Title Page

Prevalence of potentially clinically significant drug-drug interactions with antiretrovirals against HIV over three decades: a systematic review of the literature.

Short running title: Drug-Drug Interactions in HIV

Daryl Hodge PhD[a], Eva Maria Hodel PhD[b], Elen Hughes MBBCh[c], Phoebe Hazenberg MBBCh[d,e], Sandra Grañana Castillo MPharm[a], Sara Gibbons MPhil[a], Duolao Wang PhD[e], Fiona Marra MPharm[a,f], Catia Marzolini PhD[a], David Back PhD[a], Saye Khoo MD[a,d].

a) Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology, University of Liverpool.
b) Clinical Infection, Microbiology and Immunology, Institute of Infection, Veterinary & Ecological Sciences, University of Liverpool.
c) Wirral University Teaching Hospital.
d) Liverpool University Hospital Foundation Trust.
e) Department of Clinical Sciences, Liverpool School of Tropical Medicine.
f) Gartnavel General Hospital, NHS Greater Glasgow and Clyde.

Professor Khoo is the corresponding author.

khoo@liverpool.ac.uk, +44 0151 794 5560

Infection Pharmacology Group, 3nd Floor, William Henry Duncan Building, 6 West Derby Street, University of Liverpool, Liverpool, L7 8TX

Abstract presented at International Workshop on Clinical Pharmacology of HIV, Hepatitis and Other Antiviral Drugs 2021, Online.

No specific funding was received for this work. The Liverpool HIV Drug Interactions website is funded by grants from Gilead, MSD, Thera Technologies, and ViiV Healthcare.

CM has received a research grant from Gilead and honoraria for lectures from ViiV and MSD. DB has received speaker's honoraria from ViiV, Gilead, and Theratechnologies Europe. FM has received educational grants and/or consultation honoraria from Gilead, ViiV, and MSD. SK has received funding from Gilead, Janssen, GSK, ViiV, Vir and Ridgeback Biotherapeutics for research projects unrelated to this work, and speaker's honoraria from ViiV and Merck. All other authors: none to declare.

Word count: 2,930

Abstract

Background

Contemporary first-line antiretrovirals have considerably reduced liability for clinically significant drug-drug interactions (DDI). This systematic review evaluates the prevalence of DDI amongst people receiving antiretrovirals across three decades.

Methods

We searched three databases for studies reporting the prevalence of clinically significant DDIs in patients receiving antiretrovirals published between January 1987 and October 2020. Clinically significant DDIs were graded by severity. All data extractions were undertaken by 2 independent reviewers, adjudicated by a third.

Results

Of 20,601 records returned, 7,775 were duplicates. After screening the remaining 12,724 abstracts against inclusion criteria, 102 papers were included for full-text analysis, from which a final list of 29 papers were included for data synthesis. While there was a modest reduction in patients experiencing an amber DDI (1.69% per year; 95%CI= -2.65% to - .74%, *P*=0.001), the proportion of patients experiencing a red DDI did not change over time (0.43%, 95%CI= -1.39 to .52%, *P*=0.361). The most frequently reported classes of antiretrovirals involved in DDIs were protease inhibitors and non-nucleoside reverse transcriptase inhibitors; of note integrase use in the most recent studies was highly variable and ranged between 0-52%.

Conclusions

The absolute risk of amber DDIs have only moderately decreased and red DDIs have not decreased over the period covered. This is likely related to continued use of older regimens and an ageing cohort of patients. A greater reduction in DDI prevalence can be anticipated with broader uptake of regimens containing unboosted integrases, or non-nucleoside reverse transcriptase inhibitors.

Key Words: drug-drug interactions, pharmacokinetics, HIV, anti-retrovirals

Introduction

Antiretroviral treatment has transformed HIV into a chronic condition where long-term survival is the expectation [1]. Antiretroviral regimens consist of lifelong medications, frequently with significant propensity for drug-drug interactions (DDIs), where each antiretroviral agent may be a victim of a DDI (affecting antiviral efficacy or safety) or else a perpetrator, adversely affecting efficacy or toxicity of concurrent medications [2]. In the latter case, use of boosted protease inhibitors are associated with the highest risk of DDIs followed by older non-nucleoside reverse transcriptase inhibitors [3]. In contrast, modern first-line regimens based on unboosted integrase inhibitors (such as dolutegravir, bictegravir, raltegravir, and cabotegravir), newer non-nucleoside reverse transcriptase inhibitors [3] (such as rilpivirine and doravirine), or the attachment inhibitor fostemsavir have significantly less risk for DDIs [4]. While this would be expected to reduce the overall frequency of DDIs, the changing demographic resulting from an ageing cohort of people living with HIV receiving antiretrovirals, who develop other co-morbidities may push the overall frequency of DDIs in the opposite direction: for example in the UK, 42.4% of people accessing HIV care in 2019 were aged 50 or over [5]. Polypharmacy (defined as taking 5 or more co-medications in addition to antiretrovirals) is a strong predictor of risk for DDIs. DDIs may also be more likely to result in harms in older people, due to physiological changes [6].

An understanding of the prevalence and risks of DDIs in the era of modern antiretrovirals, and how this has been affected by newer regimens against a background of a global ageing population of people living with HIV (PLHIV) is important, since this informs treatment guidelines, health policy, and drug safety. We undertook this systematic review to evaluate how the risk of DDIs in PLHIV has changed over time, from the introduction of the first antiretrovirals to the current era. To our knowledge, this is the first systematic review attempting to integrate different DDI studies performed in multiple cohorts.

Methods

We undertook a systematic review of the literature. Three databases (PubMed, Web of Science, Scopus) were searched for papers published between 01/01/1987 – 07/31/2022 (the start date was chosen to coincide with the year of approval of the first antiretroviral). Inclusion criteria were studies evaluating interventions to reduce DDIs, population-based studies, and studies on medication and prescribing errors. Exclusion criteria were treatment updates, conference highlights, guidelines, studies on specific drug combinations or in specific co-morbid/co-infected patients, studies performed on subpopulations, (i.e. specific patients excluded, subpopulations of older age groups were included, with bias due to age restriction taken into account), mechanistic or pre-clinical studies, pharmacokinetic studies, modelling studies, paediatric studies, studies conducted on inpatients, reviews, and opinion papers. Papers that did not report the number of patients on antiretrovirals, the number of patients experiencing a DDI, the severity of DDIs, or the time frame over which data were gathered were considered to not have sufficient data for analysis. Papers that included interactions between co-medications or only interactions between antiretrovirals were excluded due the risk of biasing the outcome. The search parameters are listed in Table S1. Identified studies were screened for duplicates with Clarivate Endnote X9.3.3 (London, UK) [7] then imported into the Rayyan website (Cambridge, MA) [8]. Following abstract screening, full texts were sought for retrieval from 122 abstracts. In the case that these were not available, authors were contacted for manuscripts. All texts were successfully retrieved. Ninety-seven texts were selected for data extraction according to the selection criteria, of which thirty-four papers were eligible for inclusion in the systematic review. Excluded full texts are listed in Table S2. Papers were assessed for risk using a generic tool examining bias in selection participants, bias from poor or inadequate reporting, bias in choice of outcome measures, bias in reporting outcomes selectively, and bias due to conflict of interest [9]. This generic tool was used, as other tools were not applicable for synthesising retrospective chart reviews without interventions. Each stage of the review (abstract

screening, full text screening, data extraction, and risk of bias analysis) was carried out by at least two independent reviewers (DH, EH, EMH, PH) with adjudication of conflicts after unblinding by a third reviewer (SK). For Spanish full texts, a native Spanish speaker (SGC) also reviewed the text.

The following data were extracted into Microsoft Excel 365 (Redmond, WA) from the studies selected for inclusion: time frame of study, location of study and WHO region, whether participants represented a subpopulation, median or mean age of participants, prevalence of integrase inhibitor use (boosted or unboosted), tool used to detect clinically significant DDIs, total number of patients on antiretrovirals, total number of patients experiencing at least one amber DDI, at least one red DDI, or at least one potentially clinically significant DDI, top candidates for DDIs, and funding source and conflicts of interest. One paper reported two arms over different study periods; these were considered as two separate cohorts. DDIs were defined according to the Liverpool Drug Interaction protocol [10] used by the DDI checker (https://www.hiv-druginteractions.org) where a red DDI denotes a contraindication or strong recommendation not to prescribe and an amber DDI denotes the requirement for increasing monitoring, or a dose modification. Our protocol includes two grades of non-clinically significant interactions: yellow is used for a potential or theoretical pharmacokinetic interaction which is unlikely to be clinically significant and green denotes no DDI. For papers not utilising the Liverpool Drug Interactions website to identify DDIs, the tool used was converted to the equivalent Liverpool grade. We define clinically significant DDIs to include both red and amber DDIs. Following consensus of reviewers, data were collated and analysed with Rstudio 1.3.1093 (Boston, MA) using R version 4.0.2. The primary endpoint for the systematic review was the change in incidence of potentially clinically significant DDIs from 1987-2022. Studies which reported the proportion of patients experiencing at least one amber *and* the proportion of patients experiencing at least one red DDI were included in the statistical analysis to investigate this endpoint. Some studies reported the number of patients on antiretrovirals and co-medications. We chose number of patients on antiretrovirals as the denominator to (i) increase the number of studies available for analysis and (ii) to better represent the risk of DDIs to the whole population taking antiretrovirals.

For correlation with median age, studies which provided arms with different median ages were considered as independent cohorts. Statistical analyses were performed in Stata 14 (College Station, TX). Statistical significance was determined by weighted linear regression. Figures were prepared with GraphPad Prism 9.2.0 (San Diego, CA).

Details of the protocol for this systematic review were registered on PROSPERO [11] (CRD42020216066). The protocol was edited to remove an author who was unable to work on the project, to revise the method of recording time to avoid skewing the data, and to extend the search period.

Results

A total of 21,665 records were retrieved, of which 13,596 were determined to be unique after de-duplication. Of these, 122 records were determined to be appropriate for full text analysis. The high rate of attrition was due to a high incidence of pre-clinical studies in the search results. Of the 122 full texts, we identified 34 records for inclusion in our review (Figure S3). The list of studies excluded can be found in Table S2. Risk of bias analysis highlighted a few key areas of risk. Four studies [12-15] only selected patients over a certain age threshold. These studies may therefore skew towards more clinically significant DDIs due to increased polypharmacy in older age groups [16]. One study included a very low number of paediatric patients (0.49% of the cohort), but we did not consider this number to be high enough to exclude it from our review or to cause significant risk of bias [17]. Nine studies explicitly included interactions between antiretrovirals, with a further study unclear on this point. The intentional interaction of protease inhibitors with their boosters was disregarded. For a minority of studies evaluated, it was not possible to separate DDIs between antiretrovirals from those between antiretrovirals and comedications. Another possible source of bias is the difference in the extent of ascertainment of inclusion of herbal remedies, recreational drugs, and over-the-counter medication. Fifteen papers explicitly did not include over-the-counter medication and other unprescribed drugs, three included some but not all unprescribed medication, and four papers did not provide information. Despite these areas of risk, all the final 34 papers were considered sufficiently bias-free to allow integration. The full risk of bias analysis for included papers can be found in Figure S4.

The characteristics of the 34 included studies are available in Table 1. Further to data extraction, 18 papers were eligible for the statistical analysis. The percentages of patients taking antiretrovirals who experienced potentially clinically significant DDIs can be found in Table 2. The percentage of patients experiencing at least one potentially clinically significant DDI was varied across studies, with a range of 3-84.2% and a mean of 43.9%. One study (Chen 2020) had a very low prevalence of

potentially clinically significant DDIs (3%) [18]. This is due to the low use of comedication in this cohort, likely due to age (70% <50 years old). Of the papers that reported severity of DDI, 38.8% of patients experienced at least one amber DDI (range 18.3-77.3) and 4.5% experienced at least one red DDI (range 0.4-14.8). Weighted regression analysis suggests a marginally significant interaction effect between DDI severity and year on the proportion of DDI (*P*=0.066). In the amber group, the DDI was decreased by 1.69% per year (95%CI= -2.65% to -.74%, *P*=0.001) whereas the annual decrease in DDI in the Red group was no different from 0 (regression efficient: 0.43%, 95%CI=-1.39% to .52%, *P*=0.361). (Figure 1). Eighteen papers reported the incidence of integrase inhibitor use within their cohorts, with a wide range (0-88.7%) of uptake seen, even within the past five years (S5). Integrase inhibitor use did not appear to influence the incidence of clinically significant DDIs, but this was not analysed due to the inclusion of boosted integrase inhibitor regimens in some studies. There was no interaction effect between DDI severity and median age on the proportion of DDI (*P*=0.706). In addition, no association was found between median age and percentage of patients experiencing at least one red or at least one amber DDI (*P*=0.763) (Figure 2).

Our systematic review was designed to be as inclusive as possible, by searching three different databases and by not using language as an exclusion criterion. Despite this, only papers in English or Spanish were retrieved. Most of the studies were from Europe (19 papers, of which 9 were included in the statistical analysis), followed by North America (5 papers, all of which were included in the statistical analysis).

The most frequently reported antiretroviral classes involved in clinically significant DDIs were boosted protease inhibitors and non-nucleoside reverse transcriptase inhibitors. The most frequently involved comedication classes were central nervous system agents, antimicrobials, cardiovascular agents, gastrointestinal agents, statins, and corticosteroids (Table 3). The key clinically significant DDIs between these classes and their mechanisms are listed in Table S6.

Discussion

PLHIV are at risk of DDIs and many studies have been conducted to quantify that risk. To our knowledge, this is the first time a systematic review has undertaken to evaluate whether the global prevalence of clinically significant DDIs has changed over time. We observed a wide range in the data, with an overall mean prevalence of clinically significant DDIs affecting 42% of PLHIV taking antiretrovirals. The majority of these clinically significant DDIs are graded amber affecting 35% of PLHIV taking antiretrovirals. Red DDIs were less common, affecting 5% of PLHIV taking antiretrovirals. Amber DDIs have decreased slowly, but significantly over time. The proportion of patients taking antiretrovirals experiencing at least one amber DDI has fallen by 1.69% per year from 1987-2020. No such change was seen for the number of PLHIV experiencing at least one red DDI.

Despite the marked reduction of risk for DDIs with newer first-line antiretroviral regimens, we have not yet observed an equivalent reduction in the global prevalence of DDIs across the time-period surveyed. It is notable that the median age of PLWH has increased across the world, with an accompanying rise in the prevalence of multimorbidity [6], and this may offset reductions in the relative risk of DDIs with contemporary antiviral regimens. However, in this review, we did not find an association between median age and incidence of DDI. Additional compounding factors are the lag time in publication (data several years old by time of reporting), and differing rates of transition to unboosted integrase inhibitor-based regimens. Indeed, studies in this dataset published in the last 5 years (2015-2020) did not reflect a large uptake in integrase inhibitor-based regimes, despite their recommendation as a first line treatment [2]. This may, in part, be explained by a time lag between data collection and publication. Among the cohorts reporting high use of unboosted integrase inhibitors such as Lopez-Centeno et al. (39.35% of patients receiving antiretrovirals) there was a lower prevalence of amber DDIs (18%) [17]. Two surveys of the Swiss HIV Cohort carried out 10 years apart reported use of unboosted integrase inhibitors rising from 0% in 2008 to 40% in 2018, with a consequent reduction of amber DDIs from 40% to 23% [19,20]. In addition, studies from Switzerland and

the UK suggest that younger individuals (with more recent initiation of antiretroviral therapy) were more likely to be receiving first-line, integrase containing fixed dose formulations than older patients who were more likely to be optimally controlled on older antiviral regimens [21]. The classes of antiretrovirals most frequently associated with potentially clinically significant DDIs in this review were boosted protease inhibitors and non-nucleoside reverse transcriptase inhibitors. This would seem to support the hypothesis that the lack of uptake of unboosted integrase inhibitor-based regimens accounts for the surprisingly small change of incidence in DDIs seen in this review. Indeed, of the nine studies which undertook a multivariate analysis for risk factors for increased DDIs, eight found protease inhibitor use to be an independent risk factor [17,18,20,22-26]. Two studies also found that unboosted integrase inhibitor use was an independent protective factor, and was associated with decreased DDIs [17,18].

We did not find a correlation between median age and proportion of patients experiencing either a red or an amber DDI. However, as our datasets were not contemporaneous, the effect of age cannot be ruled out. Five studies found age to be an independent factor contributing to increased incidence of clinically significant DDIs in multivariate analysis [18,20,22-24]. Three studies failed to detect any such association, although one speculated this was due to age being of less impact in an African setting, having previously found age to be a factor in the UK in univariate analysis [25-27]. Finally, one paper found age greater than 50 to be associated with less red DDIs [17]. As the population of PLHIV continues to age, clinicians need to be extra vigilant of drug interactions due to increased polypharmacy in this group [28,29].

There are several limitations to this work. The time lag from study to publication means that the full impact of the transition to integrase inhibitors may not yet have been observed. Marked differences in integrase inhibitor use was observed ranging from 0-42% (Table 1). Additionally, our review may lack the sensitivity required to detect small changes given the heterogeneity of studies – the clearest example of this was the audit of DDIs repeated 10 years apart in the Swiss cohort where a 16%

decrease in DDI prevalence was associated with increased use of unboosted integrase inhibitors. Of note, the prevalence of red DDIs did not change [19,20]. The different rates of adoption of dolutegravir into first-line use, and the high prevalence of tuberculosis in some countries, may also have contributed to geographic differences. We excluded hospital inpatients due to the number of short-term comedications, along with paediatric patients who represent a distinct cohort [30] – except for López-Centeno 2020 where the numbers of patients under 18 years were very low [31]. Studies in specific co-infected or co-morbid patients were excluded to minimise bias from specific interactions e.g. tuberculosis therapy [32]. Not all studies collected comedications with the same rigour (over-the-counter, herbal, and recreational drugs), or presented data in the same way (e.g., 27 studies analysing DDI prevalence according to numbers of prescriptions rather than individuals were excluded). Four studies also only selected for older PLHIV, which may be likely to result in higher prevalence of DDIs [28]. Despite this, our systematic review suggests that DDIs continue to pose a risk for harm, and support European AIDS Clinical Society (EACS) [2] and WHO [33] recommendations to screen for DDIs when initiating or changing treatment in PLHIV.

In conclusion, despite a marked reduction in propensity for clinically significant DDIs with modern antiretroviral regimens, we found only a 1.69% decrease per year in the proportion of patients experiencing an amber DDI and no change in those experiencing a red DDI. This appears to correspond to a reduction in DDIs in cohorts with high integrase inhibitor use. The period surveyed predated the widespread adoption of unboosted integrase inhibitors. We speculate that the limited use of unboosted integrase inhibitors may be why incidence of potentially clinically significant DDIs has only slightly decreased. DDIs could be significantly reduced by pre-emptive switching (as recommended in guidelines) to contemporary regimens where possible especially in older patients with multiple comorbidities [2,33]. Prescribers need to remain vigilant when treating PLHIV and urged to check drug interactions on tools such as the Liverpool DDI checker (www.hiv-druginteractions.org).

Acknowledgements

No specific funding was received for this work. The Liverpool HIV Drug Interactions website is funded by grants from Gilead, MSD, Thera Technologies, and ViiV Healthcare.

CM has received a research grant from Gilead and honoraria for lectures from ViiV and MSD. DB has received speaker's honoraria from ViiV, Gilead, and Theratechnologies Europe. FM has received educational grants and/or consultation honoraria from Gilead, ViiV, and MSD. SK has received funding from Gilead, Janssen, GSK, ViiV, Vir and Ridgeback Biotherapeutics for research projects unrelated to this work, and speaker's honoraria from ViiV and Merck. All other authors: none to declare.

Table 1.

Reference	Start	End	No Patients on ARVs	Age (median)	Age (mean)	Sub-pop	INI use (%)	Boosted INI (%)	Non-Rx Included	No. Comeds (median)	Country	Tool	Statistical analysis
Miller 2007 [24]	May-06	Sep-06	153		48		0		No	11	USA	DHHS Guidelines, Micromedex, US Prescribing Information	✓
Evans-Jones 2010 [25]	Jun-08	Jul-08	159	41			0		Yes		UK	Liverpool	
Marzolini 2010 [19]	Apr-08	Jan-09	1497	46			0		Yes		Switzerland	Liverpool	✓
Kigen 2011 [34]	Jan-06	Nov-07	996		39		0		No		Kenya	Liverpool	✓
Patel 2011 [35]	Jan-10	May-10	229	47			17.5	0		5	USA	DHHS Guidelines, Lexicomp	✓
Holtzman 2013 [23]	Jan-06	Dec-10	3810	46			0.3*		No	3	USA	Liverpool	✓
Seden 2013 [36]	Dec-09	Oct-11	200	43			0		Yes		UK	Liverpool, SmPC	
Tseng 2013 [37]	Jan-10	Jan-12	914				14.6*		Yes		Canada	Liverpool, Canadian Product Monograph	✓
Iniesta-Navalón 2015 [38]	May-13	Sep-13	268	45.6			5.6*		No		Spain	Basede datos del medicamento del Colegio Oficial de Farmacéuticos de España (BOT)	
Seden 2015 [26]	May-12	May-12	2000	40.4							Uganda	Liverpool	
Cervero 2016 [39]	Jan-85	Dec-14	142	48							Spain	Liverpool, SmPC	
Córdova 2016 [40]	Sep-12	Nov-12	217	41			0				Argentina	Liverpool	✓
Baecke 2017 [22]	Jan-09	Apr-16	145	42			42.1*	29.5	No	4	Belgium	Liverpool	
Bastida 2017 [12]	Nov-14	Nov-14	197	71.2		≥65			No	5.6 *(mean)*	Spain	Liverpool, Hospital Clínic de Barcelona database	
Pholtawornkulchai 2017 [41]	Apr-14	Jun-14	1320		44				No		Thailand	Liverpool	
Shafiekhani 2017 [42]	Oct-14	Mar-15	200		39.5		0		No		Iran	Lexicomp	

Jiménez-Guerrero 2018 [13]	Jan-14	Dec-14	242	57.5		>50	4.6*	9.1	No		Spain	Drugs.com	
Molas 2018 [43]	Mar-15	Sep-16	1259	47			14.5*		Yes		Spain	Liverpool, Hospital Clínic de Barcelona database, Toronto General Hospital database	✓
Ranzani 2018 [14]	Jan-16	Jun-16	744	56.1		≥50	40.9*		Yes – if recorded	2	Italy	Liverpool	✓
Siefried 2018 [44]	Sep-13	Nov-15	522		50.8				Yes	3.6 *(mean)*	Australia	Liverpool, Australian Product Label, US Prescribing Information	
Halloran 2019 [45]	Jan-13	Dec-16	1044						Yes – not recreational	4	UK	Liverpool	
López-Centeno 2020 [17]	Jan-17	Jun-17	22945	48		0.5% <18	52.0*	27.0	No		Spain	Liverpool	✓
Oreagba 2019 [27]	Jan-05	Dec-15	500	46					No		Nigeria	Liverpool	
Chen 2020 [18]	Oct-18	Apr-19	1780		42.92		4.3*	4.0		1.8 *(mean)*	China	Liverpool	
Deutschmann 2020 [20]	Jan-18	Dec-18	9298	51			55.7*	28.2	Yes		Switzerland	Liverpool	✓
El Moussaoui 2020 [46]	Jan-12	Dec-12	803						No	2	Belgium	Liverpool	✓
	Jan-16	Dec-16	969						No	2	Belgium	Liverpool	✓
Pontelo 2020 [47]	Jun-15	Jul-16	304				0		No		Brazil	Liverpool	
Ruellan 2020 [15]	Jan-17	Mar-17	239	69		≥65			No		France	Liverpool, French DDI Thesaurus, SmPC	✓
Schlaeppi 2020 [48]	Jan-13	Dec-16	2069	39					No		Tanzania	Liverpool	✓
Funke 2021 [49]	Sep-16	Mar-17	453	46			58*	25.5	Yes – not recreational	2.8 *(mean)*	Germany	Liverpool	✓
Kunimoto 2021 [50]	Jan-19	Apr-19	71	45		≥20	88.7*	6.4**	No	3	Japan	Lexicomp	
Murray 2021 [51]	Jun-13	May-15	621			≥50	30.9*		No		USA	Liverpool	✓
Wang 2021 [52]	Jan-16	Dec-16	19614		39		12.8	0	No		Taiwan	Liverpool	✓

Tinggaard 2022 [53]	Sep-18	Nov-19	337	53			38*	23.4	Yes –not recreational or supplements		Denmark	Liverpool	✓

Table 2.

Reference	At least 1 clinically significant DDI (%)	At least 1 Amber (%)	At least 1 Red (%)
Miller 2007 [24]	41.2	39.2	6.5
Evans-Jones 2010 [25]	27.0		
Marzolini 2010 [19]	40.0	39.9	1.4
Kigen 2011 [34]	33.5	23.1	14.8
Patel 2011 [35]	34.1	32.8	2.6
Holtzman 2013 [23]		33.3	7.0
Seden 2013 [26,36]	57.5		
Tseng 2013 [37]	62.7	62.5	3.4
Iniesta-Navalón 2015 [38]	14.6		
Seden 2015 [26]	18.7		
Cervero 2016 [39,54]	27.5		
Córdova 2016 [40]	31.3	30.9	1.4
Baecke 2017 [22]	49.0		
Bastida 2017 [12]	65.0		
Pholtawornkulchai 2017 [41]	40.4		
Shafiekhani 2017 [42]	63.5		
Jiménez-Guerrero 2018 [13]	45.5		
Molas 2018 [43]	44.7	41.5	3.3
Ranzani 2018 [14]	53.1	47.4	5.7
Siefried 2018 [44]	45.4		
Halloran 2019 [45]	49.9		
López-Centeno 2020 [17]		18.3	3.2
Oreagba 2019 [27]	84.2		
Chen 2020 [18]	3.0		
Deutschmann 2020 [20]		22.5	1.7
El Moussaoui 2020 [46]		43.5	4.6
		40.8	4.6
Pontelo 2020 [47]	50.0		
Ruellan 2020 [15]	25.1	20.1	7.1
Schlaeppi 2020 [48]	31.2	30.7	0.4
Funke 2021 [49]		41.5	1.3
Kunimoto 2021 [50]	62.0		
Murray 2021 [51]	84.1	77.3	6.8
Wang 2021 [52]		41.1	4.8
Tinggaard 2022 [53]		51.6	4.5
n	27	19	19
Range	3.0 - 84.2	18.3 – 77.3	0.4 – 14.8
Mean	43.9	38.8	4.5
Standard Deviation	19.4	14.5	3.3

Reference	Most common ARVs	Most common comeds
Miller 2007 [24]	PI, NRTI	Steroids, GI agents.
Evans-Jones 2010 [25]	PI	CNS agents, antibiotics, recreational
Marzolini 2010 [19]	PI, NNRTI	Sedatives, CNS agents, CV agents, methadone
Kigen 2011 [34]	NNRTI	Antimicrobials
Patel 2011 [35]		Statins, PDEI, CV agents, GI agents, methadone, steroids
Holtzman 2013 [23]	PI, NNRTI	GI (PPI), statins, ED agents
Seden 2013 [36]	PI	CNS agents
Tseng 2013 [37]	PI	CV agents, narcotics, CNS agents, antimicrobials
Iniesta-valón 2015b [38]		
Seden 2015 [26]	NNRTI	Antimicrobials
Cervero 2016 [39]	PI, NNRTI	Statin, opiates, benzodiazepines
Córdova 2016 [40]	NNRTI, PI	Antimicrobial, anxiolytics
Baecke 2017 [22]		Antimicrobials, CV agents, CNS agents
Bastida 2017 [12]	PIs, NNRTIs, INI	GI agents, CNS agents, genital urinary and sex hormones
Pholtawornkulchai 2017 [41]	PI, NNRTI	Antimicrobials, statins
Shafiekhani 2017 [42]	NNRTI, NRTI	Antimicrobials
Jiménez-Guerrero 2018 [13]	PI, NNRTI	Statins, CNS agents, corticosteroids, CV agents
Molas 2018 [43]	PI, NNRTI	CNS agents, GI agents, statins
Ranzani 2018 [14]	PI, NNRTI	Urological agents, GI agents, antipsychotics
Siefried 2018 [44]	PI	Corticosteroids, CNS agents, NSAIDs, GI agents, Anti-coag, CV agents, ED agents
Halloran 2019 [45]	PI	Anti-coagulants, corticosteroids
López-Centeno 2020 [17]	PI	Corticosteroids, CNS agents, GI agents
Oreagba 2019 [27]	PI, NNRTI	Antimicrobials
Chen 2020 [18]	PI	Ca^{2+} channel blockers
Deutschmann 2020 [20]	PI, NNTRI	Corticosteroids, CNS agents
El Moussaoui 2020 [46]	PI	Cardiovascular, GI agents, respiratory
Pontelo 2020 [47]	NNRTI, PI	Antimicrobials, CNS agents, statins, ED agents
Ruellan 2020 [15]	PI	Statins, anti-coagulants, CV agents
Schlaeppi 2020 [48]	PI, NNRTI	Antimicrobial, NSAIDs, CV agents
Funke 2021 [49]	INI, PI, NNRTI	Dietary supplements, statins, CV agents, ED agents, levothyroxine
Kunimoto 2021 [50]	INI	GI agents, dietary supplements
Murray 2021 [51]		
Wang 2021 [52]	NNRTI, INI	NSAIDs, GI agents
Tinggaard 2022 [53]	INI, NNRTI, PI	GI agents, ED agents

References

1. Rathbun RC, Liedtke MD. Antiretroviral drug interactions: overview of interactions involving new and investigational agents and the role of therapeutic drug monitoring for management. *Pharmaceutics.* 2011;3(4):745-781.
2. European AIDS Clinical Society. EACS Guidelines version 11.0. https://www.eacsociety.org/guidelines/eacs-guidelines/. Published 2021. Accessed 1/11/21, 2021.
3. Barry M, Mulcahy F, Merry C, Gibbons S, Back D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. *Clin Pharmacokinet.* 1999;36(4):289-304.
4. Gibbons S, Marzolini C, Moss C, et al. Drug interaction profiles for first line antiretroviral therapy and selected fixed-dose antiretroviral combinations over 20 years of the Liverpool Drug Interaction website. *Hiv Medicine.* 2019;20:44-45.
5. Trust NA. HIV in the UK statistics. https://www.nat.org.uk/about-hiv/hiv-statistics. Published 2021. Accessed 5/10/2021.
6. Back D, Marzolini C. The challenge of HIV treatment in an era of polypharmacy. *Journal of the International Aids Society.* 2020;23(2).
7. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. *J Med Libr Assoc.* 2016;104(3):240-243.
8. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev.* 2016;5(1):210.
9. Viswanathan M, Patnode CD, Berkman ND, et al. AHRQ Methods for Effective Health Care

Assessing the Risk of Bias in Systematic Reviews of Health Care Interventions. In: *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
10. Seden K, Gibbons S, Marzolini C, et al. Development of an evidence evaluation and synthesis system for drug-drug interactions, and its application to a systematic review of HIV and malaria co-infection. *PloS one.* 2017;12(3):e0173509.
11. Hodge D, Hodel EM, Hazenberg P, Hughes E, Khoo S. Prevalence of clinically significant drug-drug interactions with antiretrovirals against HIV over time: a systematic review of the literature. PROSPERO: International prospective register of systematic reviews. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=216066. Published 2020. Accessed.
12. Bastida C, Grau A, Márquez M, et al. Polypharmacy and potential drug-drug interactions in an HIV-infected elderly population

Polifarmacia e interacciones farmacológicas potenciales en una población envejecida con infección por el VIH. *Farm Hosp.* 2017;41(5):618-624.

13. Jiménez-Guerrero L, Núñez-Núñez M, Castañeda-Macías I, Del Castillo SSF. Potential interactions in a cohort of elderly HIV-positive patients. *Farm Hosp.* 2018;42(4):163-167.
14. Ranzani A, Oreni L, Agro M, et al. Burden of Exposure to Potential Interactions Between Antiretroviral and Non-Antiretroviral Medications in a Population of HIV-Positive Patients Aged 50 Years or Older. *Jaids-Journal of Acquired Immune Deficiency Syndromes.* 2018;78(2):193-201.
15. Ruellan AL, Bourneau-Martin D, Joyau C, et al. Assessment of drug–drug interaction in an elderly human immunodeficiency virus population: Comparison of 3 expert databases. *British journal of clinical pharmacology.* 2020.
16. Guaraldi G, Milic J, Mussini C. Aging with HIV. *Current HIV/AIDS Reports.* 2019;16(6):475-481.
17. Lopez-Centeno B, Badenes-Olmedo C, Mataix-Sanjuan A, et al. Polypharmacy and Drug-Drug Interactions in People Living With Human Immunodeficiency Virus in the Region of Madrid, Spain: A Population-Based Study. *Clinical Infectious Diseases.* 2020;71(2):353-362.
18. Chen R, Chen J, Tang Q, et al. Use of comedications and potential drug-drug interactions in people living with HIV in China. *J Infect Chemother.* 2020;26(7):722-728.
19. Marzolini C, Elzi L, Gibbons S, et al. Prevalence of comedications and effect of potential drug-drug interactions in the Swiss HIV cohort study. *Antiviral Therapy.* 2010;15(3):413-423.
20. Deutschmann E, Bucher HC, Jaeckel S, et al. Prevalence of potential drug-drug interactions in patients of the Swiss HIV Cohort Study in the era of HIV integrase inhibitors. *Clin Infect Dis.* 2020.
21. Okoli C, Schwenk A, Radford M, et al. Polypharmacy and potential drug–drug interactions for people with HIV in the UK from the Climate-HIV database. *HIV Med.* 2020;21(8):471-480.
22. Baecke C, Gyssens IC, Decoutere L, Van Der Hilst JCH, Messiaen P. Prevalence of drug-drug interactions in the era of HIV integrase inhibitors: A retrospective clinical study. *Neth J Med.* 2017;75(6):235-240.
23. Holtzman C, Armon C, Tedaldi E, et al. Polypharmacy and risk of antiretroviral drug interactions among the aging hiv-infected population. *J Gen Intern Med.* 2013;28(10):1302-1310.
24. Miller CD, El-Kholi R, Faragon JJ, Lodise TP. Prevalence and risk factors for clinically significant drug interactions with antiretroviral therapy. *Pharmacotherapy.* 2007;27(10):1379-1386.
25. Evans-Jones JG, Cottle LE, Back DJ, et al. Recognition of risk for clinically significant drug interactions among HIV-infected patients receiving antiretroviral therapy. *Clinical Infectious Diseases.* 2010;50(10):1419-1421.
26. Seden K, Merry C, Hewson R, et al. Prevalence and type of drug-drug interactions involving ART in patients attending a specialist HIV outpatient clinic

in Kampala, Uganda. *The Journal of antimicrobial chemotherapy.* 2015;70(12):3317-3322.
27. Oreagba IA, Usman SO, Oshikoya KA, et al. Clinically Significant Drug-Drug Interaction in a Large Antiretroviral Treatment Centre in Lagos, Nigeria. *J Popul Ther Clin Pharmacol.* 2019;26(1):e1-e19.
28. Back D, Marzolini C. The challenge of HIV treatment in an era of polypharmacy. *J Int AIDS Soc.* 2020;23(2):e25449.
29. Courlet P, Livio F, Guidi M, et al. Polypharmacy, Drug-Drug Interactions, and Inappropriate Drugs: New Challenges in the Aging Population With HIV. *Open Forum Infect Dis.* 2019;6(12):ofz531.
30. Batchelor HK, Marriott JF. Paediatric pharmacokinetics: key considerations. *British journal of clinical pharmacology.* 2015;79(3):395-404.
31. López-Centeno B, Badenes-Olmedo C, Mataix-Sanjuan Á, et al. Polypharmacy and drug-drug interactions in people living with human immunodeficiency virus in the region of Madrid, Spain: A population-based study. *Clinical Infectious Diseases.* 2020;71(2):353-362.
32. Chen J, Raymond K. Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. *Annals of Clinical Microbiology and Antimicrobials.* 2006;5(1):3.
33. World Health Organisation. *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach.* Geneva2021.
34. Kigen G, Kimaiyo S, Nyandiko W, et al. Prevalence of potential drug-drug interactions involving antiretroviral drugs in a large kenyan cohort. *PloS one.* 2011;6(2).
35. Patel N, Abdelsayed S, Veve M, Miller CD. Predictors of clinically significant drug-drug interactions among patients treated with nonnucleoside reverse transcriptase inhibitor-, protease inhibitor-, and raltegravir-based antiretroviral regimens. *Ann Pharmacother.* 2011;45(3):317-324.
36. Seden K, Bradley M, Miller ARO, Beadsworth MBJ, Khoo SH. The clinical utility of HIV outpatient pharmacist prescreening to reduce medication error and assess adherence. *Int J STD AIDS.* 2013;24(3):237-241.
37. Tseng A, Szadkowski L, Walmsley S, Salit I, Raboud J. Association of Age With Polypharmacy and Risk of Drug Interactions With Antiretroviral Medications in HIV-Positive Patients. *Ann Pharmacother.* 2013;47(11):1429-1439.
38. Iniesta-Navalón C, Franco-Miguel J, Gascón-Cánovas J, Rentero-Redondo L. Identification of potential clinically significant drug interactions in HIV-infected patients: A comprehensive therapeutic approach. *HIV Med.* 2015;16(5):273-279.
39. Cervero M, Torres R, Jose Jusdado J, Pastor S, Luis Agud J. Predictive factors of clinically significant drug-drug interactions among regimens based on protease inhibitors, non-nucleoside reverse transcriptase inhibitors and raltegravir. *Medicina Clinica.* 2016;146(8):339-345.

40. Cordova E, Porteiro N, Loiza E, Mingrone H. Prevalence of potential drug-drug interactions involving antiretroviral drugs in Buenos Aires, Argentina. *Revista chilena de infectologia : organo oficial de la Sociedad Chilena de Infectologia.* 2016;33(Suppl1):54-59.
41. Pholtawornkulchai K, Luengsupabul S. Prevalence of potential drug-drug interactions in HIV-infected adult on antiretroviral drugs at Faculty of medicine Vajira hospital, Navamindhradhiraj university. *International Journal of Antimicrobial Agents.* 2017;50:S267-S267.
42. Shafiekhani M, Karimi S, Davarpanah MA, Vazin A. Evaluating drug interactions, adverse drug reactions, and level of adherence to highly active antiretroviral therapy regimen amongst HIV-positive patients who referred to an AIDS healthcare center in Fars, southern Iran: the first multifaceted study from Iran. *Hiv & Aids Review.* 2017;16(1):24-31.
43. Molas E, Luque S, Retamero A, et al. Frequency and severity of potential drug interactions in a cohort of HIV-infected patients Identified through a Multidisciplinary team. *HIV clinical trials.* 2018;19(1):1-7.
44. Siefried KJ, Mao L, Cysique LA, et al. Concomitant medication polypharmacy, interactions and imperfect adherence are common in Australian adults on suppressive antiretroviral therapy. *AIDS.* 2018;32(1):35-48.
45. Halloran MO, Boyle C, Kehoe B, et al. Polypharmacy and drug-drug interactions in older and younger people living with HIV: The POPPY study. *Antiviral Therapy.* 2019;24(3):193-201.
46. El Moussaoui M, Lambert I, Maes N, et al. Evolution of Drug Interactions With Antiretroviral Medication in People With HIV. *Open Forum Infect Dis.* 2020;7(11):ofaa416.
47. Pontelo BM, Greco DB, Guimarães NS, et al. Profile of drug–drug interactions and impact on the effectiveness of antiretroviral therapy among patients living with HIV followed at an Infectious Diseases Referral Center in Belo Horizonte, Brazil. *Braz J Infect Dis.* 2020;24(2):104-109.
48. Schlaeppi C, Vanobberghen F, Sikalengo G, et al. Prevalence and management of drug–drug interactions with antiretroviral treatment in 2069 people living with HIV in rural Tanzania: a prospective cohort study. *HIV Medicine.* 2020;21(1):53-63.
49. Funke B, Spinner CD, Wolf E, et al. High prevalence of comorbidities and use of concomitant medication in treated people living with HIV in Germany - results of the BESIDE study. *Int J STD AIDS.* 2021;32(2):152-161.
50. Kunimoto Y, Matamura R, Ikeda H, et al. Potential drug-drug interactions in the era of integrase strand transfer inhibitors: a cross-sectional single-center study in Japan. *J Pharm Health Care Sci.* 2021;7(1):43.
51. Murray MM, Lin J, Buros Stein A, et al. Relationship of polypharmacy to HIV RNA suppression in people aged ≥ 50 years living with HIV. *HIV Med.* 2021;22(8):742-749.

52. Wang CC, Li HJ, Shao CH, Sheng WH. Potential or contraindicated drug-drug interactions with antiretroviral therapy in real-world settings in Taiwan. *J Formos Med Assoc.* 2021.
53. Tinggaard M, David KP, Gerstoft J, et al. Potential drug-drug interactions between antiretroviral drugs and comedications, including dietary supplements, among people living with HIV: A clinical survey. *HIV Med.*
54. Cervero M, Torres R, Jusdado JJ, Pastor S, Agud JL. Predictive factors of clinically significant drug-drug interactions among regimens based on protease inhibitors, non-nucleoside reverse transcriptase inhibitors and raltegravir. *Medicina Clinica.* 2016;146(8):339-345.

Figure Captions

Table 1. Summary characteristics of included studies. *Regimens may also have included pharmacokinetic boosters. **Figure represents INI prescribed in addition to a PI. Grey boxes indicate data not reported. ARVs antiretrovirals, DDI drug-drug interaction, DHHS Department of Health and Human Services, INI integrase inhibitor, SmPC summary of product characteristics.

Table 2. Proportion of patients in the included studies who were receiving antiretrovirals and experienced at least one of the indicated DDIs.

Table 3. Most common drug classes reported to be involved in DDIs. ARVs antiretrovirals, CV cardiovascular, ED erectile dysfunction, GI gastro-intestinal, INI integrase inhibitor, NSAID non-steroidal anti-inflammatory drug, NNRTI non-nucleoside reverse transcriptase inhibitor, NRTI nucleos(t)ide reverse transcriptase inhibitor, PDEI phosphodiesterase inhibitor, PI protease inhibitor.

Figure 1. Proportion of patients experiencing at least one amber DDI had a small negative correlation with time. No correlation found for patients experiencing at least one red DDI. Significance tested by weighted linear regression with population size as the weight. Weighted linear regression suggested a marginally significant interaction between DDI severity and weight (P=0.066). Amber: regression coefficient -1.69% per year (95%CI=-2.65% to -0.74%, P=0.001); red: regression coefficient 0.43% per year (95%CI=-1.39% to 0.52%, P=0.361). ns= non-significant, ***=P≤0.001 (n=15).

Figure 2. Median age does not correlate with experiencing at least one amber or red DDI.

Significance tested by weighted linear regression with the population size as the weight. Weighted linear regression did not find a correlation between age and incidence of DDI, P=0.763, ns=non-significant, (n=11-13).