AIDS

Pharmacokinetic interactions of modern antiretroviral therapy

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Editor
AIDS

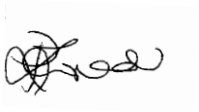
Dear Lucy Franks

We greatly appreciate the reviewers' thoughtful comments regarding the Supplemental article entitled "Pharmacokinetic interactions of modern antiretroviral therapy" for publication in *AIDS*. In the revised manuscript and in our Response-to-Reviewers document we address every comment. We hope the manuscript is now acceptable for publication.

All authors have contributed to, seen, and approved the final, submitted version of the manuscript. The manuscript has not been submitted or accepted for publication elsewhere.

Thank you for your consideration

Yours sincerely



Associate Professor

RESPONSES TO REVIEWERS' COMMENTS:
We greatly appreciate the reviewers' thoughtful comments. Below and in the manuscript, we have responded to each comment, which we believe has substantially strengthened the paper.

Reviewer #1:

"Sinxadi et al. report a brief manuscript on DDIs of modern antiretrovirals. The review is well written, concise and useful for clinicians. Despite word limitations I have a few comments mostly regarding the completeness of the data"

COMMENT 1: *"Introduction. Please consider adding a reference to "the potential for DDIs occurring in people living with HIV (PLWH) has decreased"*

RESPONSE 1: We have rephrased this sentence as suggested by reviewer 2. In page 1, line 3 of the Introduction now the sentences read as follows: "The newer antiretroviral drugs (ARTs) have significantly fewer DDIs than protease inhibitors (PIs) and boosted integrase inhibitors (INSTIs). (1, 2) However, the lower propensity of such newer antiretrovirals (e.g. unboosted INSTIs and doravirine) to cause DDIs, has been largely offset by the ageing cohort of patients with multiple comorbidities, who are taking multiple chronic medicines."

We have added two references in this paragraph (Cottrell et al, Clin Pharmacokinet 2013 and Boyle et al Clin Pharmacokinet 2019).

COMMENT 2: *"NRTIs. "TAF, the newer prodrug of tenofovir, is co-formulated with emtricitabine with or without bictegravir for the prevention and treatment of HIV", consider omitting with or without bictegravir for clarity."*

RESPONSE 2: Excellent suggestion. In page 1, line 28, the sentence now reads as follows: "TAF, the newer prodrug of tenofovir, is co-formulated with emtricitabine for the prevention and treatment of HIV."

COMMENT 3: *"NRTIs. I know it has been reported that TAF is a substrate of CYP3A4: however can you please provide a reference for this?"*

RESPONSE 3: Thank you for pointing this out. We have revised the sentence and in page 1 line 33 have added the statement: "While TAF is weak inhibitor of cytochrome P450 3A4 (CYP3A4) in vitro, it is not a CYP3A4 inhibitor or inducer in vivo." The Descovy ® and Vemlidy® package inserts are used as references.

COMMENT 4: *"NRTIs. "to ensure that efficacy is maintained AND to prevent the development of resistance"? What about the potential effect of other strong inducers (such as anticonvulsants?) or P-gp inhibitors (amiodarone?)"*

RESPONSE 4: The sentence has been amended to include "and" as suggested. In page 2 line 47 the sentence now reads as follows **"**to ensure that efficacy is maintained and to prevent the development of resistance."

We have also added a short statement about potential interactions with other strong P-gp inducers and inhibitors in page 2 line 50 and it reads as follows: **"**Coadministration of TAF with strong P-gp inducers (e.g. phenytoin and phenobarbitone) is not recommended as inducers may reduce TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. In contrast,

inhibitors of P-gp (e.g. amiodarone) are expected to increase the TAF absorption, and therefore increase the plasma concentrations. Therefore, reduced dose (10mg) of TAF is recommended. (See https://www.hiv-druginteractions.org/)"

COMMENT 5: *"INSTIs. For Dolutegravir and rifampin I would suggest to include the data of the clinical trial (https://pubmed.ncbi.nlm.nih.gov/30918967/) in order to provide data on the potential co-administration of the 2 drugs"*

RESPONSE 5: Thank you for your suggestion, a sentence has been added in page 3 line 101 and reads as follows: "This regimen was shown to be effective and well tolerated in the INSPIRING study, a noncomparative, active-control, randomized, open-label study in HIV-1-infected antiretroviral therapy-naive adults."

COMMENT 6: *"INSTIs. Maybe citing the once daily DTG 100 mg/rifampin data?"*

RESPONSE 6: These important data are currently cited in reference 26 and the study is briefly described in page 4, line 103.

COMMENT 7: *"INSTIs. Maybe considering the DTG-valproic acid DDI?"*

RESPONSE 7: Thank you for your suggestion, we have added text on DDIs on DTG and some anticonvulsants in a paragraph starting in page 4 line 135 and reads as follows: "The induction effect of phenytoin on dolutegravir has not been studied ……. Interestingly, dolutegravir concentrations were reportedly reduced after coadministration of valproate ……is unlikely to be clinically relevant."

COMMENT 8: *"INSTIs. Maybe the DTG-METFORMIN discussion can be expanded a little bit with reports suggesting no clinical relevance and other showing case reports of acidosis"*

RESPONSE 8: Thank you for the suggestion. The discussion has been revised and the short paragraph starting in page 4, line 125 now reads as follows: "Metformin is renally eliminated and is thought to be an OCT2 substrate, and increased plasma metformin exposure has been reported in healthy volunteers when dolutegravir is coadministered.(30) While hyperlactataemia was reported in a case report, (31) two retrospective studies reported no cases of lactic acidosis (32,33) ……..Prescribing information currently suggests that a dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control.(34)"

COMMENT 9 : *"INSTIs. I would recommend showing the effect of size of the predicted DDI between LA CAB/RPV and rifampin (as compared to oral compounds)"*

RESPONSE 9: We have moved effect sizes of the oral compounds to the newly added table and further simplified the text in page 6 line 173 to read as follows: "Although the DDI has not been studied in vivo, physiologically based pharmacokinetic models predicted the theoretical effect of rifampicin on cabotegravir and rilpivirine long acting intramuscular formulations and showed that coadministration may result in subtherapeutic concentrations of both antiretroviral drugs."

COMMENT 10: *"INSTIs. Maybe a Table with new drugs DDI with rifampicin/rifabutin and recommendations may be beneficial for the readers since a sizeable proportion of the manuscript concentrates of these interaction"*

RESPONSE 10: Excellent idea. Key recommendations for drug-drug interactions of rifamycins and modern antiretrovirals are shown in the added **Table 1** with reference in the text as appropriate.

COMMENT 11: "*EIs. May I suggest to somehow smooth this sentence? "Temsavir is also a substrate of P-gp and BCRP and an inhibitor of OATP1B1 and OATP1B3.(42) Therefore, co-administration with substrates of these enzymes and transporters is expected to affect the pharmacokinetics of these drugs. However, very few of these drug interactions are clinically meaningful." You are providing data on statins and OATP1B1-inhibitors afterwards."*

RESPONSE 11: Excellent suggestion. In page 6, line 194, the section has been revised for clarity and now reads as follows: "Temsavir is also a substrate of P-gp and BCRP and an inhibitor of OATP1B1 and OATP1B3.(52) Therefore, co-administration with substrates of these enzymes and transporters is expected to affect the pharmacokinetics of these drugs. For example, the effect of fostemsavir on rosuvastatin, a substrate of OATP1B1……when co-administration with fostemsavir is indicated."

COMMENT 12: "*EIs. I would also include the potential DDIs between fostemsavir and strong inducers"*

RESPONSE 12: Thank you for your suggestion. The short paragraph starting in page 6 line 201 has been revised to include a statement on strong inducers and reads as follows: "A small healthy volunteer study showed a marked reduction in temsavir exposure …….co-administration is not recommended as subtherapeutic concentrations of temsavir are expected."

Reviewer #2:

"The authors provide a welcome overview of PK interactions in ART, concentrating on the newer agents. The manuscript is very well written and manages to provide a very useful synopsis while avoiding being bogged down with the minutiae of the topic. It is a pleasure to read, and the authors are to be congratulated."

COMMENT 1: *"Introduction. Introduction, first 6 lines - although what the authors meant is apparent, the first two sentences appear superficially contradictory. The first sentence states that "the potential for DDIs in PLWH has decreased" whereas the second sentence says that the decrease is "offset by the ageing cohort of patients with multiple comorbidities". I would recommend rephrasing slightly (e.g. the first sentence could be altered to say "The new ARTs have significantly fewer DDIs than PIs and boosted InSTIs", etc.)"*

RESPONSE 1: Thank you for the suggestion. This has been addressed in response 1 above.

COMMENT 2: *"Introduction, second paragraph, 4th line - I would clarify that rifampicin results in subtherapeutic ART drug concentrations *of many drugs* (or else the sentence could be read to imply that *all* ART drugs are affected."*

RESPONSE 2: We agree with the reviewer and in Page 1, Line 12 under Introduction, we have revised the sentence to read as follows: "The potent drug metabolism induction caused by rifampicin results in subtherapeutic concentrations of some antiretroviral drugs.**"**

COMMENT 3: *"Integrase strand transfer inhibitors -2nd paragraph, final sentence - I would make it more explicit that while it is true that "in these patients, the drug concentrations achieved maintained HIV virological suppression" these patients were virally suppressed at the time of rifabutin initiation (since this is an important limit to the generalizability of these results)."*

RESPONSE 3: The sentence in page 4 line 107 was revised to read as follows: **"**Similar findings were reported in virologically suppressed HIV positive patients …. the drug concentrations achieved maintained HIV virological suppression."

COMMENT 4: *" Integrase strand transfer inhibitors - for the dolutegravir section, I would consider adding a sentence or two on the effects of other common polyvalent cations, such as iron and calcium, since these compounds are frequently used. Similarly, if space permits, the authors could consider mentioning the effects of phenytoin and carbamazepine on DTG."*

RESPONSE 4: Excellent suggestion. However, due to word limit, we are not able to incorporate all the detailed examples. However, we now mention calcium and iron in the sentence in page 4, line 112, which now reads as follows: "Dolutegravir is also susceptible to chelation-type drug interactions with divalent (Ca^{2+}, Mg^{2+}) and trivalent metal cations (Al^{3+}, Fe^{3+})..... dolutegravir can be administered two hours before or six hours after these polyvalent cations."
The effects of phenytoin and carbamazepine have been addressed in response 7 above.

COMMENT 5: *" Integrase strand transfer inhibitors, 5th paragraph , final sentence - since the issue of weight gain with the new ART combinations isn't yet settled, it may be worth softening the sentence to avoid implying that these drugs definitely cause weight gain (e.g. could change to "… the weight gain possibly seen on newer ART regimens…""*

RESPONSE 5: We agree with the reviewer and we have revised the brief discussion on metformin and dolutegravir and focused on the DDI rather than issues of weight gain and have deleted the sentence.

COMMENT 6: *"Integrase strand transfer inhibitors - for the bictegravir section, it is worth mentioning from the outset that the name of the co-formulated tablet is Biktarvy, or else when Biktarvy is mentioned lower down, it may not be clear what this is."*

RESPONSE 6: Excellent idea. This has been added and the sentence in page 5 line 146 now reads as follows: "Bictegravir, the newer second-generation INSTI, is co-formulated with emtricitabine and TAF as a single tablet regimen (Biktarvy®) for treatment of HIV in patients without past or present INSTI resistance."

COMMENT 7: *"Integrase strand transfer inhibitors - final paragraph, final sentence - the final sentence is confusing, as there basically aren't any oral long-acting antiretrovirals (the half-life of oral cabotegravir is only ~40 hours, as opposed to the MUCH longer half-life of the intramuscular form). So, for long-acting ART, there is no "drug-drug interaction at the level of the GI tract/absorption" to overcome (apart from the oral lead-in phase - if this is what is meant, I suggest rewording)."*

RESPONSE 7: That's a good point. This has now been addressed in response 9 above.

Pharmacokinetic interactions of modern antiretroviral therapy

Running Header: PK DDIs of modern ART

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Introduction

Drug-drug interactions (DDIs) have been a clinical challenge in HIV medicine for over two decades. The newer antiretroviral drugs (ARTs) have significantly fewer DDIs than protease inhibitors (PIs) and boosted integrase inhibitors (INSTIs).(1, 2) The lower propensity of such newer antiretrovirals (e.g. unboosted integrase inhibitors; doravirine) to cause DDIs, has been largely offset by the ageing cohort of patients with multiple comorbidities, who are taking multiple chronic medicines. Furthermore, the introduction of newly marketed drugs into clinical practice needs to be closely monitored, as the new drugs may be perpetrators of DDIs, leading to a potential change in the efficacy or toxicity of the coadministered antiretrovirals.

One of the most important DDIs, especially relevant in resource-limited settings where the burden of coinfection is high is co-administration of antitubercular and antiretroviral therapy.(3) The potent drug metabolism induction caused by rifampicin results in subtherapeutic concentrations of some antiretroviral drugs. Dose adjustments are not always possible, practical, or safe. This is either because effect of rifampicin on newer antiretrovirals (e.g. bictegravir, doravirine) is severe, or because studying dose optimization strategies, like rifampicin with protease inhibitors, is challenging. The development of hepatotoxicity has led to the discontinuation of many studies, especially in HIV-negative participants, thus not allowing important clinical conclusions to be drawn.(4-6)

This review focuses on pharmacokinetic drug interactions of modern antiretrovirals and modern doses of older antiretrovirals registered in the last decade: tenofovir alafenamide (TAF), low-dose efavirenz, and doravirine (the newest non-nucleoside reverse transcriptase inhibitor), second-generation integrase strand transfer inhibitors (dolutegravir, bictegravir and cabotegravir), fostemsavir (attachment inhibitor), and ibalizumab (post-attachment inhibitor).

Pharmacokinetic drug-drug interactions

Nucleotide reverse transcriptase inhibitors

TAF, the newer prodrug of tenofovir, is co-formulated with emtricitabine for the prevention and treatment of HIV.(7)TAF is hydrolyzed to form tenofovir, which is phosphorylated within cells to the active metabolite tenofovir diphosphate (TFV-DP). When compared to tenofovir disoproxil fumarate (TDF), TAF results in lower tenofovir plasma concentrations but higher intracellular concentrations of TFV-DP. TAF is a substrate of drug efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). While TAF is weak inhibitor of cytochrome P450 3A4

(CYP3A4) in vitro, it is not a CYP3A4 inhibitor or inducer in vivo.(7, 8) Therefore, drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption. A study in healthy volunteers showed that co-administration of TAF/emtricitabine and rifampicin resulted in significantly reduced plasma concentrations of TAF and TFV.(9) However, the intracellular concentrations of TFV-DP achieved when rifampicin was added to TAF /emtricitabine were still 4-fold higher than those reached by TDF administered alone. In this study, it was observed that the co-administration of rifampicin mostly affected TFV peak concentrations, and to lesser extent, the AUC_{0-24} and C_{24}. This was attributed to the P-gp mediated reduction in absorption, rather than increase in renal clearance (9). Another healthy volunteer study that compared twice daily administration of TAF in combination with rifampicin with TAF alone showed a modest decrease in plasma TFV and intracellular TFV-DP (14% and 24%, respectively).(10) These findings imply that co-administration of TAF (given as 25 mg once or twice daily) with daily rifampicin is unlikely to affect the efficacy of TAF, but studies in patients are needed to confirm which dose should be administered with rifampicin to ensure that efficacy is maintained and to prevent the development of resistance. Key recommendations for drug-drug interactions of rifamycins and modern antiretrovirals are shown in **Table 1.**

Coadministration of TAF with strong P-gp inducers (e.g. phenytoin and phenobarbitone) is not recommended as inducers may reduce TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. In contrast, inhibitors of P-gp (e.g. amiodarone) are expected to increase the TAF absorption, and therefore increase the plasma concentrations. Therefore, reduced dose (10mg) of TAF is recommended. (See https://www.hiv-druginteractions.org/)

Non-nucleoside reverse transcriptase inhibitors

For over a decade, efavirenz at a standard dose of 600 mg formed a crucial component of the first line regimens for treating HIV despite its low genetic barrier and the associated adverse effects such as neuropsychiatric adverse effects, rash and hepatotoxicity.(11) In the ENCORE1 trial, treatment-naïve, HIV-infected adults were randomly assigned to daily efavirenz 400 mg (EFV400) versus 600 mg (EFV600), and EFV400 was virologically non-inferior, with fewer adverse effects reported in the lower dose group.(12) Significantly lower concentrations of efavirenz were also seen with EFV400 when compared to EFV600, but were not associated with virological failure.(13) No dose adjustment is needed in HIV/TB coinfected patients treated with EFV600 and rifampicin.(14) Data on the drug interaction between rifampicin and EFV400 are available from i) TB-negative, HIV-positive patients that showed a modest reduction in efavirenz exposure but with concentrations similar to those measured in ENCORE1,(15) and ii) TB-positive, HIV-positive patients that showed

similar efavirenz concentration results.(16) In both studies, patients did not experience virological failure.(15, 16)

Doravirine is the novel non-nucleoside reverse transcriptase inhibitor (NNRTI). It is available as a single entity (Pifeltro™) or co-formulated as a fixed-dose combination with TDF and lamivudine (Delstrigo™).(17, 18) Doravirine is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A affect its clearance.(19) Studies in healthy volunteers have shown that doravirine is markedly reduced when co-administered with rifampicin, therefore co-administration of these two drugs is not recommended(19, 20). On the other hand, co-administration of doravirine with rifabutin is potentially still considered a viable option in patients with HIV/tuberculosis co-infection, when doravirine is given 100 mg twice daily.(2, 21-23)

There are no published data with other moderate CYP3A inducers, such as bosentan, modafinil or thioridazine, and co-administration of these drugs should be avoided if possible. If coadministration cannot be avoided, doravirine 100 mg should be administered twice daily and this dose continued for further two weeks after cessation of the moderate inducer.(17)

Coadministration of doravirine and CYP3A inhibitors, such as ritonavir and ketoconazole, may result in increased plasma concentrations of doravirine.(21, 22) However, no dose adjustment is needed, as the increases are not considered to be clinically relevant.

Integrase strand transfer inhibitors

Modern integrase strand transfer inhibitors (INSTIs) like dolutegravir, bictegravir and cabotegravir do not affect cytochrome P450 (CYP) isoenzymes or uridine 5'-diphospho-glucuronosyltransferase (UGT) and have a low potential for DDIs. However, the few interactions may have significant clinical consequences.

Dolutegravir, a second-generation INSTI, is now widely prescribed with the nucleoside reverse transcriptase inhibitor backbone as the first-line regimen for treating HIV worldwide.(24) It is a substrate of the drug efflux pumps P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and is primarily metabolised by UGT1A1 together with a minor contribution from CYP3A4. Currently, twice-daily dolutegravir is recommended to overcome the drug-interaction when it is coadministered with rifampicin in patients in with HIV and TB co-infection (see **Table 1**).(24) This regimen was shown to be effective and well tolerated in the INSPIRING study, a

noncomparative, active-control, randomized, open-label study in HIV-1-infected antiretroviral therapy-naive adults.(25) Interestingly, a healthy volunteer study investigating a drug interaction between different doses of dolutegravir (50 and 100 mg daily) and rifampicin showed that concentrations of both dolutegravir 50 mg and 100 mg once daily with rifampicin were still above the protein-binding-adjusted IC_{90} (drug concentration required to inhibit 90% of *in-vitro* viral replication) of 64 ng/mL.(26) Similar findings were reported in virologically suppressed HIV positive patients taking dolutegravir given at a standard 50 mg once-daily dose with 12-week rifapentine–isoniazid. Moreover, in these patients, the drug concentrations achieved maintained HIV virological suppression.(27)

Dolutegravir is also susceptible to chelation-type drug interactions with divalent (Ca^{2+}, Mg^{2+}) and trivalent metal cations (Al^{3+}, Fe^{3+}).(28) In healthy volunteers, simultaneous administration with Al^{3+}-and Mg^{2+}-containing antacid substantially decreased dolutegravir concentrations (AUC by 74%, C_{max} by 72%, and C_{24} by 74%). This reduction improved when the antacid was given two hours after dolutegravir. Subsequently, simultaneous administration of dolutegravir and antacids, calcium or iron supplements is currently not recommended, but dolutegravir can be administered two hours before or six hours after these polyvalent cations.

Dolutegravir is also an inhibitor of the organic cation transporter 2 (OCT2), which is responsible for tubular secretion of creatinine, and a transient rise in creatinine has been reported on dolutegravir initiation.(29) This does not signify renal damage, but may complicate with evaluations of creatinine rises when dolutegravir is combined with TDF.

Metformin is renally eliminated and is thought to be an OCT2 substrate, and increased plasma metformin exposure has been reported in healthy volunteers when dolutegravir is coadministered.(30) While hyperlactataemia was reported in a case report,(31) two retrospective studies reported no cases of lactic acidosis.(32, 33) In the Italian study, no changes in glycaemic control or clinically relevant adverse outcomes were observed when metformin at standard doses was coadministered with dolutegravir. (32) This interaction has not been prospectively evaluated in HIV-positive diabetic patients and the clinical relevance of this DDI needs further elucidation. Prescribing information currently suggests that a dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control.(34)

The induction effect of phenytoin on dolutegravir has not been studied but coadministration is not recommended as the dolutegravir concentrations are expected to decrease. On the other hand, carbamazepine has been shown to reduce dolutegravir exposure in healthy volunteers and in an analysis from therapeutic

drug monitoring (TDM) registry and the dose adjustment to 50 mg twice daily dolutegravir is recommended to overcome the DDI.(35) Interestingly, dolutegravir concentrations were reportedly reduced after coadministration of valproate in 2 patients, (36) and in an analysis from a therapeutic drug monitoring (TDM) registry.(37) Furthermore, a prospective study showed that while the dolutegravir concentrations were reduced, the unbound dolutegravir fraction remained above the protein-binding-adjusted IC_{90}.(38) Thus, this interaction thought to be primarily based on protein displacement, is unlikely to be clinically relevant. (38)

Bictegravir, the newer second-generation INSTI, is co-formulated with emtricitabine and TAF as a single tablet regimen (Biktarvy®) for treatment of HIV in patients without past or present INSTI resistance.(39, 40) It is a substrate of CYP3A4 and UGT1A1, (41) and is likely to be a victim of drug interactions by potent inducers or inhibitors of these enzymes with resultant decrease or increase of drug exposure, respectively. In a healthy volunteer study, twice daily administration of bictegravir/emtrictabine/TAF did not mitigate the induction effect of rifampicin on bictegravir.(42) Therefore, coadministration with rifampicin is contraindicated due to the effect of rifampicin on the bictegravir component of Biktarvy (see **Table 1**). Bictegravir is both a P-gp and a BCRP substrate.(43) The clinical relevance of this feature is not established. Therefore, caution is recommended when bictegravir is combined with medicinal products known to inhibit P-gp and/or BCRP (e.g. macrolides, ciclosporin, verapamil, dronedarone, glecaprevir/pibrentasvir).(44) Similar to dolutegravir, bictegravir should not be taken simultaneously with antacids or supplements containing polyvalent cations such as aluminium, calcium, magnesium, iron due to the expected substantial decrease of bictegravir absorption.(44)

Bictegravir is also an inhibitor of OCT2 and MATE1, and a modest increase in metformin C_{max} and AUC (28% and 39%, respectively) was observed when it was co-administered with bictegravir/emtricitabine/TAF.(44) Co-administration of metformin and bictegravir/emtricitabine/TAF requires risk/benefit consideration in the US, while monitoring/dosage adjustment is recommended if being co-administered in patients with renal impairment in the EU. (43)

Cabotegravir is a novel INSTI in development as an oral and long-acting injectable preparation for HIV treatment and prevention.(45, 46) It is metabolized by UGT1A1 and UGT1A9.(47) At clinically relevant concentrations, cabotegravir did not inhibit or induce any phase I or phase II metabolic enzymes, but significantly inhibits OAT1 and OAT3 drug transporters.(48) However, a healthy volunteer study on oral cabotegravir and rifampicin showed marked increased oral

clearance, with the reduction the cabotegravir $AUC_{0-\infty}$ and the half-life (see **Table 1**).(49) Although the DDI has not been studied in vivo, physiologically based pharmacokinetic models predicted the theoretical effect of rifampicin on cabotegravir and rilpivirine long acting intramuscular formulations and showed that coadministration may result in subtherapeutic concentrations of both antiretroviral drugs. (50)

Entry inhibitors

Two new entry inhibitors were registered by the US Food and Drug Administration in 2020. The first is the CD4-directed post-attachment HIV-1 inhibitor, ibalizumab-uiyk marketed at Trogarzo®. It is administered intravenously with a loading dose of 2 g and a maintenance dose of 800 mg every two weeks.(51) No DDI studies have been conducted to date. Ibalizumab disposition is likely to be like other monoclonal antibodies: target mediated intracellular catabolism.(52) Therefore, DDIs are not expected.

Fostemsavir binds to HIV gp120 near the CD4 binding site and thus blocks HIV attachment to the CD4 receptor on T cells. As a first in its class, in combination with other antiretroviral(s), it is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.(53) It is an oral prodrug of temsavir, which gets metabolized primarily by an esterase-mediated hydrolysis pathway and partly via a CYP3A4-medicated oxidative pathway with a negligible contribution by UGT.(53) Temsavir is also a substrate of P-gp and BCRP and an inhibitor of OATP1B1 and OATP1B3.(53) Therefore, co-administration with substrates of these enzymes and transporters is expected to affect the pharmacokinetics of these drugs. For example, the effect of fostemsavir on rosuvastatin, a substrate of OATP1B1, was studied and showed that there was an increase in rosuvastatin exposure. Thus, it is recommended that only the lowest effective dose of statins should be used when co-administration with fostemsavir is indicated.(53)

A small healthy volunteer study showed a marked reduction in temsavir exposure when fostemsavir, given as 1.2 g single dose, was co-administered with rifampicin, a strong inducer. Therefore, co-administration is not recommended (see **Table 1**). There was a slight reduction in temsavir concentrations during rifabutin coadministration and dose adjustment is not warranted. DDIs with other strong inducers, such as phenytoin and carbamazepine, have not been studied.

However, co-administration is not recommended as subtherapeutic concentrations of temsavir are expected.

Expectedly, another small healthy volunteer study showed increased temsavir exposure with pharmacokinetic enhancers, ritonavir (C_{max} by 53% and AUC by 45%) and cobicistat (C_{max} by 71% and AUC by 93%). However, these drug interactions were not considered clinically relevant.

Conclusion

The potential for DDIs in clinical medicine has been markedly reduced by moving away from protease-inhibitor based regimens to prescribing modern antiretrovirals. However, undesired consequences of DDIs, such as therapeutic failure or toxicity, can still occur and clinical care providers need to be aware of these. DDIs with anti-tuberculous agents remain a major public health concern globally, with newer agents such as bictegravir, cabotegravir, and doravirine adversely impacted by rifampicin. Drug interactions between dolutegravir and metformin require further evaluation, as co-administration of these drugs is likely to increase with a growing obesity epidemic. While dose and dosing regimens for different rifamycins continues to be evaluated (e.g. high-dose rifampicin, daily versus weekly rifapentine) the impact of these changes on DDIs with modern antiretroviral drugs remains unclear. In addition, newer agents developed for comorbidities may affect the pharmacokinetics of modern antiretrovirals. Therefore, access to up-to-date electronic drug-drug interactions databases such as the Liverpool website (see https://www.hiv-druginteractions.org/) is fundamental to avoid unwanted consequences of DDIs.

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Conflict of interest

None of the authors declared any conflict of interest for the submitted work. Outside of the submitted work, MB has received travel and research grants from and has been advisor for Janssen,

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Table

Table 1. Key recommendations for drug-drug interactions of rifamycins and modern antiretrovirals

	Rifampicin (RIF) 600mg daily		Rifabutin (RFB) 300mg daily	
Antiretroviral	PK interaction	Recommendation	PK interaction	Recommendation
Nucleotide reverse transcriptase inhibitor				
Tenofovir alafenamide 25mg daily	AUC ↓ 47% Cmax ↓45% TFV-DP AUC ↓ 36%	Use standard dose as intracellular diphosphate still 82% higher than with TDF	Not studied. TAF exposure likely to be reduced by rifabutin	Do not co-administer
Nonnucleoside reverse transcriptase inhibitor				
Low dose efavirenz 400mg daily	Similar trough concentrations seen in ENCORE(1-3)	More data in patients with HIV-TB coinfection. Standard dose efavirenz should be used when RIF is prescribed.	Bidirectional interaction induction at standard doses. Drug interaction not studied with low dose	Double the dose of rifabutin with standard dose efavirenz
Doravirine 100 mg daily	AUC ↓ 88% Cmax ↓57% Cmin↓ 97%	Do not co-administer. Wait at least 4 weeks after stopping RIF before initiating doravirine	AUC ↓ 50%, Cmax ↓ 1% Cmin↓ 68%	Increase doravirine to 100 mg twice daily and continue at this dose for 2 weeks after stopping
Integrase strand transfer inhibitors				
Dolutegravir 50 mg twice daily	AUC ↓ 54% Cmax ↓43% Cmin↓ 72%	Increase dolutegravir dose to 50mg twice daily	$AUC ↓ 5% $Cmax ↑16% $Cmin↓ 30%	No dose adjustment needed
Bictegravir	≠AUC ↓ 61%, ≠Cmax ↓47% ≠Cmin↓ 80%	Do not co-administer	*AUC ↓ 38%, *Cmax ↓20% *Cmin↓ 56%	Do not co-administer
Cabotegravir Oral 30 mg daily	AUC ↓ 59%, Cmax ↓6% Oral CL↓ 2.4-fold	Do not co-administer	AUC ↓ 23%, Cmax ↓17% Cmin↓ 26%	Although the interaction is not clinically significant, the co-administration of oral cabotegravir and rifamycins is not recommended due the effect on the concomitant rilpivirine.
Entry inhibitors				
Fostemsavir 1200 mg single dose	Temsavir AUC ↓ 82% Cmax ↓76%	Do not co-administer	AUC ↓ 30% Cmax ↓27% Cmin↓ 41%	No dose adjustment needed
Ibalizumab	Not studied	No recommendation, but drug interactions not expected	Not studied	No recommendation, but drug interactions not expected

Data obtained from Liverpool drug interaction website (https://www.hiv-druginteractions.org/checker)
AUC= area under the concentration time curve, Cmax=maximum concentration, Cmin=minimum concentration, CL=clearance
$dolutegravir 50 mg once daily was studied, ≠BIC/FTC/TAF 50/200/25 mg, twice daily was studied, *Bictegravir 75mg given alone was studied.

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