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Evaluation of US Food and Drug Administration Drug Label Recommendations for Coadministration of Antivirals and Acid-Reducing Agents

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Abstract

Coadministration with acid-reducing agents (ARAs), including proton pump inhibitors (PPIs), histamine H_2-receptor antagonists (H_2 blockers), and antacids has been demonstrated to reduce antiviral exposure and efficacy. Therefore, it is essential that US Food and Drug Administration (FDA) drug labels include recommendations to manage these drug–drug interactions (DDIs). This investigation analyzed information in FDA drug labels to manage DDIs between ARAs and antivirals approved from 1998 to 2019. To ascertain clinical adoption, we assessed whether FDA label recommendations were incorporated into current antiviral clinical practice guidelines. We identified 82 label recommendations for 43 antiviral approvals. Overall, 56.1% of recommendations were deemed clinically actionable, with the most common actionable management strategies being dose adjustment during coadministration (40.2%) and coadministration not recommended (9.8%). The sources informing DDI recommendations were clinical DDI studies (59.8%) and predictions of altered exposure (40.2%). Antivirals with low aqueous solubility were more likely to have label recommendations and were more commonly investigated using clinical DDI studies ($P < 0.01$). For recommendations informed by clinical DDI studies, changes in drug exposure were associated with actionable label recommendations ($P < 0.01$). The frequency of exposure changes in clinical DDI studies was similar across antiviral indications, but exposure changes were numerically higher for antacids (71.4%) relative to PPIs (42.9%) and H_2 blockers (28.6%). Of DDI pairs identified within drug labels, 76.8% were included in guidelines, and recommended management strategies were concordant in 90.5% of cases. Our findings demonstrate that current regulatory oversight mostly (but not completely) results in actionable label recommendations to manage DDIs for high-risk antivirals.

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AUTHOR CONTRIBUTIONS

T.S., N.R.P., P.J.M., T.C.S., and I.R.Y. wrote the manuscript. T.S., N.R.P., P.J.M., T.C.S., and I.R.Y. designed the research. T.S. and N.R.P. performed the research. T.S. and N.R.P. analyzed the data.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

CONFLICT OF INTEREST

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Over the past two decades, advances in antiviral therapy have greatly improved outcomes for patients infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). However, one remaining challenge to effective antiviral therapy is the high propensity for drug–drug interactions (DDIs) that affect antiviral exposure.[1–3] In particular, acid-reducing agents (ARAs), including proton pump inhibitors (PPIs), histamine H_2-receptor antagonists (H_2 blockers), and antacids, have been shown to reduce the gastrointestinal solubility of antiviral agents and thereby reduce their systemic exposure.[4–6] Several studies in HIV and HCV patients have found that reduced antiviral exposure from coadministration with ARAs resulted in increased therapeutic failure.[7–9] The potential clinical impact of DDIs between ARAs and antivirals is vast given that these agents are commonly co-prescribed, as evidenced by past investigations that have found that ~ 37% of patients taking HIV antivirals and ~ 31% of patients taking HCV antivirals were co-prescribed ARAs.[10,11]

To mitigate the risk for clinically significant DDIs, it is critical to identify the potential for DDIs between ARAs and candidate antivirals during drug development. Accordingly, the US Food and Drug Administration (FDA) has issued a draft guidance to industry to promote thorough investigation of DDIs between ARAs and candidate drugs with a high potential for pH-dependent DDIs, including many antivirals with low aqueous solubility.[12] This guidance includes recommendations for when and how to perform dedicated clinical DDI studies, wherein candidate drugs are administered to study subjects in the presence and absence of ARAs to assess the effect on exposure. Findings from these studies offer empirical evidence to guide the use of antivirals during coadministration with ARAs. Given that FDA drug labels are intended to provide clinicians with essential information to inform safe and effective medication use (21CFR201.56), it is important that FDA labels communicate appropriate recommendations to clinicians to inform appropriate use of antivirals in combination with ARAs. However, to our knowledge, no investigation has systematically analyzed FDA drug label recommendations to guide coadministration of antivirals and ARAs.

Accordingly, the objective of this study was to thoroughly evaluate FDA drug label recommendations to guide the concomitant use of ARAs with antiviral new molecular entities (NMEs) approved between 1998 and 2019. Our rationale for performing this study included (i) to determine whether current regulatory practices result in adequate characterization of the potential for antiviral–ARA DDIs in drug labels and (ii) to synthesize existing antiviral–ARA study data to gain insights on optimal study design. To assess the clinical adoption of label recommendations, we also investigated whether recommendations for antiviral–ARA pairs identified in drug labels were included in current clinical practice guidelines from prominent US infectious diseases medical organizations (e.g., the Infectious Disease Society of America).

METHODS

Data collection

Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/) was used to identify antiviral NME new drug application approvals between January 1998 and December 2019. For each approval, recommendations to manage concomitant administration of antivirals

with ARAs, including antacids, H_2 blockers, PPIs, and sucralfate (full drug list included in Table S1) were collected from (i) original drug labels issued at the time of approval, (ii) the most recent versions of drug labels, and (iii) clinical pharmacology review documents, when available. The following recommendation elements were collected: the antiviral indication and ARA class (e.g., PPI, HIV antiviral); the Biopharmaceutics Classification System (BCS) class of the antiviral, which was collected from the literature when not provided in FDA review documents; the recommended clinical strategy to manage the DDI; the source that served as the evidence basis for the recommendation; if the source was a clinical DDI study, the study methodology elements and exposure changes of the antiviral during ARA coadministration; and information on the timing of when the study was conducted (i.e., whether conducted during premarketing or postmarketing periods). Only drug label recommendations that considered the potential for altered antiviral exposure (i.e., the antiviral as the victim drug) were included in our analyses. For antiviral–ARA DDI pairs that we identified in drug labels, we searched current versions of professional organization clinical practice guidelines for recommendations to manage these DDI pairs (the list of guidelines that were searched is shown in Table S1). Collected data from guidelines included the antiviral and ARA involved and the recommended clinical strategy to manage the DDI. All data were independently collected by two study team members, and discrepancies were adjudicated. Data were collected until and finalized for analysis on March 5, 2021.

Full methods detailing the categorization of recommended clinical management strategies, changes in drug exposure within clinical DDI studies, and other drug label recommendation elements are presented in the Supplemental Methods and are briefly summarized as follows. Recommended clinical management strategies contained within drug labels or clinical practice guidelines were categorized based on language into the following categories: Coadministration contraindicated (CI); Coadministration not recommended (NR); Dose adjustment recommended during coadministration (DA); Use with caution during coadministration (UWC); No dose adjustment recommended during coadministration (NDA). When no information of this nature was available, the DDI pair was assumed to require NDA. Recommendations of CI, NR, DA, and UWC were classified as clinically actionable in our analyses, since each recommends specific clinical action to mitigate the DDI. For clinical DDI studies mentioned in drug labels, the magnitude of a DDI was recorded as the geometric mean ratio (GMR) of the area under the curve (AUC) and/or maximum blood concentration (C_{max}) of the antiviral in the presence vs. the absence of the ARA. GMRs for AUC and/or C_{max} outside of the established bioequivalence range (GMR: 0.8–1.25) were classified as positive changes in exposure, with GMRs < 0.5 or > 2.0 being classified as “severe” changes.

Statistical analyses

All data were summarized using descriptive statistics. Statistical comparisons were performed with χ^2 or Fisher’s exact tests using GraphPad Prism v.8.4.3 (GraphPad Software, Inc.; San Diego, CA). For all tests, the prespecified alpha level of significance was $P < 0.05$.

RESULTS

Distributions of antiviral-ARA DDI label recommendations

We analyzed 82 DDI recommendations for concomitant administration of antiviral medications and ARAs from the drug labels of 43 antiviral NMEs approved between January 1998 and December 2019 (full data set available in Supplemental File S1). The majority of antiviral approvals (62.8%) had at least one DDI recommendation to inform coadministration with ARAs. Most recommendations (86.6%) were present on the original label at the time of approval. The frequencies of recommended strategies to manage coadministration of antivirals and ARAs is shown in Table 1. The most common recommended management strategies were NDA (43.9%), DA (40.2%), and NR (9.8%). Overall, 56.1% of recommendations were deemed clinically actionable.

The most common sources of information that informed DDI recommendations were clinical DDI studies (59.8%) and predictions of altered exposure during increased gastrointestinal pH based on drug physicochemical properties or observations from other representative antiviral–ARA DDI studies (40.2%). No DDI recommendations were based on the other sources we assessed, which included predictions from population pharmacokinetic and physiologically-based pharmacokinetic (PBPK) modeling methods and experience from premarketing or postmarketing clinical trials. Figure 1 enumerates the sources of information serving as the basis for DDI label recommendations, along with the number of NME approvals, throughout the investigational period of 1998–2019. We observed that antivirals approved after 2010 more commonly had at least one label recommendation to manage antiviral–ARA DDIs relative to those approved from 1998 to 2010 (85.7% vs. 40.9%); however, this difference is likely attributable to the facts that more antivirals approved between 1998 and 2010 had high solubility (and therefore had reduced susceptibility to pH-dependent DDIs) or were approved only for local use (e.g., topical, ophthalmic). When comparing the frequency of antiviral–ARA DDI label recommendations by the BCS class of the antiviral, we found that those with low solubility (classes II or IV) were more likely to have recommendations relative to high solubility (classes I or III) antivirals (92.9% vs. 9.1%; $P < 0.01$).

Table S3 shows the frequencies of antiviral–ARA DDI label recommendations grouped by the antiviral indication and the pharmacologic class of the ARA. DDI recommendations were included in labels for 100% of CMV approvals (1/1), 90% of HCV approvals (9/10), 75% of HIV approvals (15/20), 50% of influenza approvals (2/4), and 0% of hepatitis B virus (0/2) and smallpox (0/1) approvals. PPIs (contained in recommendations for 51.2% of approvals), antacids (41.9%), and H2 blockers (37.2%) were all commonly included in DDI recommendations (actionable or not actionable).

Changes in drug exposure in clinical DDI studies and association with clinically actionable DDI label recommendations

Overall, clinical DDI studies with ARAs were performed for 23 antivirals (53.5% of those approved during the period), including a total of 49 antiviral–ARA pairs that were assessed in clinical studies. Within these studies, a forest plot summarizing GMRs for AUC and

C_{max} during coadministration of antivirals with ARAs is shown in Figure 2. These same GMR data are summarized based on their relationship to the conventional bioequivalence range, defined as a GMR of 0.8–1.25, for AUC, C_{max}, and a composite measure that considered whichever parameter (i.e., AUC or C_{max}) was most affected in Figure 3. Changes in AUC and C_{max} were below the bioequivalence range (GMR < 0.8) for 32.7% and 42.9% of studied antiviral–ARA pairs, respectively, and both parameters were reduced by >50% (GMR < 0.5) for 18.4% of antiviral–ARA pairs.

We next assessed whether changes in drug exposure, including those that involved a doubling or halving of AUC or C_{max} (i.e., "severe" changes), were associated with actionable DDI label recommendations. As displayed in Table 2, actionable label recommendations were more common for antiviral–ARA pairs with changes in composite drug exposure (i.e., GMRs outside of the bioequivalence range) compared with pairs without changes in exposure (69.9% vs. 19.2%; $P < 0.01$). The rate of actionable label recommendations was even higher for DDI pairs with changes in exposure deemed to be severe (88.9%). The most extreme change occurred during coadministration of atazanavir and omeprazole, during which the C_{max} and AUC of atazanavir were reduced by 96% and 94%, respectively, relative to treatment with atazanavir alone. Antivirals that did not have actionable label recommendations despite having changes in drug exposure during coadministration with ARAs included daclatasvir, elbasvir/grazoprevir, etravirine, glecaprevir/pibrentasvir, raltegravir, and tipranavir.

Clinical DDI study methodology and association with changes in drug exposure

Table S4 summarizes the study methodology, including the type of subjects enrolled, the design of study cohorts and sequence, and the study dosing regimens for the 49 clinical DDI studies assessing antiviral–ARA pairs. All clinical DDI studies between antivirals and ARAs were conducted in healthy participants. The most common cohort and sequence design was randomized crossover (~ 64%). Clinical DDI studies most commonly administered a single dose of the victim and perpetrator drugs (41.3%) or multiple doses of both victim and perpetrator drugs (34.8%). While the type of subjects and the dosing regimens were often included in the drug label and/or review documents (available for 63% and 94% of studies, respectively), the sequence design was infrequently included (29%). Clinical studies were performed more frequently for antivirals with low solubility (BCS II or IV) relative to high solubility (BCS I or III) antivirals (78.6% vs. 9.1%, $P < 0.01$). When assessing associations between clinical DDI study methodology elements and changes in drug exposure, we found that the cohort and sequence design was not associated with changes in AUC or C_{max} (P values of 0.74 and 0.72, respectively); similarly, dosing regimen was also not associated with changes in AUC or C_{max} (P values of 0.63 and 0.12, respectively).

Association of antiviral indication and ARA class with changes in antiviral exposure and actionable DDI label recommendations

We assessed whether antiviral indication or ARA class were associated with changes in composite antiviral exposure or actionable DDI label recommendations, with results shown in Table S5. Within clinical DDI studies, the rates of changes in antiviral exposure outside of the bioequivalence range were identical between antivirals indicated for HIV (50.0% had

exposure changes) and HCV (50.0%). The rates of actionable DDI label recommendations were also similar for HIV (61.8%) and HCV antivirals (42.9%; $P = 0.20$). The remaining antiviral indications, influenza and CMV, had actionable label frequencies of 25.0% and 100%, though there were only four and two recommendations for each respective indication.

Changes in antiviral exposure were numerically higher for antacids (71.4%) relative to PPIs (42.9%) and H_2 blockers (28.6%; Table S5), although this difference did not reach statistical significance ($P = 0.07$). A similar trend was observed for rates of actionable label recommendations by ARA class ($P = 0.40$), with actionable strategies being recommended for 65.2%, 52.9%, and 45.5% of antiviral–ARA DDI pairs containing antacids, PPIs, and H_2 blockers, respectively. Sucralfate was not assessed in any clinical DDI studies but was included in three label recommendations, all of which recommended actionable management strategies.

The relationship between ARA class and observed changes in antiviral exposure was also assessed for 18 antivirals that had clinical DDI studies performed during coadministration with two or more classes of ARAs (results shown in Table 3). Coadministration with antacids resulted in pharmacokinetic changes outside of the bioequivalence range for six of the nine assessed antivirals, and in each of these cases the pharmacokinetic changes with antacids were more severe than those found with the same antiviral during coadministration with H_2 blockers and/or PPIs. The potential for pharmacokinetic changes with H_2 blockers and PPIs appeared mostly similar for the assessed antivirals, with H_2 blockers having numerically lower rates of any composite change outside of the bioequivalence range (4/14 (28.6%)) and severe change (2/14 (14.3%)) compared with PPIs (7/16 (43.8%) and 3/16 (18.8%), respectively).

Adoption of drug label recommendations for coadministration of antivirals with ARAs within professional organization clinical practice guidelines

To ascertain the clinical adoption of DDI label recommendations for coadministration of antivirals with ARAs, we searched for recommendations for antiviral–ARA pairs identified in drug labels within current versions of prominent professional organization guidelines. Of the 82 DDI pairs identified from drug labels, 63 (76.8%) were included within guidelines. As shown in Table 4, DDI recommendations were included in guidelines for 90.9% and 61.9% of DDI pairs containing antivirals that treat HIV and HCV, respectively. In contrast, recommendations to manage coadministration with ARAs were not present in guidelines for influenza or CMV. Recommended clinical management strategies contained in guidelines were concordant with those from drug labels in 90.5% of cases overall, including in 92.0% of cases involving HIV antivirals and in 84.6% of cases involving HCV antivirals. The distribution of clinical strategies recommended within guidelines to manage coadministration of antivirals and ARAs is shown in Table 1.

DISCUSSION

Multiple investigations have found significant reductions in exposure for HCV and HIV antivirals during coadministration with ARAs.[4,5,13–15] Studies have also demonstrated that coadministration with ARAs can reduce the efficacy of HCV and HIV antivirals,[7,9,16]

though conflicting data exist.[5,17] Given these important clinical implications, it is essential that FDA drug labels communicate appropriate recommendations to clinicians to manage DDIs between antivirals and ARAs. Accordingly, this investigation comprehensively analyzed information in FDA drug labels related to the management of DDIs between ARAs and antivirals approved from 1998 to 2019.

Broadly, our findings indicate that investigation of the potential for DDIs with ARAs is commonly performed for antiviral FDA approvals, particularly for antivirals with a high propensity for clinically significant DDIs. For instance, we found that drug labels included information to manage DDIs with ARAs for ~ 93% of antivirals with low aqueous solubility (BCS class II or IV), which are particularly susceptible to pH-dependent DDIs.[6,18] Our results also demonstrate the importance of clinical DDI studies to empirically determine the risk for DDIs between antivirals and ARAs; this is evidenced by the fact that nearly 60% of label recommendations to manage DDIs between antivirals and ARAs were informed by clinical DDI studies. In addition, many of the label recommendations that were based on predictions of altered pharmacokinetics included antivirals that were evaluated in clinical DDI studies with other ARAs within the same class, as was the case for atazanavir.[19] We also found that for antivirals with low solubility (BCS class II or IV), clinical DDI studies were performed in the majority (78.6%) of cases. The importance of clinical DDI studies is also reflected by our finding that changes in antiviral exposure outside of the bioequivalence range were associated with label recommendations for actionable clinical management strategies.

Conversely, our findings highlight the need for additional regulatory/industry focus to mitigate the potential for clinically relevant antiviral–ARA DDIs. For instance, 13 of 40 systemically acting antivirals approved during the study period (~ 33%) did not contain information in the drug label to guide coadministration with ARAs. Although we are not aware of evidence indicating a high susceptibility for pH-dependent DDIs with these agents, it may be clinically useful to include recommendations for coadministration with ARAs for all systemically acting antivirals, even if no dose adjustment was required, given the growing clinical appreciation for potentially significant antiviral–ARA DDIs. The recent FDA draft guidance to industry also supports including negative findings from dedicated antiviral–ARA DDI studies in drug labels.[12] In addition, ~ 30% (7/23) of antiviral–ARA DDI pairs that resulted in changes in exposure (C_{max} and/or AUC) within clinical DDI studies did not have corresponding actionable drug label recommendations (the relevant antivirals are mentioned in the results). In the majority of these cases the C_{max} was altered while the AUC was either unaltered or only minimally altered; however, the rationale for the lack of actionable recommendations despite changes in exposure was not frequently included in drug labels and/or review documents. Finally, potential exposure changes during coadministration with ARAs were not assessed in clinical studies for six low-solubility (BCS class II or IV) antivirals (amprenavir, baloxavir, letermovir, nitazoxanide, simeprevir, and tecovirimat), and recommendations to manage DDIs with ARAs were not included in the nitazoxanide and tecovirimat labels. Notably, sofosbuvir was the only high-solubility antiviral that exhibited exposure changes during coadministration with ARAs.

Findings from our study also reveal insights to optimize future evaluation of DDIs between ARAs and candidate antivirals. With regard to study methodology, we did not observe significant differences in whether clinical DDI studies resulted in changes in pharmacokinetic parameters based on the design of the study cohorts and sequence (i.e., randomized crossover vs. fixed sequential vs. parallel group) or the dosing regimens (i.e., single vs. multiple doses). Since changes in AUC were numerically highest in studies using single doses of ARA and antiviral drugs, this methodology may be preferable to multiple dose regimens because it is both time-efficient and cost-efficient and exposes subjects to fewer drug administration-related risks. In addition, our finding that clinical DDI studies were performed for < 10% of highly soluble antivirals (BCS class I or III) suggests that *in vitro* experiments, including solubility and dissolution testing and establishing drug physicochemical properties (e.g., whether the drug is a weak base), are currently being used to estimate DDI risk with ARAs. These findings are supported by results from a recent analysis that found that data from drug solubility and dissolution profiles at different pH conditions were able to predict the outcomes of clinical DDI studies with ARAs for 67–80% of analyzed weak base drugs.[18] Although *in vitro* experiments have not demonstrated sufficient accuracy to be the sole determinants of DDI risk, they offer valuable information to guide the decision of whether a dedicated clinical DDI study should be conducted. Finally, while still a developing methodology during the study period, PBPK modeling now offers the potential to efficiently address the potential clinical relevance of DDIs with ARAs using parameters from *in vitro* experiments as inputs.[20] PBPK modeling has emerged as an important source to inform recommendations for other aspects of FDA drug labeling, including DDIs with cytochromes P450 enzymes and drug transporters,[21] and the recent FDA draft guidance for pH-dependent DDIs details roles for PBPK modeling to inform clinical DDI study design and drug labeling.[12]

It is essential that recommendations for appropriate clinical strategies to manage DDIs between antivirals and ARAs are incorporated into professional organization guidelines because they ultimately determine clinical best practice and inform health policy decisions.[22] Our findings reveal that ~ 77% of antiviral–ARA pairs with DDI recommendations in drug labels also had recommendations in current professional organization guidelines. Recommendations for coadministration with ARAs were present in guidelines for the vast majority of HIV antivirals (~ 91%). While DDI recommendations were present for ~ 62% of HCV antivirals, the eight cases in which guideline recommendations were not provided were for antiviral–ARA pairs with FDA label recommendations of no dose adjustment during coadministration. Therefore, our findings indicate an appreciation for the clinical significance of antiviral–ARA DDIs by prominent HIV and HCV professional organizations. In contrast, recommendations to manage DDIs between antivirals and ARAs were not present in guidelines for CMV or influenza, despite the fact that three of six antiviral–ARA pairs in these therapeutic areas had actionable drug label recommendations; the antivirals included in these DDI pairs were baloxavir and letermovir. While numerous reasons might explain omission of DDI recommendations from guidelines (e.g., if DDIs were deemed to be outside of the guidelines' scopes), these findings suggest that the clinical significance of antiviral–ARA DDIs may be underappreciated in these therapeutic areas.

We also found that when both FDA labels and guidelines provided recommendations for the same antiviral–ARA pair, the recommended clinical management strategies were largely concordant. Discordant recommendations were present for 2 of 13 (~ 15%) assessed HCV and 4 of 50 (8%) assessed HIV antiviral–ARA pairs. In half of these cases, though, both documents recommended differing actionable management strategies that were seemingly appropriate (e.g., the drug label recommends to avoid coadministration of sofosbuvir/velpatasvir with omeprazole while the guidelines recommends to temporally separate dosing or use with caution).[23,24] However, for glecaprevir/pibrentasvir-omeprazole, lopinavir/ritonavir-omeprazole, and tipranavir-aluminum and magnesium hydroxide, the FDA label recommends no dose adjustment while guidelines recommend actionable management strategies.[23–27] These discordant instances may present an opportunity to update guideline recommendations or provide rationale for the discordance relative to FDA labels.

Our investigation identified additional findings with potential clinical relevance. Of the three major classes of ARAs, we found that reduced antiviral exposure was numerically most common with antacids (though this difference was not statistically significant), perhaps due to their direct acid-neutralizing effects. These findings included clinical DDI studies with elbasvir/grazoprevir, two combination products containing cobicistat/elvitegravir/emtricitabine/tenofovir, dolutegravir, raltegravir, and tipranavir/ritonavir in which coadministration with antacids reduced antiviral exposure while coadministration with H_2 blockers and/or PPIs did not. While our findings suggest that antacids may generally produce the greatest impact on antiviral exposure when administered simultaneously, administration of antacids and antivirals can often be staggered to avoid DDIs, as is recommended in numerous antiviral labels (e.g., the dolutegravir label recommends administration 2 hours before or 6 hours after antacids).[28] Our findings also suggest that H_2 blockers may generally impact antiviral exposure less than PPIs, including within clinical DDI studies for sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, atazanavir, and etravirine; however, the opposite effect was observed for rilpivirine, in which coadministration with famotidine produced greater changes in exposure than during coadministration with omeprazole.[29]

In November 2020, the FDA published a draft guidance for industry to provide recommendations on how to characterize the potential for pH-dependent DDIs during drug development.[12] The specific topics covered in the guidance included (i) when clinical DDI studies with ARA are needed, (ii) how to design studies, (iii) how to interpret study results, and (iv) how to communicate study findings in drug labels. Although the antivirals in our study were approved prior to publication of this guidance, the methods for DDI risk assessment identified in our survey are largely consistent with guidance recommendations. For example, the guidance stresses the need to characterize the potential for pH-dependent DDIs in weak base drugs with low aqueous solubility. While we did not collect information related to the acid/base character of candidate antivirals, we found that, of the 28 antiviral approvals with one or more active pharmaceutical ingredient with low aqueous solubility, 26 (92.9%) had recommendations to guide coadministration with ≥ 1 ARA and 22 (78.6%) were assessed within clinical DDI studies. Furthermore, the most common clinical DDI study design elements from our survey, including the preferential use of healthy volunteers

and crossover study designs, the sufficiency of single dose regimens in most cases, and the preferential use of PPIs to represent the "worst-case scenario" for pH-dependent DDIs, are in accordance with recommendations from the FDA guidance. Therefore, our findings suggest that, even though the FDA recommendations for characterization of pH-dependent DDIs were not formally published until recently, these principles were likely being considered during drug approval in many cases prior to publication. We anticipate that increased adherence to these recommendations will improve the efficiency and completeness of the evaluation of pH-dependent DDIs during drug development and the communication of key findings in drug labels.

Our study was limited by only having access to publicly available data contained in drug labels, FDA review documents, and clinical practice guidelines, which is reflected in the fact that clinical DDI study methodology elements were unknown in many cases. This limitation also impacted our ability to interpret the rationale for antiviral–ARA DDI recommendations in cases where it was not explicitly stated. In the future, these unclarities may be overcome by more standardized and detailed reporting of clinical DDI study findings in FDA labels and/or review documents, including for antivirals where clinically significant DDIs were not found or suspected.

In conclusion, our investigation thoroughly analyzed FDA drug label recommendations to manage DDIs between ARAs and recently-approved antivirals, identifying associations with potential regulatory and clinical implications. Our findings demonstrate that current regulatory oversight resulted in actionable drug label recommendations for high-risk antivirals in most but not all cases. Our findings also identify opportunities to improve the efficiency of antiviral–ARA DDI evaluation and the completeness of communicating recommendations in drug labels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Coadministration with acid-reducing agents (ARAs) can reduce the exposure and efficacy of antivirals. To inform effective medication use, US Food and Drug Administration (FDA) drug labels should include appropriate recommendations to manage these drug–drug interactions (DDIs).

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study systematically analyzed FDA drug label recommendations to manage DDIs between ARAs and antivirals approved from 1998 to 2019 and assessed whether FDA recommendations were incorporated into current antiviral clinical practice guidelines.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We found that DDI recommendations were included in drug labels for high-risk antivirals in most but not all cases. Similarly, actionable FDA recommendations were also incorporated into antiviral guidelines with concordant recommendations in most cases. We also identified important considerations to optimize investigation of DDI risk during drug development.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ By synthesizing the landscape of regulatory and clinical appreciation of antiviral–ARA DDIs, this work identifies current successful practices and areas for improvement and offers insights to optimize future antiviral–ARA DDI risk assessment.

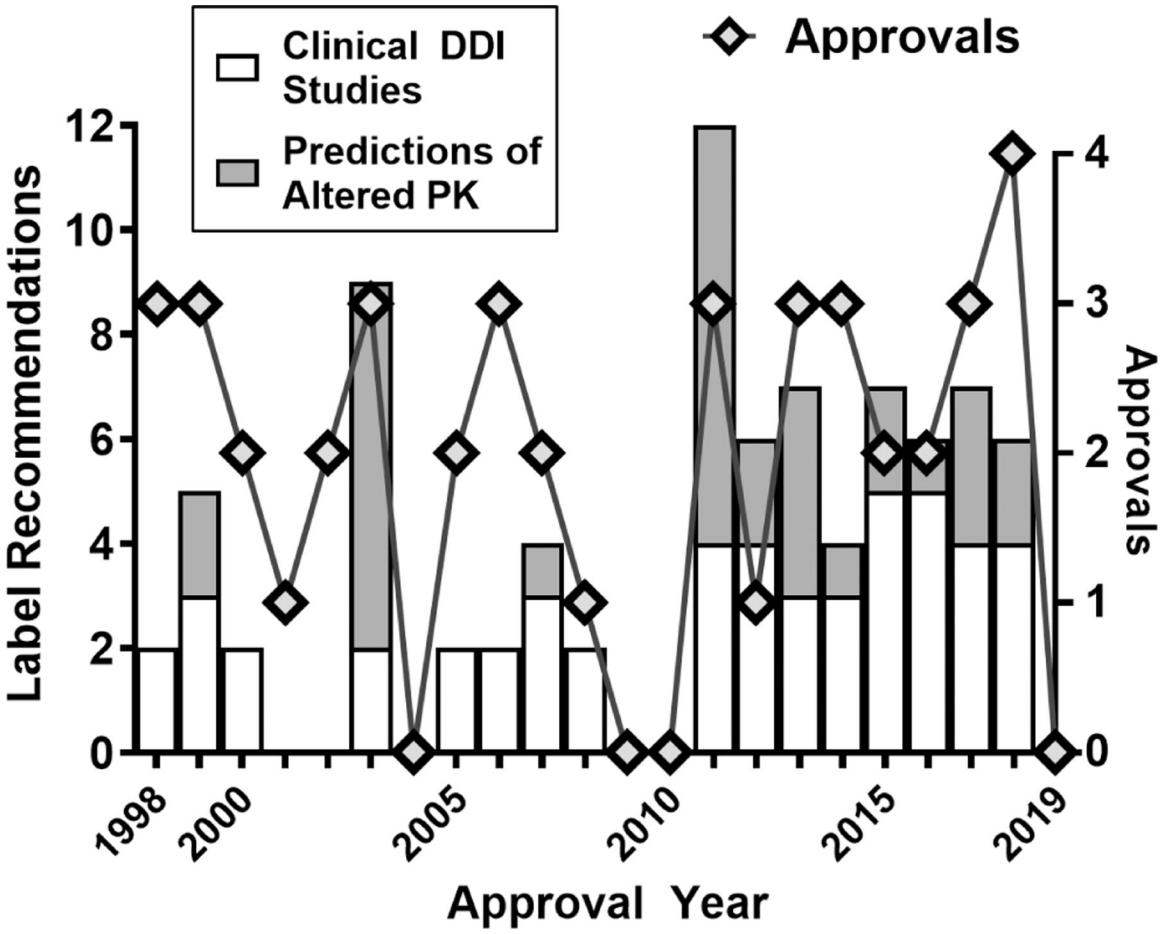

Figure 1.

Timeline of US Food and Drug Administration drug label recommendations for coadministration of new molecular entity antiviral approvals and acid-reducing agents, along with sources informing and number of antiviral approvals per year, during the study period of 1998 through 2019. DDI, drug–drug interaction; PK, pharmacokinetics.

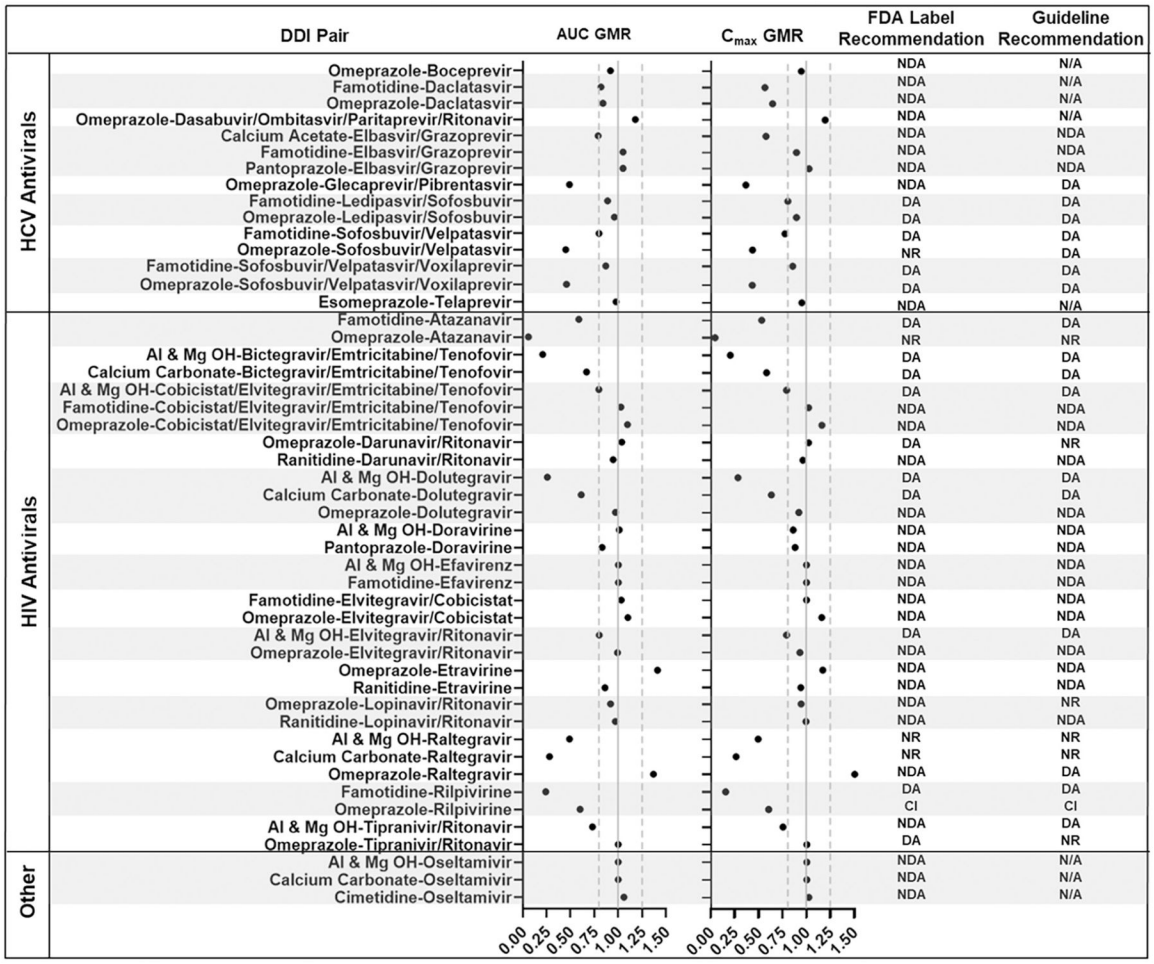

Figure 2.

Forest plot summarizing geometric mean ratios (GMRs) for area-under-the-curve (AUC) and maximum concentration (C_{max}) from clinical DDI studies with antivirals and acid-reducing agents as reported in US Food and Drug Administration (FDA) drug labels. Recommended clinical strategies to manage these drug-drug interactions (DDIs) from FDA labels and US professional organization clinical practice guidelines are shown for each drug-drug pair. DDI pairs are stratified by antiviral indication and sorted alphabetically by antiviral generic name. The vertical solid line in the forest plot represents exact bioequivalence (GMR ratio = 1), and the vertical dashed lines represent the conventional bioequivalence range of ±20% (GMR ratio: $0.8 \leq x \leq 1.25$). AI & Mg OH, aluminum hydroxide and magnesium hydroxide; CI, contraindication; DA, dose adjustment; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NDA, no dose adjustment; NR, coadministration not recommended; N/A, not applicable.

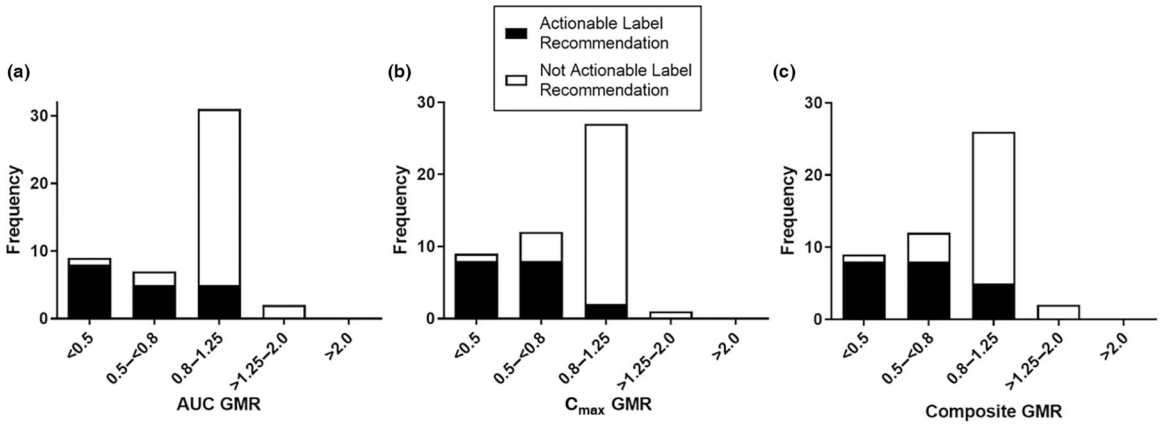

Figure 3.

Frequency distributions of GMRs (geometric mean ratios) for (**a**) AUC (area under the curve), (**b**) C_{max} (maximum concentration), and (**c**) the composite exposure measure, which considers the pharmacokinetic parameter most affected (i.e., AUC or C_{max}), during coadministration of antivirals and acid-reducing agents and whether these drug–drug interactions had corresponding recommendations for actionable clinical management strategies within US Food and Drug Administration drug labels. Frequencies are organized based on thresholds for the established bioequivalence range (0.8–1.25) and for thresholds for "severe" changes in exposure, defined by GMRs indicating a halving (< 0.5) or doubling (> 2.0) of the pharmacokinetic parameter.

Table 1

Distribution of clinical management strategies contained within FDA labels and clinical practice guidelines for DDIs between acid-reducing agents and antivirals

FDA drug labels			Clinical practice guidelines		
Management strategy	**Number**	**Percentage**	**Management strategy**	**Number**	**Percentage**
Contraindication	5	6.1%	Contraindication	5	7.9%
Not recommended	8	9.8%	Not recommended	10	15.9%
Dose adjustment	33	40.2%	Dose adjustment	27	42.9%
Use with caution	0	0%	Use with caution	0	0%
Total actionable	*46*	*56.1%*	*Total actionable*	*42*	*66.7%*
No dose adjustment	36	43.9%	No dose adjustment	21	33.3%
Total	82		Total	63	

DDIs, drug–drug interactions; FDA, US Food and Drug Administration.

Table 2

Distributions of clinical management strategies informed by clinical DDI studies involving antivirals and ARAs based on composite changes in drug exposure

Change in composite drug exposure	Management strategy	Number	Percentage
No change GMR: 0.8–1.25	Contraindication	0	0%
	Not Recommended	0	0%
	Dose Adjustment	5	19.2%
	Use with Caution	0	0%
	Total Actionable	*5*	*19.2%*
	No Dose Adjustment	21	80.8%
	Total	26	
All positive GMR: < 0.8, > 1.25	Contraindication	1	4.3%
	Not Recommended	4	17.4%
	Dose Adjustment	11	47.8%
	Use with Caution	0	0%
	Total Actionable	*16*	*69.6%*
	No Dose Adjustment	7	30.4%
	Total	23	
Severe GMR: < 0.5, > 2.0	Contraindication	0	0%
	Not Recommended	4	44.4%
	Dose Adjustment	4	44.4%
	Use with Caution	0	0%
	Total Actionable	*8*	*88.9%*
	No Dose Adjustment	1	11.1%
	Total	9	

ARAs, acid-reducing agents; DDI, drug–drug interaction; GMR, geometric mean ratio.

Table 3

Changes in drug exposure by ARA class in clinical DDI studies with antivirals and multiple classes of ARA

Antiviral	PK changes with antacid	PK changes with H_2 blockers	PK changes with PPI
Hepatitis C virus			
Daclatasvir		AUC: ↓18%; C_{max}: ↓44%	AUC: ↓16%; C_{max}: ↓36%
Elbasvir/grazoprevir	AUC: ↓21%; C_{max}: ↓43%	AUC: ↓10%; C_{max}: ↓11%	AUC: ↑12%; C_{max}: ↑10%
Ledipasvir/sofosbuvir		AUC: ↓11%; C_{max}: ↓20%	AUC: ↓4%; C_{max}: ↓11%
Sofosbuvir/velpatasvir		AUC: ↓20%; C_{max}: ↓23%	AUC: ↓55%; C_{max}: ↓57%
Sofosbuvir/velpatasvir/voxiiaprevir		AUC: ↓13%; C_{max}: ↓15%	AUC: ↓54%; C_{max}: ↓57%
Human immunodeficiency virus			
Atazanavir		AUC: ↓41%; C_{max}: ↓47%	AUC: ↓94%; C_{max}: ↓96%
Cobicistat/elvitegravir/emtricitabine/tenofovir (Stribild)	AUC: ↓20%; C_{max}: ↓21%	AUC: NC; C_{max}: ↑3%	AUC: ↑10%; C_{max}: ↑16%
Cobicistat/elvitegravir/emtricitabine/tenofovir (Genvoya)	AUC: ↓20%; C_{max}: ↓21%	AUC: ↑2%; C_{max}: ↑3%	AUC: ↑10%; C_{max}: ↑16%
Darunavir/ritonavir		AUC: ↓5%; C_{max}: ↓4%	AUC: ↑4%; C_{max}: ↑2%
Dolutegravir	AUC: ↓74%; C_{max}: ↓72%		AUC: ↓3%; C_{max}: ↓8%
Doravirine	AUC: ↑1%; C_{max}: ↓496		AUC: ↓17%; C_{max}: ↓12%
Efavirenz	AUC: NC; C_{max}: NC	AUC: NC; C_{max}: NC	
Etravirine		AUC: ↓14%; C_{max}: ↓6%	AUC: ↑41%; C_{max}: ↑17%
Lopinavir/ritonavir		AUC: ↓3%; C_{max}: ↓1%	AUC: ↑8%; C_{max}: ↓6%
Raltegravir	AUC: ↓72%; C_{max}: ↓74%		AUC: ↑37%; C_{max}: ↑51%
Rilpivirine		AUC: ↓76%; Cm„: ↓85%	AUC: ↓40%; C_{max}: ↓40%
Tipranavir/ritonavir	AUC: ↓27%; C_{max}: ↓25%		AUC: NC; C_{max}: NC
Other antivirals			
Oseitamivir	AUC: NC; C_{max}: NC	AUC: ↑6; C_{max}: ↑2%	

Key: = change in GMR of PK parameter: 0.55≤x<0.8 or 1.25<x≤2.0 = change in GMR of PK parameter: <0.5 or >2.0; = not studied.

ARA, acid-reducing agents; AUC, area under the curve; CI, contraindication; C_{max}, maximum concentration; DDI, drug-drug interaction; H_2 blocker, histamine H_2 receptor antagonist; GMR, geometric mean ratio; NC, "no change in exposure" was stated in label and/or review documents, without providing a percent change; PK, pharmacokinetic; PPI, proton pump inhibitor. [Colour version of this Table can be viewed at wileyonlinelibrary.com]

Table 4

Whether DDI recommendations for antiviral-ARA pairs identified in FDA drug labels were included in clinical practice guidelines and, if included, whether recommended clinical management strategies were concordant

Category	Included in guidelines? (%)	Concordant management strategy? (%)
All DDI pairs	63 (76.8)	57 (90.5)
Antiviral clinical indication		
Human immunodeficiency virus	50 (90.9)	46 (92.0)
Hepatitis C virus	13 (61.9)	11 (84.6)
Influenza	0 (0)	N/A
Cytomegalovirus	0 (0)	N/A

ARA, acid-reducing agent; DDI, drug–drug interaction; FDA, US Food and Drug Administration, N/A, not applicable.