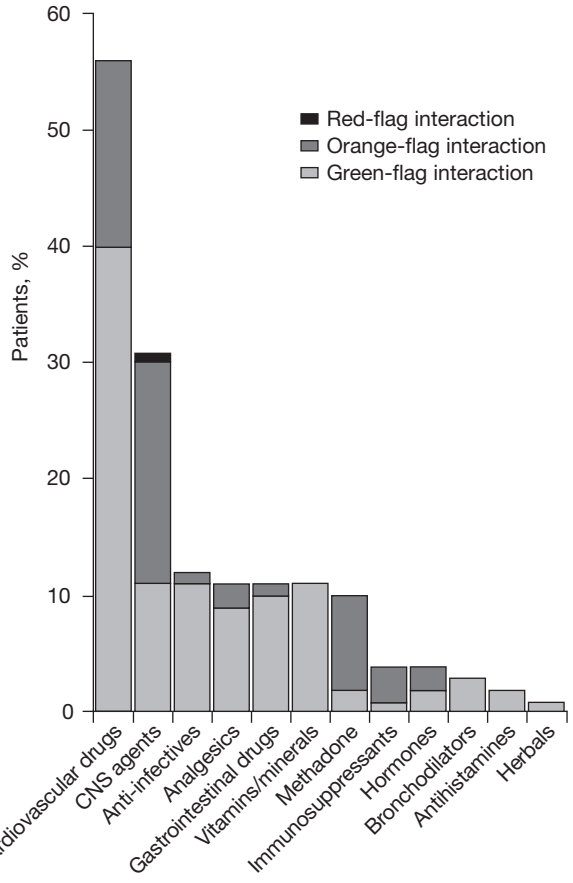
Overall, 68% (1,013/1,497) of participants had ≥1 comedication (Figure 1). The list of comedications, including prescription and over-the-counter drugs, is shown in Figure 2. The two most commonly prescribed therapeutic classes were cardiovascular and central nervous system (CNS) drugs, taken by 56% and 31% of the patients, respectively. Overall, the consumption of over-the-counter drugs, as well as the use of herbals, was relatively low as compared with prescription drugs. The use of a specific therapeutic class was correlated with socio-demographic factors; thus, analgesics and hormones were more often prescribed to women (20% [women] versus 12% [men] and 14% [women] versus 2% [men], respectively; $P<0.001$), whereas cardiovascular drugs were more often administered to men and older patients (50% [men] versus 32% [women] and 67% [>50 years] versus 31% [<50 years], respectively; $P<0.001$). Methadone and CNS agents were more frequently prescribed to active illicit drug users (IDUs; 41% [IDUs] versus 6% [non-IDUs] and 56% [IDUs] versus 29% [non-IDUs], respectively; $P<0.001$). Similarly, patients with HCV more often took methadone (39% [patients with HCV] versus 1% [patients without HCV]; $P<0.001$), CNS agents (48% [patients with HCV] versus 28% [patients without HCV]; $P<0.001$) and anti-infectives (19% [patients with HCV] versus 14% [patients without HCV]; $P=0.021$).

Prevalence, characteristics and effect of the identified potential drug–drug interactions

Overall, 40% (599/1,497) of patients had ≥1 PDDI (1 PDDI, 2 PDDIs and 3 PDDIs in 54%, 24% and 12% of patients, respectively; a maximum of 11 PDDIs were observed in two individuals). The characteristics of the patients treated with ART and a comedication according to the presence or absence of PDDIs are depicted in Table 1.

Red-flag and orange-flag interactions were found in 2% (21/1,013) and 59% (597/1,013) of participants with comedication, respectively (Figure 1). Red-flag interactions included mainly the coadministration of PIs or EFV with midazolam, whereas orange-flag interactions involved predominantly EFV (26%), boosted LPV (22%) and boosted ATV (21%) with CNS drugs (49%), cardiovascular agents (34%) and methadone (19%; Table 2). Interactions between HIV–HIV drugs were detected in 3% (28/1,013) of patients with comedication and were essentially characterized by the coadministration of unboosted ATV with nevirapine (NVP) or TDF (Table 2). PDDIs that could have lowered the HIV drug concentration and/or impaired viral suppression were found in 4% (41/1,013) of patients with comedication. Such interactions included nelfinavir or ATV plus esomeprazole, ATV plus NVP, ATV plus TDF, fosamprenavir plus LPV, EFV plus LPV, EFV plus rifampin, EFV plus ginkgo, EFV or ATV plus hops, ATV plus ranitidine and the combination abacavir (ABC)/lamivudine (3TC)/TDF with no PIs or NNRTIs. Overall, two identified drug interactions were pharmacodynamic in nature and resulted in potentially additive toxicities (that is, didanosine

Figure 2. Comedications used by the 1,497 participants



The bars represent the percentage of patients using one or more drugs of the corresponding therapeutic class. Cardiovascular drugs included antilipidemics (16%), antiplatelets/anticoagulants (9%), angiotensin converting enzyme inhibitors (8%), β-blockers (6%), diuretics (5%), angiotensin II inhibitors (5%), insulin/antidiabetics (4%) and calcium channel inhibitors (3%). Central nervous system (CNS) agents included anxiolytics/sedatives (13%), antidepressants (12%), antipsychotics (3%) and anticonvulsants (3%). Anti-infectives included antibacterials (6%), antivirals (3%), antifungals (2%) and antimycobacterials (2%). Analgesics included anti-inflammatory drugs (5%), paracetamol (4%) and narcotic analgesics (2%). Gastrointestinal drugs included proton pump inhibitors (7%), antidiarrheals (3%) and H_2 blockers (1%). A red flag indicates drugs that should not be coadministered as they might lead to serious adverse events or profoundly impair antiretroviral therapy efficacy. An orange flag indicates a potential interaction that might require dosage modification or close monitoring to minimize clinical consequences. A green flag represents no known or anticipated interaction. The percentage of patients with red-flag, orange-flag and green-flag interactions among the 1,497 participants are represented with different shades in the corresponding therapeutic class.

plus stavudine and zidovudine plus ribavirin). With the exception of the ABC/3TC/TDF combination, the remaining drug interactions were pharmacokinetic in nature and included potential alteration of absorption (that is, nelfinavir or ATV plus esomeprazole, and ATV plus ranitidine), decrease in renal excretion (that is, TDF plus valaciclovir) and predominantly inhibition or induction of CYP450.

Factors associated with the presence of a comedication and potential drug–drug interactions

In the multivariate analyses, after adjustment for sociodemographic and HIV-related variables, advanced age, female gender, obesity and coinfection with HCV were independently associated with a higher risk of having a comedication. By contrast, higher CD4$^+$ T-cell count and triple-NRTI regimens were associated with a lower risk (Table 3).

Among patients with comedication, independent risk factors for PDDIs were current illicit drug use, coinfection with HCV, complex ART regimen and ≥2 comedications in a multivariate analysis, adjusted as previously (Table 4). After additional adjustment for the most frequent comedications, higher risk of PDDIs was observed in individuals receiving a complex ART regimen, ≥2 comedications and those treated with CNS drugs and methadone, suggesting that the association between PDDIs and HCV or current illicit drug use was explained by the higher use of CNS drugs and methadone in these patients.

Table 1. Characteristics of the 1,013 HIV-infected individuals treated with ART and comedication according to the presence of a drug interaction

Characteristic	Drug interaction (*n*=599)	No interaction (*n*=414)	*P*-value
Median age, years (IQR)	48 (42–55)	46 (40–55)	0.006
Male gender, *n* (%)	420 (70)	266 (64)	0.050
Median body mass index, kg/m^2 (IQR)	24 (21–26)	23 (21–26)	0.711
White ethnicity, *n* (%)	532 (89)	325 (79)	<0.001
Transmission risk			<0.001
MSM, *n* (%)	187 (31)	141 (34)	
Heterosexual, *n* (%)	222 (37)	193 (47)	
Intravenous drug use, *n* (%)	190 (32)	80 (19)	
Current illicit drug use, *n* (%)	147 (25)	51 (12)	<0.001
Prior AIDS-defining condition, *n* (%)	209 (35)	117 (28)	0.026
Education			0.133
Low, *n* (%)	159 (5)	122 (30)	
Middle, *n* (%)	291 (50)	177 (43)	
High, *n* (%)	136 (23)	110 (27)	
HCV coinfection, *n* (%)	221 (37)	88 (21)	<0.001
HBV coinfection (HBsAg-positive), *n* (%)	26 (4)	24 (6)	0.293
Median CD4$^+$ T-cell count, cells/μl (IQR)	493 (347–670)	523 (355–693)	0.330
Viral suppression <50 copies/ml, *n* (%)	506 (85)	357 (86)	0.386
Treatment-naive, *n* (%)	51 (9)	50 (12)	0.063
Backbone			0.694
TDF/FTC or TDF/3TC, *n* (%)	243 (41)	160 (39)	
ABC/3TC, *n* (%)	116 (19)	75 (18)	
AZT/3TC, *n* (%)	72 (12)	59 (14)	
Other, *n* (%)	168 (28)	120 (29)	
Drug class			<0.001
PI, *n* (%)	312 (52)	175 (42)	
NNRTI, *n* (%)	213 (36)	173 (42)	
PI and NNRTI, *n* (%)	67 (11)	10 (2)	
Triple-NRTI, *n* (%)	7 (1)	56 (14)	
Comedication			<0.001
1 drug, *n* (%)	144 (24)	229 (56)	
2 drugs, *n* (%)	145 (24)	111 (27)	
≥3 drugs, *n* (%)	308 (52)	71 (17)	
Methadone, *n* (%)	120 (20)	10 (2)	<0.001

ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; IQR, interquartile range; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Table 2. Description of the potentially clinically relevant drug–drug interactions[a]

Interaction	Drug 1	Drug 2	Description of the interaction and recommendation	*n* (%)
Red-flag interactions	PI or efavirenz	Midazolam	Risk of prolonged sedation or respiratory depression, avoid	8 (1)
	Abacavir plus lamivudine plus tenofovir disoproxil fumarate	–	Risk of viral failure (viral selection), administer with PI	3 (<1)
	PI	Triazolam	Risk of prolonged sedation or respiratory depression, avoid	2 (<1)
	Atazanavir/nelfinavir	Esomeprazole	Substantial reduction in PI exposure, avoid	2 (<1)
	Tipranavir	Metoprolol	Risk of bradycardia and arrhythmias, avoid	1 (<1)
	PI	Alfuzosin	Substantial increase in alfuzosin exposure, avoid	1 (<1)
	PI	Darifenacin	Substantial increase in darifenacin exposure, avoid	1 (<1)
	PI	Lercanidipine	Substantial increase in lercanidipine exposure, avoid	1 (<1)
	Zidovudine	Ribavirin	Exacerbation of anaemia, hepatic decompensation, avoid	1 (<1)
	Didanosine	Stavudine	Increased risk of neuropathy, pancreatitis and lactic acidosis, avoid	1 (<1)
Orange-flag interactions (most frequent)	PI/NNRTI	Antidepressants	Increase/decrease of antidepressant exposure, monitor	139 (23)
	PI/NNRTI	Statins	Increase/decrease of statin exposure, dosage adjustment	123 (21)
	PI/NNRTI	Methadone	Decrease of methadone level, monitor plus dosage adjustment	115 (19)
	PI/NNRTI	Anxiolytics/sedatives	Increase/decrease of benzodiazepine exposure, monitor	99 (17)
	PI	β-blockers	Increase of β-blocker exposure, monitor plus dosage adjustment	40 (7)
	PI/NNRTI	Hormones	Decrease of hormone exposure, dosage adjustment	40 (7)
	PI/NNRTI	Antipsychotics	Increase/decrease of antipsychotic exposure, monitor	37 (6)
	PI/NNRTI	Calcium channel inhibitors	Increase/decrease of calcium channel inhibitor exposure, monitor plus dosage adjustment	34 (6)
	PI/NNRTI	Narcotic analgesics	Increase/decrease of narcotic analgesic exposure, monitor	27 (4)
	PI/NNRTI	Anticonvulsants	Increase/decrease of anticonvulsant exposure, monitor	19 (3)
	PI/NNRTI	Erectile agents	Increase/decrease of erectile agent exposure, monitor	17 (3)
	Tenofovir disoproxil fumarate	Valaciclovir	Increase in tenofovir disoproxil fumarate level caused by decreased renal excretion, monitor renal function	14 (2)
HIV–HIV drug interactions	Atazanavir	Nevirapine	Decrease atazanavir C_{min}, increase nevirapine level, TDM	10 (2)
	Atazanavir	Tenofovir disoproxil fumarate	Decrease of atazanavir AUC, boost with ritonavir, TDM	12 (2)
	Fosamprenavir	Lopinavir	Decrease of fosamprenavir AUC, TDM	3 (<1)
	Efavirenz	Lopinavir	Decrease of lopinavir level, TDM	3 (<1)

[a]*n*=599. AUC, area under the curve; C_{min}, concentration at the end of the dosing interval; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDM, therapeutic drug monitoring.

Table 3. Factors associated with comedication in 1,497 HIV-infected individuals treated with ART

Characteristic	OR (95% CI)[a]	*P*-value
Age, per 10 years older	1.79 (1.56–2.05)	<0.001
Female gender	1.36 (1.02–1.81)	0.035
Body mass index		
20–25 kg/m²	1	-
<20 kg/m²	0.91 (0.64–1.30)	0.610
>25 kg/m²	1.48 (1.13–1.93)	0.004
Non-White ethnicity	0.81 (0.58–1.13)	0.216
Current illicit drug use	1.38 (0.98–1.96)	0.076
Prior AIDS-defining condition	1.27 (0.97–1.68)	0.083
HCV (anti-HCV antibodies)	2.14 (1.55–2.95)	<0.001
HBV (HBsAg-positive)	1.05 (0.59–1.84)	0.879
CD4⁺ T-cell count		
<350 cells/μl	1	-
350–500 cells/μl	0.68 (0.48–0.96)	0.029
>500 cells/μl	0.79 (0.58–1.09)	0.150
Viral suppression <50 copies/ml	1.09 (0.78–1.52)	0.619
Treatment-naive	0.85 (0.59–1.22)	0.376
Backbone		
TDF/FTC or TDF/3TC	1	-
ABC/3TC	1.24 (0.88–1.73)	0.217
AZT/3TC	1.24 (0.84–1.82)	0.276
Other	1.26 (0.90–1.77)	0.175
Drug class		
PI	1	–
NNRTI	0.88 (0.68–1.15)	0.351
PI and NNRTI	1.09 (0.62–1.89)	0.774
Triple-NRTI	0.33 (0.20–0.52)	<0.001

[a]Odds ratio (OR), adjusted for all variables listed in the table. ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; CI, confidence interval; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Table 4. Factors associated with drug interactions in 1,013 patients treated with ART and receiving comedication

Characteristic	OR (95% CI)[a]	*P*-value
Age, per 10 years older	0.99 (0.82–1.14)	0.702
Female gender	0.77 (0.54–1.10)	0.154
Body mass index		
20–25 kg/m²	1	–
<20 kg/m²	1.17 (0.75–1.84)	0.494
>25 kg/m²	1.17 (0.83–1.64)	0.368
Non-White ethnicity	0.60 (0.37–0.98)	0.039
Current illicit drug use	2.0 (1.29–3.10)	0.002
Prior AIDS-defining condition	0.88 (0.63–1.22)	0.434
HCV (anti-HCV antibodies)	1.74 (1.19–2.56)	0.005
HBV (HBsAg-positive)	0.66 (0.34–1.29)	0.226
CD4⁺ T-cell count		
<350 cells/μl	1	–
350–500 cells/μl	1.14 (0.74–1.75)	0.554
>500 cells/μl	1.11 (0.76–1.64)	0.586
Viral suppression <50 copies/ml	0.72 (0.46–1.12)	0.148
Treatment-naive	0.71 (0.43–1.17)	0.175
Backbone		
TDF/FTC or TDF/3TC	1	–
ABC/3TC	0.91 (0.60–1.38)	0.666
AZT/3TC	0.93 (0.58–1.48)	0.757
Other	1.50 (0.99–2.25)	0.053
Drug class		
PI	1	–
NNRTI	0.78 (0.56–1.07)	0.117
PI and NNRTI	3.06 (1.44–6.48)	0.004
Triple-NRTI	0.03 (0.01–0.07)	<0.001
Comedication		
1 drug	1	–
2 drugs	1.89 (1.32–2.70)	0.001
≥3 drugs	8.57 (5.75–12.76)	<0.001

[a]Odds ratios (OR), adjusted for all variables listed in the table. ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; CI, confidence interval; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Medical management of potential deleterious drug–drug interactions

Overall, 60 patients had a red flag and/or PDDIs that could have altered ARV drug levels. The medical management of these PDDIs, after informing the physician and providing recommendations, is shown in Table 5. The overall adherence to our recommendations was 38%. The medical decision for not modifying or monitoring a treatment when suggested was essentially motivated by clinical observations, such as maintenance of the viral suppression and absence of side effects. In a few patients, midazolam had to be maintained because of the patient's addiction to this drug.

Outcome at 6–12 months

At the time of comedication assessment, viral suppression was noted in 84.5% of patients with PDDIs compared with 86.4% without PDDIs (*P*=0.386), and was observed in 87.3% versus 88.2%, respectively, after 6–12 months of follow-up (*P*=0.685). In a subgroup analysis, we compared patients with PDDIs likely to be associated with virological failure (*n*=41) with patients with PDDIs that do not lower ARV drug concentrations (*n*=560). In this analysis, a similar outcome was documented (88% of patients with PDDIs lowering ARV versus 84% of patients with PDDIs not lowering ARV had virological suppression <50% copies/ml, respectively) after 6–12 months of follow-up (*P*=0.554). The CD4⁺ T-cell count after 6–12 months did not differ between the patients with and without PDDIs (514 versus 515 cells/μl; *P*=0.480).

During the follow-up period, ART was modified in 134 participants with comedication (76 with PDDIs and 58 without PDDIs; *P*=0.524). Of these, toxicity was the main reason for ART modification in 26% of patients with PDDIs versus 24% without PDDIs

Table 5. Medical management of red-flag interactions[a] and interactions that could have lowered ARV level[b]

Interaction	Recommendation	Medical feedback	*n*
Atazanavir plus tenofovir disoproxil fumarate	Boost with ritonavir, monitor ARV level	Change of NRTI	1
		VL not affected, TDM	3
		VL not affected	7
		VL not affected, no alternative	1
Atazanavir plus nevirapine	Monitor ARV level	VL not affected, TDM	2
		VL not affected	6
		VL not affected, no alternative	1
		VL not affected, not relevant	1
Fosamprenavir or efavirenz plus lopinavir	Monitor ARV level	TDM	2
		Treatment changed	1
		VL not affected	3
Efavirenz plus rifampin	Monitor ARV level	TDM	1
Efavirenz plus hops or ginkgo	Monitor ARV level	Herbal stopped	1
		Changed NNRTI	1
		VL not affected	3
		VL not affected, not relevant	1
Atazanavir plus ranitidine	Separate administration, monitor ARV level	VL not affected, TDM	2
		Antacid stopped	2
Atazanavir or nelfinavir plus esomeprazole	Contraindicated	Antacid stopped	2
PI/efavirenz plus midazolam or triazolam	Contraindicated	Benzodiazepine stopped	4
		No side effect	6
PI plus metoprolol/alfusozin/ darifenacin/lercanidipine	Contraindicated	No side effect	2
		No side effect, not relevant	2
Zidovudine plus ribavirin	Contraindicated	Close monitoring of blood value	1
Didanosine plus stavudine	Contraindicated	No side effect, no alternative	1
Abacavir plus lamivudine plus tenofovir disoproxil fumarate	Contraindicated	Treatment changed	1
		VL not affected	1
		VL not affected, no alternative	1

[a]*n*=21. [b]*n*=41. ARV, antiretroviral; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDM, therapeutic drug monitoring; VL, viral load.

(*P*=0.774). Treatment change because of viral failure occurred in 7% of patients with PDDIs versus 5% without PDDIs (*P*=0.517).

Discussion

PDDIs in HIV therapy are increasing with more complex ART and associated comorbidities. No adverse effects were noted on ART efficacy or tolerability in a large HIV cohort; however, PDDIs were primarily related to the ARV acting on the comedication. The majority of identified PDDIs occurred between PI- or NNRTI- and CNS- (49%) or cardiovascular (34%) drugs, the two most prescribed therapeutic classes among our study population. The high proportion of CNS drugs is explained by the fact that individuals with psychiatric illness, including substance abuse, represent a considerable part of the HIV-infected population [22]. Cardiovascular drugs result from the ageing HIV population and the increased risk for cardiovascular diseases associated with ART itself and possibly HIV [23]. For the major part, PDDIs were orange-flag interactions requiring a potential dose adjustment or close monitoring to minimize clinical consequences. Only 2% of the drug combinations were contraindicated and only 4% could have lowered the ARV drug concentration. There was no evidence that ART efficacy was compromised. The limited number of patients with deleterious interactions probably reflects the expert care in HIV clinics with specialized physicians and nurses, but does not exclude that PDDIs might be more frequent in non-HIV settings. Other factors might also have played a role in limiting interactions, such as the use of web-based HIV drug interaction databases by the physicians, as well as the consultation with clinical pharmacologists or pharmacists and the rather low reported use of non-prescription drugs in our population. The analysis of the medical management of deleterious interactions suggests that the introduction of interaction alert systems could possibly anticipate interactions and further improve the quality of prescribing. In our study, the pharmacological advice was provided after initiating the drug combination, which was thereafter maintained in absence of adverse clinical outcome.

Knowledge of the risk factors for PDDIs might help clinicians prevent drug interactions. Risk factors that were independently associated with PDDIs included more complex ART regimens, generally administered after viral resistance has developed, and the presence of methadone or CNS agents, which were more often used by patients with substance abuse and/or with HCV infection in our study. The recognition of these factors should promote particular attention in terms of drug prescription and drug interaction screening. As expected, the risk for PDDIs increased with the number of comedications. Polypharmacy was more frequent in older or obese patients as a consequence of increased risk for cardiovascular diseases [3], and in patients with HCV infection because of a higher incidence of opportunistic infections or substance abuse in this particular population [24,25]. Also, gender differences in the consumption of prescription and over-the-counter drugs have been previously reported in another HIV-infected population study [9]. For instance, the use of analgesics was shown to be more frequent in women, which is consistent with our observation.

Online drug interactions databases are valuable tools in clinical practice; however, these databases have several limitations that include discrepancies between databases [26], their reliability is highly dependent on timely updates and the clinical relevance of PDDIs cannot be precisely predicted or extrapolated. The latter limitation relies upon the fact that the database describes drug interactions between two compounds, whereas HIV therapy often combines multiple drugs that will mutually interact. Also, some interactions are not recognized until the publication of case reports as they imply new mechanisms, for example, the interaction between rosuvastatin and LPV occurs possibly through the hepatic influx transporter OATP1B1 [27]; therefore, physicians are encouraged to consult clinical pharmacologists or pharmacists for complex regimens or drug combinations with limited data.

The use of external databases for checking drug–drug interactions is of particular value in developing countries where the risk of PDDI is increased because of a higher incidence of coinfections, such as tuberculosis, and because of the limited access to ARV therapeutic drug monitoring. However, the management of PDDIs in resource-poor settings is problematic because of the lack of affordable alternative treatments and the use of fixed-dose formulations for ARV [28]. Drug interaction studies between combination ART and agents used in resource-limited settings, and the establishment of protocols for treatment of coinfection taking into account local drug availability, are urgently needed.

Some limitations of our study should be acknowledged. The ARV plasma levels were available only in a minority of participants with comedication and the dose or eventual dose adjustment of the comedications was not systematically reported; thus, clinicians might have been aware of interactions but decided to prescribe potentially interactive drugs with adjusted dose or under close monitoring as their benefit exceeded their harm. As a result, the percentage of PDDIs might have been overestimated. Another limitation resides in the fact that a potential drug interaction might not always turn into an actual drug interaction in a given person because of the large interindividual variability in drug disposition that can be partly explained by genetic variations in CYP450 or drug transporters. The gap between potential and actual drug interactions might also reflect the degree of evidence used to categorize the severity of an interaction. To limit this issue, the Liverpool drug interaction database is moving towards the GRADE system of quality of evidence and strength of recommendation [29]. Toxicities in relation to interactions leading to increased drug levels of the ARV or comedication were not specifically assessed using a detailed questionnaire as the study was not designed for that purpose. However, the analysis of ART modification provided an indirect measure of the toxicity as treatment changes can be motivated by clinical or serious laboratory adverse events. Several strengths should be noted. The large population, as well as the multicentre and prospective design, provide valuable data on PDDIs as it reflects the general prescribing patterns and documents an individual's complete drug regimen, although we cannot fully exclude under-reporting bias. Finally, participants were followed-up for the consequences of PDDIs on ART response and tolerability.

In summary, potentially clinically relevant drug interactions have become a major issue in HIV therapy because of the ageing HIV population and increasing prevalence of comorbidities; however, the majority are manageable if particular attention is paid to select the most appropriate and least interactive drug, and if dose adjustments or monitoring are made accordingly. For that purpose, clinician's self-education about interacting drugs, the knowledge of a patient's complete drug regimen and the risk factors associated with PDDIs are crucial to prevent, recognize and manage unwanted pharmacological effects.

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MB, DB, SK, BL and CM designed the study. CM, LE and SG conducted the analyses. LE, RW, CF, HF, JPC, MC, EB, AC, PV and MB were responsible for patient recruitment and clinical assessment. CM, LE and MB wrote the report, assisted by all co-authors. MB was the guarantor. All authors had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure statement

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Additional file

Additional file 1: A list of members of the Swiss HIV Cohort Study can be found at http://www.intmedpress.com/uploads/documents/AVT-10-OA-1535_Marzolini_Add_file1.pdf

References

1. Sterne JA, Hernan MA, Ledergerber B, *et al*. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet* 2005; **366:**378–384.
2. Antiretroviral therapy cohort collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008; **372:**293–299.
3. Simone MJ, Appelbaum J. HIV in older adults. *Geriatrics* 2008; **63:**6–12.
4. Barry M, Mulcahy F, Merry C, Gibbons S, Back D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patient with HIV infection. *Clin Pharmacokinet* 1999; **36:**289–304.
5. Kim RB. Drug transporters in HIV therapy. *Top HIV Med* 2003; **11:**136–139.
6. Kiang TKL, Ensom MHH, Chang TKH. UDP-gluconosyltransferases and clinical drug–drug interactions. *Pharmacol Ther* 2005; **106:**97–132.
7. Marzolini C, Tirona RG, Lee W, *et al*. Unexpected complexity in nuclear receptor activation by HIV protease inhibitors and induction of CYP enzymes and transporters. *11th Conference on Retroviruses and Opportunistic Infections*. 8–11 February 2004, San Francisco, CA, USA. Abstract 135.
8. Béïque L, Giguère P, la Porte C, Angel J. Interactions between protease inhibitors and acid-reducing agents: a systematic review. *HIV Med* 2007; **8:**335–345.
9. Furler MD, Einarson TR, Walmsley S, Millson M, Bendayan R. Polypharmacy in HIV: impact of data source and gender on reported drug utilization. *AIDS Patient Care STDS* 2004; **18:**568–586.
10. de Maat MMR, Frankfort SV, Mathot RAA, *et al*. Discrepancies between medical and pharmacy records for patients on anti-HIV drugs. *Ann Pharmacother* 2002; **36:**410–415.
11. Park-Wyllie LY, Levine MA, Holbrook A, *et al*. Outcomes of dosage adjustments used to manage antiretroviral drug interactions. *Clin Infect Dis* 2007; **45:**933–936.
12. Shah S, McGowan J, Opulski B, Lieblein A, Saperstein A. Identification of drug interactions involving antiretroviral therapy (ART) in New York City HIV specialty clinics. *14th Conference on Retroviruses and Opportunistic Infections*. 25–28 February 2007, Los Angeles, CA, USA. Abstract 573.
13. de Maat MMR, de Boer A, Koks CHW, *et al*. Evaluation of clinical pharmacist interventions on drug interactions in outpatient pharmaceutical HIV-care. *J Clin Pharm Ther* 2004; **29:**121–130.
14. Kigen G, Kimaiyo S, Owen A, *et al*. Prevalence of drug interactions between antiretroviral and co-administered drugs in Kenya. *9th International Congress on Drug Therapy in HIV Infection*. 9–13 November 2008, Glasgow, UK. Abstract O122.
15. Miller CD, El-Kholi R, Faragon JJ, Lodise TP. Prevalence and risk factors for clinically significant drug interactions with antiretroviral therapy. *Pharmacotherapy* 2007; **27:**1379–1386.
16. Swiss HIV Cohort Study. (Accessed 4 March 2010.) Available from http://www.SHCS.ch
17. Liverpool HIV drug interactions. (Accessed 4 March 2010.) Available from http://www.hiv-druginteractions.org

18. Li L, Stanton JD, Tolson AH, Luo Y, Wang H. Bioactive terpenoids and flavonoids from *ginkgo biloba* extract induce the expression of hepatic drug metabolizing enzymes through pregnane X receptor, constitutive androstane receptor, and aryl hydrocarbon receptor-mediated pathways. *Pharm Res* 2009; **26:**872–882.
19. Teotico DG, Bischof JJ, Peng L, Kliewer SA, Redinbo MR. Structural basis of human PXR activation by the hops constituent colupulone. *Mol Pharmacol* 2008; **74:**1512–1520.
20. US Food and Drug Administration. (Accessed 4 March 2010.) Available from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
21. European Medicines Agency. (Accessed 4 March 2010.) Available from http://www.ema.europa.eu/htms/human/epar/eparintro.htm
22. Meade CS, Sikkema KJ. HIV risk behaviour among adults with severe mental illness: a systematic review. *Clin Psychol Rev* 2005; **25:**433–457.
23. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; **349:**1993–2003.
24. d'Arminio Monforte A, Cozzi-Lepri A, Castagno A, *et al*. Risk of developing specific AIDS defining illnesses in patients co-infected with HIV and hepatitis C virus with or without liver cirrhosis. *Clin Infect Dis* 2009; **49:**612–622.
25. Mohsen AH, Murad S, Easterbrook PJ. Prevalence of hepatitis C in an ethnically diverse HIV-1-infected cohort in south London. *HIV Med* 2005; **6:**206–215.
26. Pham PA. Drug–drug interaction programs in clinical practice. *Clin Pharmacol Ther* 2008; **83:**396–398.
27. Kiser J, Gerber J, Predhomme J, *et al*. Drug/drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. *J Acquir Immune Defic Syndr* 2008; **47:**570–578.
28. Dooley KE, Flexner C, Andrade AS. Drug interactions involving combination antiretroviral therapy and other anti-infective agents: repercussions for resource-limited countries. *J Infect Dis* 2008; **198:**948–961.
29. GRADE working group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328:**e1490.

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