ORIGINAL RESEARCH

Polypharmacy and potential drug–drug interactions for people with HIV in the UK from the Climate-HIV database

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Objectives

People with HIV (PWHIV) are likely to need therapies for comorbidities as they age. We assessed risk of drug–drug interactions (DDIs) in PWHIV.

Methods

The Climate-HIV electronic recording system was used to cross-sectionally analyse records from PWHIV aged ≥ 18 years attending four UK HIV units with a current antiretroviral (ARV) prescription in February 2018. Antiretroviral and non-ARV medications were categorized by clinical significance of DDIs (University of Liverpool DDI tool). Potential DDIs were predicted using treatment guidelines for commonly recorded comorbidities.

Results

Among 4630 PWHIV (44% female), 41% were ≥ 50 years old. The average number of non-ARV comedications increased from < 1 for patients aged ≤ 24 years to > 5 for patients aged ≥ 75 years; 65% were taking one or more non-ARV comedications. The median (interquartile range) number of non-ARVs was 1 (0–2) and 2 (1–5) for those aged < 50 and ≥ 50 years, respectively. Common comorbidities/concurrent health conditions occurred more frequently in patients aged ≥ 50 years *vs.* < 50 (53% *vs.* 34%). Boosted protease inhibitors were associated with the highest proportion of contraindicated comedications; dolutegravir and raltegravir had the fewest. For non-ARVs, sildenafil and quetiapine were most likely to result in DDIs. Guideline-recommended treatments for hepatitis C, hepatitis B, and tuberculosis had the highest proportions of contraindications when combined with ARV regimens, while treatments for hepatitis C, malignancy, and mental health conditions had the highest proportion of combinations potentially causing DDIs requiring dose monitoring or adjustment.

Conclusions

Non-ARV use by PWHIV is high and increases with age. Treatment decisions for ageing PWHIV should consider guideline recommendations for comorbidities.

Keywords: comorbidity, concomitant medication, drug–drug interactions, HIV, polypharmacy

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Introduction

The introduction of antiretroviral (ARV) medications has led to substantial increases in the life span of people with HIV (PWHIV) [1]. However, as PWHIV live longer, the risk of developing additional health conditions that require concomitant medications increases, and the management of these medications while on combination ARV therapy is a challenging aspect of HIV care [2]. Older

PWHIV with comorbidities are routinely prescribed multiple medications and are likely to be managed by several specialist physicians, each focusing on a single aspect of their health [2,3]. This increases the risk of serious adverse drug events and drug–drug interactions (DDIs) [4]. Co-administration of multiple medications can also affect adherence and, therefore, effectiveness of treatment if not managed appropriately [2].

Real-world data indicate that up to 40% of PWHIV have at least one potential DDI involving ARV medications, with interactions between protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) and central nervous system or cardiovascular drugs accounting for the majority of DDIs in patients aged ≥ 50 years [5].

Some potential DDIs can be managed by dose adjustment or monitoring (classified as amber according to the University of Liverpool DDI tool used in this study), requiring ongoing communication between clinicians and from patients. Other DDIs may require a change to alternative therapies for HIV or the associated comorbidities [6]. With the introduction of regimens based on integrase strand transfer inhibitors (INSTIs) such as dolutegravir (DTG), raltegravir (RAL), and bictegravir, opportunities have arisen to reduce the risk of DDIs associated with PIs and NNRTIs [7]. Additionally, using DTG-based two-drug regimens to manage HIV may reduce the risk of associated DDIs.

Recognition of DDIs in real-world settings can be challenging [8]. Care record systems for clinical management of PWHIV are often separate from the main hospital health record for confidentiality reasons, and records of prescriptions issued in general practice or other clinical settings may not be captured reliably. With patients living longer and having greater access to medicines (including online, over-the-counter, and prescribed by healthcare professionals), there is an increased risk of DDIs when prescribing ARV medications without an accurate and up-to-date drug history. Real-world analyses of prescriptions of concomitant medication and DDIs with ARV therapy are generally lacking, particularly in women and minorities. The purpose of this study was to evaluate the types of concomitant medications used with ARV therapy and to explore the risk of DDIs associated with common comorbidities and ARV medications in a real-world heterogeneous population.

Methods

Study design

This was a cross-sectional analysis of PWHIV receiving care at participating hospital trusts using Climate-HIV, an electronic patient record system used to manage PWHIV, conducted from December 2012 through March 2018. Climate-HIV is updated in real time and contains patient information recorded by the multidisciplinary team, including referral letters, diagnostic information, and drug histories. Patient information is collected and manually entered by the specialist pharmacist during the clinic appointment. For this study, data were included from North Middlesex University Hospital NHS Trust, Nottingham University Hospitals NHS Trust, Birmingham Heartlands Hospital, and Homerton University Hospital NHS Foundation Trust.

Potential interactions between ARV medications and guideline-recommended therapies for other conditions were reported [e.g. guideline treatment recommendations for diabetes include metformin, which the University of Liverpool DDI tool indicates has no interaction with the ARV medication efavirenz (EFV)]. The proportion of individuals with documented health conditions as recorded by their physician in Climate-HIV was also reported.

Patients

All PWHIV included in the study had a recorded diagnosis of HIV-1; were aged ≥ 18 years at the index date; were registered at the clinic (or had a record within the 18 months before the index date); were prescribed an ARV regimen within the year before the index date; and had a current ARV prescription in February 2018. The study period included data from the time of patient record entry into Climate-HIV. The index date was the most recent record in Climate-HIV and was required to be within 18 months before data extraction. The most recent record rather than the most recent ARV prescription was used in the analyses, allowing inclusion of potential concomitant non-ARV therapies prescribed after or added to the last ARV medication.

Assessment of DDIs

All 'current' medications/drug treatments were included in the analysis of DDIs. Drug–drug interactions between ARV and non-ARV medications were determined using University of Liverpool HIV interactions database [9] and categorized as red (do not co-administer), amber (potential interaction; may be managed by dose adjustment or monitoring), yellow (potential interaction likely to be of weak intensity; unlikely to require dose adjustment or additional monitoring), and green (no interaction expected) [6].

Drug–drug interaction charts by ARV class and comedication were cross-tabulated against medications observed

at the patient and population level using R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Statistical analysis

Patient characteristics, including sex, ethnicity, and age, as well as time from HIV diagnosis to index date, were summarized using descriptive statistics [median and interquartile range (IQR); Table 1].

Patient- and interaction-level DDIs

The number of non-ARV therapies at baseline was described, in addition to the number of concomitant therapies [category, mean (SD), and median (IQR)]. The number and type of health conditions were similarly determined [n (%), mean (SD), and median (IQR)]. The number of patients without any recorded non-ARV medications was also determined. For patients with non-ARV medications, DDIs with ARV medications were identified, and the analyses were stratified by age group (< 50 and ≥ 50 years). The proportions of the study population with red, amber, yellow, and green interactions were reported, as well as the proportion of interactions for each regimen of each colour.

A stepwise logistic regression model was derived to determine which factors increased the odds of a red or amber interaction based on the observed ARV/non-ARV medications in the overall population. Because of the low frequency of red interactions observed in the study population, red and amber interactions were given an equal weighting in the model. Age (< 50 and ≥ 50 years), sex, current ARV regimen, number of concomitant drugs, and the presence of any comorbidity or concurrent health condition were included in the baseline model. Stepwise selection was then used to choose other variables for selection. Initially, individual comorbidities/health conditions and ethnicity were also included; however, these variables were removed from the final model because of under-reporting and collinearity, respectively. Aside from ethnicity, no other variables exhibited collinearity. The model with the lowest Akaike information criterion was selected.

Theoretical DDIs

To evaluate the propensity for DDIs in PWHIV when adhering to clinical guidelines for treating common comorbidities/health conditions, we first identified those occurring at high prevalence in the UK Climate-HIV database as follows: type 2 diabetes, hypertension, hyperlipidaemia, chronic obstructive pulmonary disease, asthma, chronic kidney disease, hepatitis B, hepatitis C, malignancy, tuberculosis, cardiovascular disease, peripheral neuropathy, osteoporosis, and mental health disorders (depression, anxiety, bipolar disorder, schizophrenia, mania, and psychosis). Next, we selected recommended first-line comedications based on adherence to UK National Institute for Health and Care Excellence (NICE) treatment guidelines. Finally, we evaluated the likelihood of DDIs with the ARV regimens currently used in our study population, using the University of Liverpool DDI tool. For the high-prevalence comorbidities, the proportion of possible interactions [n (%) of red, amber, yellow, and green interactions for each condition] with the observed medication groups was determined. This analysis represented theoretical DDIs encountered if neither the ARV regimen nor treatment for comorbidities was changed.

Results

Patient characteristics

The study population included 4630 PWHIV (Table 1); median time since HIV diagnosis or transfer into an HIV clinic using Climate-HIV was 11 years (IQR: 5.7–15.7), and patients had received a median of 3 (IQR: 2–5) previous ARV regimens.

Antiretroviral medications and regimens

Overall, 96% of patients had three or more ARV medications in their regimen, excluding ritonavir or cobicistat [median = 3 (IQR: 3–3)], and all regimens were composed of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent. When ARV regimens were grouped by the third agent, the largest proportion of patients were taking EFV + two NRTIs (23%, n = 1049), followed by DTG + two NRTIs (18%, n = 826). Overall, the most

Table 1 Patient characteristics

Parameter	Overall study population (N = 4630)
Sex, female [n (%)]	2021 (44)
Race/ethnicity [n (%)]	
Black, African heritage	2064 (45)
White	1582 (34)
Black, Caribbean heritage/other	446 (10)
Asian	155 (3)
Mixed/unknown	383 (8)
Age, median (IQR) (years)	47 (39–54)
Age ≥ 50 years at baseline [n (%)]	1898 (41)
Time since HIV-1 diagnosis, median (IQR) (years)	11 (5.7–15.7)

IQR, interquartile range.

frequently recorded ARV regimens were EFV/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (18%, $n = 811$); DTG/abacavir (ABC)/lamivudine (3TC) (14%, $n = 644$); and rilpivirine (RPV)/FTC/TDF (7%, $n = 308$). A larger proportion of patients aged < 50 years were taking DTG/ABC/3TC than patients aged ≥ 50 years (18% *vs.* 8%; Table 2).

Concomitant medications

Overall, 65% of patients ($n = 2992$) were taking ≥ 1 non-ARV medication, and 17% ($n = 770$) were taking ≥ 5 non-ARV medications (Table 3). Among patients aged ≥ 50 years, 27% ($n = 508$) were taking ≥ 5 non-ARV medications, compared with 10% ($n = 262$) of patients aged < 50 years ($P < 0.0001$). Similarly, a higher proportion of patients aged < 50 years were taking no comedications compared with those aged ≥ 50 years (43% *vs.* 24%). The most frequently recorded non-ARV medications were cholecalciferol (25%), atorvastatin (9%), and co-trimoxazole (9%). Differences in non-ARV medications were noted between patients aged < 50 *vs.* ≥ 50 years, where the use of atorvastatin (3% *vs.* 19%), amlodipine (4% *vs.* 12%), and ramipril (2% *vs.* 11%) increased with age (Table 3).

Comorbid or concurrent health conditions

Overall, 40% ($n = 1838$) of patients had one or more comorbid or concurrent health conditions, with a lower proportion of patients aged < 50 years recording one or more comorbidity/health conditions compared with those

aged ≥ 50 years (32% *vs.* 50%). The median number of health conditions in addition to HIV was 0 (IQR: 0–1) for patients aged < 50 years and 1 (IQR: 0–1) for those aged ≥ 50 years. Among selected health conditions, the most prevalent were hepatitis B, mental health disorders, and hypertension (6% each). The prevalence of hypertension demonstrated the most pronounced difference between patients aged < 50 years and those aged ≥ 50 years, affecting 3% of younger patients *vs.* 10% of older patients (Table 3). Assessment of combinations of comorbid/concurrent health conditions indicated that diabetes and hypertension were the most frequent combination

Table 2 Antiretroviral (ARV) regimens

Parameter	Overall study population (N = 4630)	Age < 50 years (N = 2732)	Age ≥ 50 years (N = 1898)
Number of pills in current ARV regimen, median (IQR)	2 (1–3)	2 (1–2)	2 (2–3)
Number of ARV medications in current regimen, median (IQR)	3 (3–3)	3 (3–3)	3 (3–3)
ARV regimens [*n* (%)]			
EFV + two NRTIs	1049 (23)	602 (22)	447 (24)
DTG + two NRTIs	826 (18)	582 (21)	244 (13)
RPV + two NRTIs	308 (7)	212 (8)	96 (5)
NVP + two NRTIs	392 (8)	205 (8)	187 (10)
RAL + two NRTIs	332 (7)	169 (6)	163 (9)
EVG/c + two NRTIs	89 (2)	69 (3)	20 (1)
ATV/r/c + two NRTIs	188 (4)	122 (4)	66 (3)
DRV/r/c + two NRTIs	653 (14)	436 (16)	217 (11)
DRV/r/DTG	31 (1)	12 (< 1)	19 (1)

ATV, atazanavir; c, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; r, ritonavir; RAL, raltegravir; RPV, rilpivirine.

Table 3 Concomitant medications and comorbid/concurrent health conditions

Parameter	Overall study population (N = 4630)	Age < 50 years (N = 2732)	Age ≥ 50 years (N = 1898)
Concomitant medications			
Patients with ≥ 1 concomitant non-ARV medication reported [*n* (%)]	2992 (65)	1556 (57)	1436 (76)
Number of concomitant non-ARV medications, median (IQR)	1 (0–3)	1 (0–2)	2 (1–5)
Most commonly reported (≥ 5%) concomitant non-ARV medications [*n* (%)]			
Cholecalciferol	1162 (25)	668 (24)	494 (26)
Atorvastatin	424 (9)	72 (3)	352 (19)
Co-trimoxazole	418 (9)	247 (9)	171 (9)
Amlodipine	325 (7)	96 (4)	229 (12)
Salbutamol	325 (7)	151 (6)	174 (9)
Ramipril	266 (6)	66 (2)	200 (11)
Lansoprazole	253 (5)	95 (3)	158 (8)
Paracetamol	220 (5)	84 (3)	136 (7)
Comorbid/concurrent health conditions			
Patients with ≥ 1 comorbid/concurrent health condition [*n* (%)]	1838 (40)	885 (32)	953 (50)
Number of comorbid/concurrent health conditions, median (IQR)	0 (0–1)	0 (0–1)	1 (0–1)
Most commonly reported (≥ 5%) comorbid/concurrent health conditions [*n* (%)]			
Hepatitis B	290 (6)	154 (6)	136 (7)
Mental health condition	282 (6)	147 (5)	135 (7)
Hypertension	271 (6)	80 (3)	191 (10)
Tuberculosis	230 (5)	131 (5)	99 (5)
Pregnancy†	207 (10)	180 (13)	27 (4)

ARV, antiretroviral; IQR, interquartile range.
†$N = 2021$ for overall study population; $N = 1334$ for patients aged < 50 years; and $N = 687$ for patient aged ≥ 50 years.

(1% of patients overall), increasing from < 1% in patients aged < 50 years to 2% in those aged ≥ 50 years.

Patient-level DDIs

Drug–drug interactions were assessed at the patient level using the University of Liverpool DDI tool and categorized by colour. In total, 40 red and 1458 amber DDIs were observed in this patient population. Sildenafil and quetiapine were most frequently associated with red interactions, with sildenafil resulting in a red interaction for 18 (5.3%) patients taking ritonavir- or cobicistat-boosted darunavir (DRV/r/c) + two NRTIs and quetiapine resulting in a red interaction for four (1.2%) patients taking the same regimen. Red interactions were also identified with lansoprazole for three (5.5%) patients taking a regimen of RPV + two NRTIs; with omeprazole for two (2.7%) patients taking a regimen of ATV/r/c + two NRTIs; and with norethisterone, desogestrel, and etonogestrel, each for two (0.4%) patients taking a regimen of EFV + two NRTIs. Cholecalciferol and atorvastatin accounted for the greatest proportion of amber interactions.

In a logistic regression model, compared with DTG + two NRTIs, all regimens [aside from RPV + two NRTIs (data not shown)] significantly increased the risk of red or amber DDIs ($P < 0.002$; Fig. 1). The most pronounced increased risk was for elvitegravir [EVG/c; odds ratio (OR) = 8.5 (95% CI: 3.9–18.8)] and atazanavir [ATV/r/c; OR = 5.8 (95% CI: 3.4–10.0)]. Addition of a single non-ARV medication [OR = 1.3 (95% CI: 1.2–1.3)] and a comorbid diagnosis [OR = 1.4 (95% CI: 1.2–1.7)] also increased the risk of DDIs by at least 28%, irrespective of ARV regimen. Age and sex did not influence the risk of DDI; however, the number of concomitant non-ARV medications did increase with age, and this factor was significant but not collinear [OR = 1.3 (95% CI: 1.2–1.3)].

Interaction-level DDIs

A separate analysis of DDIs was conducted at the interaction level based on the observed combinations of ARV/non-ARV medications. The prescribed non-ARV medications observed for all patients taking each ARV regimen were cross-tabulated to summarize the proportion of colour classifications. Figure 2 shows the proportion of non-ARV medications that had an interaction or did not interact with the ARV medication of interest. The denominators are the number of different non-ARV medications recorded by patients taking each of the regimens. The highest proportion of red or amber interactions occurred with ATV/r/c + two NRTIs (58%, $n = 57$), followed by DRV/r/c + two NRTIs (48%, $n = 128$). DTG + two NRTIs (87%, $n = 194$) and RAL + two NRTIs (84%, $n = 147$) had the greatest proportion of green medication combinations (Fig. 2a).

Rates of DDIs with DTG were similar between patients aged ≥ 50 years and those aged < 50 years (14% each; Fig. 2b). Results were comparable for patients taking RAL-based regimens, where DDIs were identified for 14% of the comedication pairings for patients aged ≥ 50 years and for 18% of those aged < 50 years; however, there was a higher proportion of DDIs classified as amber (drugs that potentially interact) among patients aged ≥ 50 years than among those aged < 50 years (14% vs. 10%; Fig. 2b). Overall, the slightly higher rates of observed amber and yellow DDIs with RAL compared with DTG (13% vs. 15%; Fig. 2a) can be attributed to the more frequent prescription of TDF/FTC with RAL vs. ABC/3TC with DTG.

Propensity for DDIs with common comorbidities/concurrent health conditions

Table 4 illustrates that for the common comorbidities/concurrent health conditions, adherence to NICE-recommended guidelines yielded the greatest potential risk of DDIs in patients with hepatitis C co-infection, with red (22%) and amber (58%) interactions across all current ARV regimens. Additionally, 50% of treatment combinations for malignancy and 32% for mental health conditions resulted in amber interactions.

Discussion

In this large cross-sectional study, we evaluated DDIs in a population of PWHIV in the UK using data from Climate-HIV. The results confirm previous findings, demonstrating that polypharmacy and the risk of DDIs in PWHIV increase with age [5]. This study represents one of the largest, real-world, heterogeneous populations of PWHIV in which DDIs were evaluated. Of the overall population in this study, 2021 patients (44%) were women, 3048 (66%) were non-white, and 1898 (41%) were aged ≥ 50 years. This is in comparison with previous studies evaluating DDIs in PWHIV, which have focused on populations that are predominantly white and male [5,10].

Most PWHIV are treated with regimens composed of three ARV drugs; therefore, only two additional medications would result in polypharmacy according to the most commonly used definition (≥ 5 drugs) [11]. In this study, 47% (2195/4630) of patients were taking at least two non-ARV drugs, and the proportion was higher [61% (1154/1898)] for patients aged ≥ 50 years compared with
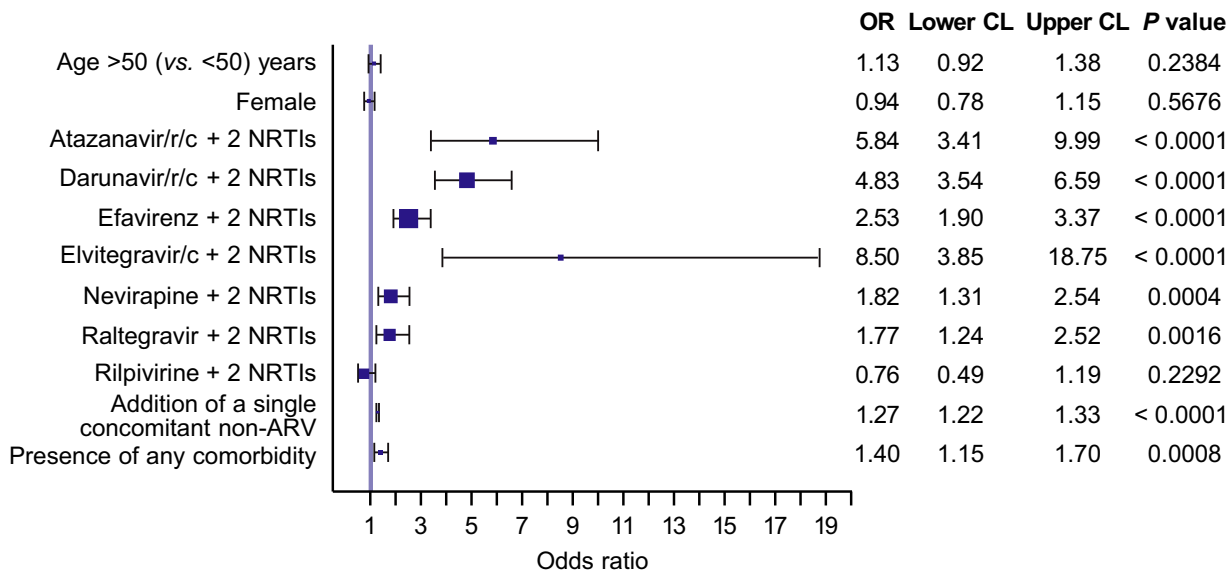
	OR	Lower CL	Upper CL	*P* value
Age >50 (*vs.* <50) years	1.13	0.92	1.38	0.2384
Female	0.94	0.78	1.15	0.5676
Atazanavir/r/c + 2 NRTIs	5.84	3.41	9.99	< 0.0001
Darunavir/r/c + 2 NRTIs	4.83	3.54	6.59	< 0.0001
Efavirenz + 2 NRTIs	2.53	1.90	3.37	< 0.0001
Elvitegravir/c + 2 NRTIs	8.50	3.85	18.75	< 0.0001
Nevirapine + 2 NRTIs	1.82	1.31	2.54	0.0004
Raltegravir + 2 NRTIs	1.77	1.24	2.52	0.0016
Rilpivirine + 2 NRTIs	0.76	0.49	1.19	0.2292
Addition of a single concomitant non-ARV	1.27	1.22	1.33	< 0.0001
Presence of any comorbidity	1.40	1.15	1.70	0.0008

Fig. 1 Logistic regression analysis assessing factors influencing the risk of red or amber drug–drug interactions relative to regimens based on dolutegravir. For odds ratios (ORs) associated with antiretroviral (ARV) regimens, the reference regimen is dolutegravir. The symbol size represents the relative number of patients. c, cobicistat; CL, confidence level; NRTI, nucleoside reverse transcriptase inhibitor; r, ritonavir.

those aged < 50 years [38% (1041/2732)]. In addition to an increased risk of DDIs, polypharmacy is associated with worst reported outcomes, including elevated risk of adverse drug reactions and non-adherence in the general population and increased risk of geriatric syndromes such as falls, fractures, and dementia in the elderly population [2,12,13].

In this study, the most prevalent recorded comorbidities were hepatitis B, mental health conditions and hypertension (6% each); this differs from the results of a previous real-world study that indicated much higher prevalence of hepatitis B (24%), mental health conditions (22%), cardiovascular disease (20%), hepatitis C (14%), and diabetes (11%) in PWHIV [14]. In the present study, clinicians recorded patient-reported prescriptions received outside of the participating hospital as well as over-the-counter medications in Climate-HIV; however, as these are patient-reported clinician-entered data, they may not have always been captured reliably, potentially leading to under-reporting of comorbidities. For instance, under-reported use of proton pump inhibitors, which are contraindicated in patients receiving RPV, could have resulted in under-reported DDIs. However, while non-ARV use overall may have been under-estimated, the relative risks of DDIs for different ARV regimens are not expected to be affected, representing a strength of this study.

Despite the possibility of under-reporting, mental health conditions were among the most commonly reported comorbidities, and approximately one in three

(32%) of the therapies used for mental health conditions resulted in an amber DDI. Conversely, this observation is consistent with other studies reporting that mental health problems are the most prevalent comorbidities in HIV, with 39–57% of patients having received a mental health diagnosis within the previous 2 years [15,16]. As medications for mental health conditions are most likely to be prescribed by a psychiatrist, they may not appear in medical records for primary care, increasing the risk of inadvertent prescription of interacting drugs. An additional risk that was not recorded in this study is the potential for DDIs when dosages are altered. In this situation, the drug itself remains the same but the change in dosage may lead to a DDI; an alteration may not have been observed until the next clinic appointment with another specialist qualified to amend the dosage or withdraw any interacting drugs.

This analysis found frequent red interactions at the patient level when cross-tabulating the commonly prescribed drug quetiapine with common ARV regimens, though notably, no DDIs are expected between quetiapine and DTG-, RAL-, or RPV-based regimens [17].

The number of concomitant non-ARV medications tended to increase as patients aged, suggesting an increased presence of comorbid conditions. A previous study also found that comedication use among PWHIV in Switzerland tended to increase with age [5]. Our results indicate that the addition of one non-ARV medication or the presence of any comorbidity or concurrent health
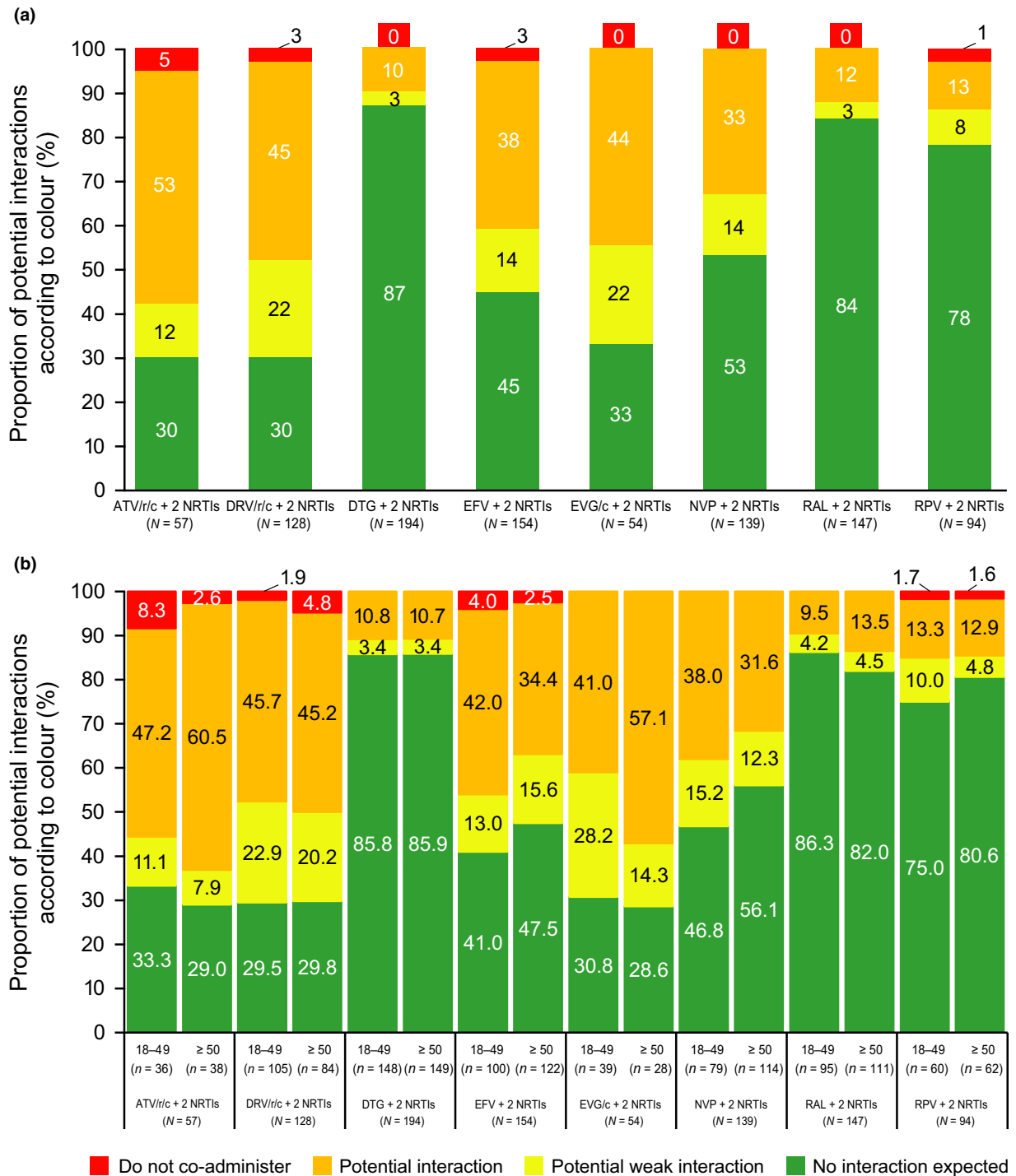
Fig. 2 Proportion of potential drug-drug interactions based on observed non-antiretroviral (non-ARV) medications taken with ARV regimens (a) in the overall population and (b) stratified by patient age. All regimens listed are taken with two nucleoside reverse transcriptase inhibitors (NRTIs). N represents the number of non-ARV medications recorded by the population using each specific regimen. ATV, atazanavir; c, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; NVP, nevirapine; r, ritonavir; RAL, raltegravir; RPV, rilpivirine.

Table 4 Proportion of antiretroviral/non-antiretroviral combinations resulting in drug–drug interactions based on National Institute for Health and Care Excellence-recommended therapies for selected health conditions

Condition	Red (%)	Amber (%)	Yellow (%)
Hepatitis C	22	58	0
Hepatitis B	20	20	0
Tuberculosis	14	14	0
Cardiovascular disease	5	23	9
Hyperlipidaemia	4	14	10
Mental health	3	32	19
COPD	3	13	8
Asthma	3	12	9
Hypertension	2	19	9
Peripheral neuropathy	1	23	19
Malignancy	0	50	4
Diabetes	0	31	2
Chronic kidney disease	0	3	13

COPD, chronic obstructive pulmonary disorder.

condition significantly increased the risk of a red or amber DDI. Overall, regimens based on ATV/r/c or DRV/r/c tended to represent the greatest proportion of patients experiencing red or amber interactions, and the proportion of red and amber interactions also increased with age; regimens based on boosted EVG demonstrated a similar pattern. These regimens were also associated with a greater likelihood of DDI in logistic regression when compared with DTG, as were regimens based on EFV, nevirapine, and RAL ($P < 0.05$). Dolutegravir and RAL were associated with the highest proportion of green interactions and had no potential red interactions observed.

These results are consistent with previous studies reporting the risks of potential DDIs for PWHIV treated with various ARV regimens. In an analysis from the Swiss HIV Cohort Study, PI- and NNRTI-based therapies were associated with an increased risk of potential DDIs [5]. In a cohort study of PWHIV aged > 65 years treated in France, an increased risk of red DDIs was observed with boosted PIs or EVG (adjusted OR *vs.* NNRTI-based regimens, 4.12; 95% CI: 3.34–5.10; $P < 0.0001$) and a decreased risk was observed with DTG- or RAL-based regimens (adjusted OR = 0.02; 95% CI: 0.005–0.050; $P < 0.0001$) [18]. Another recent population-based study evaluated risk of DDIs in PWHIV in a drug-dispensing registry in Madrid, Spain [19]. The greatest risk of red interactions was observed with boosted DRV, while treatment with unboosted INSTI-based regimens was statistically significantly associated with a reduced risk of red interactions (adjusted OR = 0.72; 95% CI: 0.60–0.88; $P = 0.001$) [19].

The majority of guideline-recommended therapies for treatment of chronic conditions do not consider concurrent conditions. Per the NICE guidelines, the recommended therapies for hepatitis C, hepatitis B, and tuberculosis generated the highest proportions of red DDIs when administered in combination with ARVs. Additionally, recommended therapies for hepatitis C, malignancy, and mental health conditions generated the greatest proportion of amber DDIs, suggesting that these comorbidities require the most interpretation and monitoring by clinicians. However, when reviewing the observed non-ARVs at the patient level, the lipid-lowering medication atorvastatin, the calcium channel blocker amlodipine, and the vasodilator sildenafil were among the most common concomitant medications in this study. These medicines were associated with red, amber or yellow DDIs for most ARV regimens and are all used for the management of cardiovascular disease.

Understanding the classification of DDIs is important for prescribing clinicians, particularly for the red and amber classifications. The red classification designates specific medications that should not be prescribed together. However, the amber classification allows for greater interpretation by the specialist clinician, and the possible dose adjustment and/or monitoring may be associated with greater inter- and intrapatient variability. Therefore, the amber classification may require more interpretation from the multidisciplinary team and better communication with patients. Overall, there were more amber DDI classifications than red or yellow in this study.

This study has several limitations. Data were derived from four selected UK sites and may not be representative of the entire population with HIV in the UK. Concordance between comedications and health conditions was not assessed in this analysis. Additionally, it is unclear whether some potential DDIs identified in this study were managed with dose adaptation, as this would require a longitudinal analysis. Furthermore, we were unable to assess for actual clinical harms resulting from these potential DDIs as data were not collated at a patient level. However, it could be assumed that DDIs classified as red would likely lead to clinical harm. Finally, patients reported prescriptions received outside of the participating hospital along with over-the-counter medications to the clinician at each visit; however, some of these medications may not have been reported as patients may not have been asked by the clinician, patients may have failed to accurately recall them, or prescriptions may have been incorrectly coded when entered into the database. Therefore, medications and comorbidities that were not recorded in the Climate-HIV database may have resulted in misclassification or missing prescription data and under-reporting of DDIs.

This study represents one of the largest, real-world, heterogeneous populations of PWHIV (44% women, 66% non-white) in which DDIs were evaluated. This analysis demonstrated that the use of comedications in PWHIV is high and increases with age, resulting in an elevated risk of polypharmacy and DDIs, which is similar to previous findings from clinical trials and other real-world populations [5,10]. In countries like the UK, most PWHIV on ARVs have undetectable viral loads, see their HIV clinician once or twice annually, and have greater access to medicines over the counter and online. Therefore, efforts to increase communication between healthcare professionals, empower patients and reduce drug burden should be seriously pursued. The results of this study reinforce the importance of ongoing and up-to-date reviews of concomitant medications and comorbidities when seeing a patient in clinic and choosing ARV regimens that can mitigate the associated risks of polypharmacy and DDIs.

Author contributions

CO and SK contributed to the conception of the study. CO, MR, PB and AP contributed to the design of the study. AS, ST, AD, JB, AF, FG, IR, SM and AC contributed to the acquisition of the data. CO, MR, MM, NB and SK contributed to the analysis of the data. CO, AS, ST, AD, JB, AF, IR, PB, AP, JvW and SK contributed to the interpretation of the data. CO, MR, MM, PB, AP and JvW contributed to drafting the manuscript. CO, AS, MR, MM, ST, AD, JB, AF, FG, PB, AP, JvW and SK contributed to critical revision of the manuscript for important intellectual content. All authors approved the manuscript for publication.

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