**Polypharmacy and drug-drug interactions in HIV-infected subjects in the region of Madrid (Spain): a population-based study**

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**Summary**

**Background:** We assessed polypharmacy and drug-drug interactions (DDIs) between antiretrovirals (ARVs) and non-ARV medications (Co-meds) in HIV-infected subjects (HIV+S) in the region of Madrid.

**Methods:** We analysed the drug dispensation registry of the Madrid Regional Health Service between January 1 and June 30, 2017. Co-meds were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Polypharmacy was considered as the intake of ≥ 5 Co-meds. DDIs between ARVs and Co-meds were screened with the University of Liverpool drug interactions database and summarised with a traffic light method.

**Findings:** A total of 6,636,451 individuals (22,945 HIV+S) received medications in Madrid. Antiretroviral therapy (ART) was predominantly integrase strand transfer inhibitors (INSTI)-based (51⋅96%). Polypharmacy was observed in 32⋅94% HIV+S and 22⋅16% non–HIV+, P<0⋅001; and was more frequent among the formers in comparison with the laters across all age strata, except for individuals aged ≥75 years. Among HIV+S, the prevalence of red-flag and orange-flag DDIs were 3⋅18% and 18⋅27%, respectively. The most frequent involved medications in red-flag and DDIs were boosted drugs (PIs or INSTIs) and non-nucleoside reverse transcriptase inhibitors (nnRTIs) among ARVs, and corticosteroids, quetiapine, and antithrombotic agents among Co-meds. Among HIV+S, unboosted INSTI-based ART was associated with an adjusted odds ratio (95% confidence interval) of 0⋅72 (0⋅60 – 0⋅88); P=0⋅001 for red-flag DDIs, and 0⋅79 (0⋅71 – 0⋅87); P<0⋅001 for orange-flag DDIs.

**Interpretation:** Polypharmacy was more frequent among HIV+S than among non–HIV+S across all age strata, except for individuals aged ≥75 years. The prevalence of red-flag DDIs was 3⋅18%. The most frequent involved medications in red-flag DDIs were boosted PIs, nnRTIs and boosted INSTIs among ARVs, and corticosteroids, quetiapine, and antithrombotic agents among Co-meds. The use of non-boosted INSTIs as anchor ARV drugs was independently associated with a reduced odds of both red-flag and orange-flag DDIs.

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**Research in context**

**Evidence before this study**

There is substantial evidence that polypharmacy is an important issue for antiretroviral (ART)-treated individuals. D Ware et al. found that HIV infection, older age, white race, and having medication insurance coverage was associated with an increased likelihood of polypharmacy among 3,160 HIV-infected and uninfected men in the Multicenter AIDS Cohort Study in the period from 2004 to 2016. AC Justice et al. analysed the clinical course of 9,473 HIV-infected and 39,812 HIV-uninfected individuals who were receiving at least one prescription medication in the US Veterans Affairs Healthcare System from 2009 through 2015, and found a dose-response association between the number of non-ART medication count and increased hospitalisation and mortality rates in both HIV-infected and -uninfected individuals after adjusting for demographics and severity of underlying comorbidity. The literature about drug-drug interactions (DDIs) in HIV-infected individuals, however, is far from comprehensive. Most of the information on the subject comes from studies carried out in single institutions with a few hundred patients or have been performed in specific population groups such as older HIV-infected adults or involve specific interactions between ART drugs and specific non-ART drugs. A few large cohort studies on DDIs in HIV-infected individuals have been conducted in resource-limited settings in sub-Saharan Africa, in populations in which lopinavir and efavirenz were the most commonly used anchor ART drugs and in which rifampicin, azoles, and antiparasitic drugs constituted most of the non-ART drugs involved in DDIs. C Marzolini et al. reported in 2010 the most extensive study in resource-rich settings, with almost 1,500 patients included in the Swiss HIV Cohort Study most of which were on boosted protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (nnRTIs) as anchor ART drugs.

**Added value of this study**

Among 6,636,451 different individuals, 22,945 of which were HIV-infected, who received medications in the region of Madrid between January 1 and June 30, 2017, polypharmacy (defined as the intake of ≥ 5 non-ART medications) was more common in women than in men, increased with age, and was statistically significantly higher among HIV-infected in comparison with HIV-uninfected individuals across all age strata except for those aged ≥75 years. ARVs among HIV-infected individuals the most frequently used anchor ARVs were INSTIs accounting for just over half of the patients, and the most frequently dispensed Co-meds were nervous system drugs.

Among HIV-infected individuals, the prevalence of contraindicated combinations involving ART and non-ART drugs (red-flag DDIs) was 3⋅18%, and the prevalence of combinations requiring dosage modification or close monitoring to minimise clinical consequences (orange-flag DDIs) was 18⋅27%. The most frequently involved medications in red-flag DDIs were boosted PIs, boosted integrase strand transfer inhibitors (INSTI), and nnRTIs among ART medications; and corticosteroids, quetiapine, and antithrombotic agents among non-ART medications. Ten specific combinations accounted for three-quarters of the observed red-flag DDIs; of these, darunavir was the ART drug involved in seven and corticosteroids were the non-ART drugs involved in four of these top ten interactions. Of note, the use of a non-boosted INSTI as an anchor ART drug was independently associated with a decreased odds of having both red-flag and orange-flag DDIs.

**Implications of all the available evidence**

Our study confirms that polypharmacy is more frequent among HIV-infected in comparison with HIV-uninfected individuals across all age strata, except for the very old. We have identified that most red-flag DDIs involved a boosted drug among ART medications, and corticosteroids and quetiapine among non-ART medications. The finding that the use of regimens based of non-boosted INSTIs was independently associated with a reduced risk of red-flag DDI gives further support to the current recommendations of these drugs as preferred anchor ART drugs in many clinical practice guidelines.

**Introduction**

The expectancy of life of HIV-infected individuals has increased worldwide since combination antiretroviral therapy (ART) has been available and continues to improve 1,2. As a consequence of improved survival, HIV-infected individuals are growing older 3, meaning that they may be at higher risk of both comorbid diseases and harm from polypharmacy, risks that likely increase with age and physiologic frailty 4,5. Potential concerns associated with polypharmacy include increased pill burden, decreased medication adherence, potential clinically significant drug-drug interactions (DDIs), adverse drug reactions including organ system injury, hospitalisation, death, and rising treatment-related costs 6,7.

Prior research suggests that polypharmacy and medication-related problems such as DDIs are an important issue for HIV-infected individuals on ART 8-13. Besides, a substantial percentage of patients are prescribed antiretrovirals (ARVs) and non-antiretroviral medications (Co-meds) that are contraindicated or had the potential for a DDI 11; and these are frequently unrecognised by physicians 9.

Most of the information about DDI among HIV-infected individuals come from studies carried out in single institutions 8,9,14, in the setting of cohort studies 10,11, or in specific population groups such as older HIV-infected adults 11-13; however little information is available about the subject at a population level. Moreover, newer ARVs, with different profiles for DDIs, have been approved over the last years including rilpivirine, elvitegravir, dolutegravir, and cobicistat. As a consequence, and because of new information about long-term safety issues of older drugs, ART guidelines have also changed significantly in the last years, particularly in scenarios such as first-line therapy and switch therapy 15-17.

We aimed to appraise the number of Co-meds in HIV-infected persons on ART in the region of Madrid, categorised by age and gender and to compare the number of Co-meds between the ART-treated population and HIV-uninfected population. We also aimed to evaluate the prevalence of potential DDIs between ARVs and Co-meds in ART-treated individuals, with a description of the types of harm expected from each different potential DDIs identified.

**Methods**

**Study design**

This was a cross-sectional population-based study involving no intervention or patient contact carried out in the region of Madrid between January 31 to June 30, 2017. Prescription drugs in Madrid are covered by the Madrid Health Service (SERMAS [*Servicio Madrileño de Salud*]). ARVs are dispensed by hospital pharmacies, and Co-meds are dispensed mainly by community pharmacies, although some are dispensed by hospital pharmacies (i.e. anticancer drugs, anti-HCV drugs, etc.). Refills of medications are done monthly, although in some HIV-infected individuals refills of ARVs are done every two or three months. SERMAS has a unique regional patient identification code (CIPA [*Código de Identificación de Paciente Autonómico]*), that permits the access to personal information (age, sex, and income status) and also to all prescription drugs (ARVs and Co-meds) dispensed. The SERMAS drug-database is updated monthly; however, the lag time between drug dispensation at pharmacies and recording of this information in the database is one month for hospital pharmacies and two months for community pharmacies.

**Participants**

From the SERMAS database, we downloaded the registries to build the working database with information about all patients who picked up ARVs or Co-meds in the study period. The working database was free of fields containing information that could lead to identifying the patient (i.e. CIPA code). Patients were classified as HIV-infected or HIV-uninfected according to whether or not they received ARVs.

**Prescription drugs**

ARVs were categorised according to class: nucleoside or nucleotide reverse transcriptase inhibitors (nRTIs), non-nucleoside reverse transcriptase inhibitors (nnRTIs), boosted protease inhibitors (PIs), boosted and unboosted integrase strand transfer inhibitors (INSTIs), and CCR-5 inhibitors. Ritonavir, and cobicistat, when used as a boosting agent were not counted as a separate medication. For this study, all ARVs except nRTIs were also referred to as anchor drugs. Co-meds were categorised according to the Anatomical Therapeutic Chemical (ATC) classification system 18, in which the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified in groups at five different levels, being the 5th the chemical substance. For combination medications, individual components were counted separately. Non-antiretroviral polypharmacy was considered as the intake of ≥ 5 Co-meds.

**Drug-drug interactions**

We developed a customised application programming interface connecting the SERMAS database and the University of Liverpool drug interactions database 19 - a comprehensive database of HIV DDIs widely utilised throughout Europe - to detect potential DDIs between ARVs and Co-meds. An evaluation of the likely interaction was generated according to a flag classification: i) Red-flag for medicaments that should not be coadministered as they might lead to serious adverse events or profoundly affect ART efficacy, ii) Orange-flag indicating a potential interaction that might require dosage modification or close monitoring to minimize clinical consequences, iii) Yellow-flag indicating weak potential interaction, and not requiring additional monitoring or dosage adjustment, iv) Green-flag representing no known of anticipated interaction, and vi) Grey-flag when there was no data indicating interaction.

**Statistical analysis**

For the descriptive study, values were expressed as absolute number and percentage, and median and interquartile range (IQR). Differences between groups were analysed using the chi-square test. Logistic regression analysis was used to investigate factors associated with polypharmacy and potential DDIs. IBM SPSS Statistics for Windows, Version 21⋅0, was used for all calculations. All statistical tests were performed two-sided and a P-value of <0⋅05 was considered statistically significant.

**Role of the funding source**

The funder of the study, MSD, had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

**Patients and non-antiretroviral polypharmacy**

During the study period, 6,636,451 different individuals received medications in the region of Madrid. Of them, 22,945 (0⋅35%) were infected with HIV. The proportion of females was 21⋅72% among HIV-infected patients and 51⋅98% among HIV-uninfected patients, P<0⋅001. The median (interquartile range [IQR]) age was 48 years (39-54) among HIV-infected patients; and 41 years (24-57) among HIV-uninfected patients; P<0⋅001.

Overall, polypharmacy was observed in 7,557 HIV-infected individuals (32⋅94%), and 1,465,552 non–HIV-infected individuals (22⋅16%) (OR 1⋅73; 95% CI, 1⋅68–1⋅77; *P*<0⋅001. Polypharmacy was more common among females than males, increased with age, and was statistically significantly higher among HIV-infected individuals than among non–HIV-infected individuals across all age strata except for those aged ≥75 years) (**Figure 1**).

In HIV-infected patients, polypharmacy was observed in 17 (15⋅18%) paediatric patients and 7,540 (33⋅02%) adults. Among adults, polypharmacy was more common among older adults (≥ 50 years) than among young adults (≥ 18 to 50 years), 47⋅26% vs. 21⋅78%; P<0⋅001. Of note, 2,020 (8⋅85%) adult patients were taking more than 10 Co-meds, something that was found in 13⋅99% of older adults and in 4⋅79% of young adults, P <0⋅001.

**Prescription drugs among HIV-infected individuals**

Prescription drugs were analysed for the 22,945 HIV-infected individuals, 112 (0⋅49%) of whom were paediatric patients (<18 years).

**Antiretroviral drugs**

A description of ARV classes broken down by paediatric patients and adults is shown in **Table 1.** Overall, 20,661 (90⋅05%) patients were treated with at least one nRTI. The most frequently used nRTI combinations in children were abacavir/lamivudine (ABC/3TC) in 38 children taking it (33⋅93% of total children), followed by tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in 33 children taking it (29⋅46% of total children), and tenofovir alafenamide/emtricitabine (TAF/FTC) in 12 children taking it (10⋅71% of total children). The most frequently used nRTI combinations in adults were TDF/FTC in 9,731 adults taking it (42⋅62% of total adults) followed by 3TC/ABC in 8,518 adults taking it (37⋅31% of total adults), and TAF/FTC in 2,273 adults taking it (11⋅93% of total adults).

The most frequently used anchor ARVs among HIV-infected individuals were INSTIs (51⋅96%), followed by nnRTIs (41⋅34%), and bPIs (23⋅12%). In paediatric patients, the most frequently used anchor drugs were efavirenz (EFV) (20⋅54%) and raltegravir (RAL) (20⋅54%), followed by lopinavir/ritonavir (LPV/r) (14⋅29%). In adults, the most frequently used anchor drugs were dolutegravir (DTG) (30⋅92%), followed by rilpivirine (RPV) (19⋅41%), and darunavir boosted with cobicistat or ritonavir (bDRV) (17⋅99%).

**Comedications**

Among HIV-infected individuals, the frequency of intake of at least one Co-med was 16,402 (71⋅48%) overall, 66 (58⋅93%) among paediatric patients, and 16,336 (71⋅55%) among adults.

A summary of Co-meds classified according to the ATC anatomic code categorized in three age strata (< 18 years, ≥ 18 to 50 years, and ≥ 50 years) is shown in **Figure 2**. Among paediatric patients (< 18 years), the most frequently dispensed Co-meds were anti-infectives for systemic use (46⋅97%), nervous system drugs (39⋅39%), and gastrointestinal & metabolism drugs (27⋅27%). Among young adults, the most frequently dispensed Co-meds were nervous system drugs (56⋅29%), anti-infectives for systemic use (43⋅87%), and gastrointestinal & metabolism drugs (41⋅66%). Among older adults, the most frequently dispensed Co-meds were nervous system drugs (66⋅79%), gastrointestinal & metabolism drugs (64⋅37%), and cardiovascular drugs (57⋅01%). Among HIV-infected adults, the dispensation of drugs from any of the 14 ATC categories was significantly more common among older adults than in young adults, with the exception of anti-infectives and dermatological drugs. Shown as supplementary material is a description of Co-meds classified by ATC therapeutic subgroup in the three age strata (**Supplementary material Table S1**).

**Drug-drug interactions among HIV-infected individuals**

Overall, 14,341 HIV-infected individuals (62⋅50%) had at least one DDI. The prevalence of the different categories of DDIs among HIV-infected individuals according to University of Liverpool drug interactions criteria were: red-flag 729 (3⋅18%), orange-flag 4,193 (18⋅27%), yellow-flag 2,363 (10⋅30%), green-flag 11,811 (51⋅48%), and grey-flag 26 (0⋅11%) (**Figure 3**).

Potential DDIs categorized by anchor ARVs in the 22,945 HIV-infected patients are shown in **Table 2**. The most frequent involved ARVs in red-flag DDIs were boosted PIs, followed by nnRTIs, and boosted INSTIs. The frequency of red-flag interactions were 616 (2⋅68%) for boosted PIs, 89 (0⋅39%) for nnRTIs, 46 (0⋅20%) for boosted INSTIs; a single red-flag interaction was caused by non-boosted INSTIs. The most frequent involved ARVs in orange-flag DDIs were boosted PIs (8⋅50%), followed by nnRTIs (8⋅33%), and non-boosted INSTIs (1⋅60%).

Potential DDIs categorized by Co-meds are shown in **Table 3.** The most frequent involved group of drugs in red-flag DDIs according to the the ATC code were respiratory system drugs (1⋅37%), followed by dermatological drugs (0⋅51%), nervous system drugs (0⋅50%), cardiovascular drugs (0⋅42%), gastrointestinal & metabolism drugs (0⋅27%), and blood drugs (0⋅27%). The most frequent involved Co-meds in orange-flag DDIs were nervous system drugs (7⋅99%), followed by cardiovascular drugs (2⋅94%), musculoskeletal system drugs (2⋅51%), and systemic hormones (2⋅03%).

A detailed description of the 729 potential red-flag DDIs found among the 22,945 HIV-infected individuals is shown in **Table 4**. Overall, the most frequently involved Co-meds in red-flag DDIs were corticosteroids including budesonide, mometasone, fluticasone and triamcinolone (56⋅65%), followed by the antipsychotic drug quetiapine (14⋅54%), antitrombotic agents including clopidogrel and ticagrelor (8⋅50%), imidazole and triazole derivatives such as ketoconazole and itraconazole (8⋅37%), domperidone (7⋅27%), and simvastatine (6⋅45%),

Ten interactions accounted for 546 (74⋅90%) of all potential red-flag DDIs (**Supplementary material Table S2**). Of note, bDRV was the ARV involved in 7 of these top ten interactions accounting for 479 (65⋅71%) of all potential red-flag DDIs. Corticosteroids were the Co-meds involved in 4 of these top ten interactions accounting for 294 (40⋅33%) of all potential red-flag DDIs.

**Factors associated with drug-drug interactions**

The results of multivariable analyses to identify factors associated with DDIs are shown in **table 5**. Factors independently associated with decreased odds of having a red-flag DDI included age ≥ 50 years and treatment with non-boosted INSTIs as anchor ARVs. Factors independently associated with increased odds of having a red-flag DDI included treatment with boosted PIs, boosted INSTIs and nnRTIs as anchor ARVs, polypharmacy, and treatment with the following Co-meds according to the ATC code: respiratory system, dermatological drugs, blood drugs, nervous system drugs, cardiovascular drugs, and systemic hormones.

The only factor independently associated with decreased odds of having an orange-flag DDI was treatment with non-boosted INSTIs as anchor ARVs. Factors independently associated with increased odds of having an orange-flag DDI included male gender, treatment with any ARV except non-boosted INSTIs, polypharmacy, and treatment with any Co-med with the exception of antineoplastic and immunomodulating drugs and sensory organ drugs.

**Discussion**

In this large population-based study including just over 6,6 million individuals of which approximately 23,000 were infected with HIV, one third of the population was found to have non-antiretroviral polypharmacy. Polypharmacy was more common among females, increased with age, and was higher among HIV-infected individuals than among non–HIV-infected individuals across all age strata except for those aged ≥75 years.

Polypharmacy is an important issue for HIV-infected individuals. In an analysis of 3,160 HIV-infected and uninfected men in the Multicenter AIDS Cohort Study from 2004 to 2016, it was found that HIV infection, older age, white race, and having medication insurance coverage was associated with an increased likelihood of polypharmacy 20. In a recent report that analysed the clinical course of 9,473 HIV-infected and 39,812 HIV-uninfected individuals who were receiving at least one prescription medication in the US Veterans Affairs Healthcare System from 2009 through 2015, it was found a dose-response association between the number of non-ARV drugs and increased hospitalisation and mortality rates in both HIV-infected and -uninfected individuals after adjusting for demographics and severity of underlying comorbidity 7.

In Madrid, the most frequently used anchor ARVs were INSTIs, used in just over half of the HIV-infected individuals, followed by nnRTIs and boosted PIs. As for Co-meds, nervous system drugs and gastrointestinal & metabolism drugs were among the two of the three most frequently used across all age strata. The third most common Co-med category were anti-infectives among paediatric patients and young adults, and cardiovascular drugs among older adults. The prevalence of red-flag and orange-flag DDIs among HIV-infected individuals were 3⋅18% and 18⋅27%, respectively. The most frequent involved medications in red-flag DDIs were boosted PIs, boosted INSTIs, and nnRTIs among ARVs; and corticosteroids, quetiapine, and antithrombotic agents among Co-meds.

The literature about DDIs in HIV-infected individuals, is far from comprehensive and reflects the experience of an era in which EFV and boosted PIs were the predominant anchor ARVs, and in which INSTI-based regimens were inexistent. Two large studies have been done in sub-Saharan countries, one in Kenia with 1,000 consecutive patients enrolled in an ART programme of which approximately one-third of the patients were at risk of a DDI 21, and another in Uganda with 2,000 HIV-infected patients on ART, 18⋅7% of which had one or more clinically significant DDI 22. In these studies, anti-infectives including rifampicin, antifungal, antimalarial or anthelminthic were the most frequently Co-meds involved in DDIs 21-23. To the best of our knowledge, the largest survey to date in a resource rich setting to this date was carried out with the Swiss HIV Cohort Study in which the prevalence of red-flag and orange-flag DDIs among 1,497 HIV-infected individuals on ART were found to be 1⋅40%, and 39⋅88%, respectively 10. In this study, red-flag DDIs involved mainly the coadministration of boosted PIs or EFV with midazolam; and most orange-flag DDIs involved the coadministration EFV and boosted PIs with central nervous system drugs, cardiovascular drugs and methadone 10. In a multicentre study carried out in Australia between 2013 and 2015 with 522 consecutive HIV-infected individuals on ART, polypharmacy and red-flag DDIs were identified in 23% and 3.3% of all participants. Most red-flag interactions were related to boosted PIs followed by EFV 24.

We identified different factors independently associated with increased odds of having a red-flag DDI including therapy with boosted PIs, boosted INSTIs and nnRTIs as anchor ARVs, polypharmacy, and treatment with different Co-meds according to the ATC code such as respiratory system drugs, dermatological drugs, blood drugs, nervous system drugs, cardiovascular drugs, and systemic hormones. Of note, age ≥ 50 years and treatment with non-boosted INSTIs as anchor ARVs were identified as factors independently associated with decreased odds of having a red-flag DDI. In Uganda, the factors found to increase the risk of DDIs included the use of two or more Co-meds, a PI-based regimen, the use of an anti-infective, and WHO clinical stage 3–4 22. In Switzerland, factors independently associated with DDIs included use of PIs or nnRTIs as anchor ARVs, the use of more than two Co-meds, illicit drug use and HCV infection.

Limitations of our study include the absence of information about characteristics of HIV-infected patients other than age and sex and the lack of information about medical management and clinical outcomes of HIV-infected individual with potential deleterious DDIs. Besides, as the link of the SERMAS database and the University of Liverpool drug interactions database was the ATC code, the prevalence of DDIs found in our study may be underestimated as not all the drugs in the SERMAS database are codified in the Liverpool database. Another limitation is the lack of information about over the counter medication particularly supplements containing magnesium or calcium that may interact with INSTIs and have been reported to account for 3⋅7% of all the potential DDIs in a recent report 24. Our study has the strengths of being population-based and its large sample size. Besides, both ARVs and Co-meds were automatically retrieved from an official and comprehensive database, and DDIs were analysed with an automated cross-checking of the working database with a reliable HIV drug interactions database. Finally, our study includes ARVs approved over the last years in Europe that to the best of our knowledge, have not been assessed for potential DDIs in population-based studies so far.

Our study illustrates that a computerised system to detect and monitor population DDIs is feasible. We believe that periodical monitoring of interactions among HIV-infected individuals should be carried out for several reasons; first because ageing and comorbidities are increasingly common problems among HIV-infected individuals; second, because commonly used ARVs and Co-meds are changing; and third, because safety, quality of life, and patient report outcomes are increasingly relevant issues in this era in which most HIV-infected individuals on ART are fully suppressed.

**Conclusions**

In conclusion, we found that in the region of Madrid with a census just over 6,5 million inhabitants, non-antiretroviral polypharmacy was more frequent among HIV-infected individuals than among non–HIV-infected individuals across all age strata, except for individuals aged ≥75 years. We also found a prevalence of red-flag DDIs of 3⋅18%. The most frequent involved medications in red-flag DDIs were boosted PIs, nnRTIs and boosted INSTIs among ARVs, and corticosteroids, quetiapine, and antithrombotic agents among Co-meds. The use of non-boosted INSTIs as anchor ARVs was independently associated with decreased odds of having both red-flag and orange-flag DDIs.

**Declaration of interests**

Summarising key conflicts from ICMJE forms

**Contributors**

JB conceived the study. JB, BL, SK, and MJC contributed to the study design. BL, CB, AM, KM, SG, AA, MJC and SG were involved in the data collection. JMB, BL, and CB, the statistical analyses. JB supervised the analyses. JB and BL wrote the first draft of the paper. All authors contributed to the data interpretation and approved the final version

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