

Clinically significant interactions between antiretroviral and co-prescribed drugs for HIV-infected children: profiling and comparison of two drug databases

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Background: Drug–drug interactions are an important therapeutic challenge among human immunodeficiency virus-infected patients. Early recognition of drug–drug interactions is important, but conflicts do exist among drug compendia on drug interaction information. We aimed to evaluate the consistencies of two drug information resources with regards to the severity rating and categorization of the potential interactions between antiretroviral and co-prescribed drugs.

Methods: We reviewed the case files of human immunodeficiency virus-infected children who were receiving treatment at the human immunodeficiency virus (HIV) clinic of the Lagos University Teaching Hospital, Idi Araba, between January 2005 and December 2010. All of the co-prescribed and antiretroviral drug pairs were screened for potential interactions using the Medscape Drug Interaction Checker and the Monthly Index of Medical Specialties Interaction Checker. Drug–drug interaction (DDI) severity and categorization were rated on a scale of A (no known interaction); B (minor/no action needed); C (moderate/monitor therapy); D (major/therapy modification); and X (contraindicated/avoid combination).

Results: A total of 280 patients were at risk of 596 potential DDIs. The databases showed discrepancies, with Medscape database identifying 504 (84.6%) and USA MIMS database identifying 302 (50.7%) potential DDIs. Simultaneous identification of DDIs by both databases occurred for only 275 (46.1%) listed interactions. Both databases have a weak correlation on the severity rating ($r_s = 0.45$; $P < 0.001$). The most common DDIs identified by the databases were nevirapine and artemisinin-based combination therapy (170; 28.5%), nevirapine and fluconazole (58; 9.7%), and zidovudine and fluconazole (55; 9.2%). There were 272 (45.6%) interaction severity agreements between the databases.

Conclusion: Discrepancies occurred in DDI listings between Medscape and USA MIMS databases. Health care professionals may need to consult more than one DDI information database to ensure safe concomitant prescribing for HIV patients.

Keywords: drug–drug interactions, severity rating, drug interaction checkers, pediatric population, category of interaction, concomitant medication

Introduction

Drug–drug interactions are an important therapeutic challenge among human immunodeficiency virus-infected patients on antiretroviral drugs. They are often observed in these patients because they frequently receive multiple medications concomitantly with the antiretroviral therapy for treating the numerous infections and systemic consequences of human immunodeficiency virus/acquired immunodeficiency syndrome.^{1,2}

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Highly active antiretroviral (ARV) therapy, defined as the combination of three or more ARV agents taken concurrently to suppress human immunodeficiency virus (HIV) replication, represents the current standard of care of ARV therapy for HIV-infected patients.³ This strategy evolved from the recognition that treatment of chronic HIV infection with only one or two ARV drugs typically results in rapid treatment failure and the development of ARV resistance, which may compromise future therapeutic options.^{3,4}

An important means of preventing drug–drug interactions in HIV-infected patients is early recognition. This may involve using drug compendia or electronic databases as a source of drug–drug interaction (DDI) information before prescribing. Currently, a number of commercial DDI databases are available; compendia such as MICROMEDEX^{®5} and Lexicomp^{®6} are commonly used resources that can provide detailed DDI information including onset, severity, scientific evidence, pharmacologic effects, mechanisms of action, and management. However, these resources may not be available in the developing countries; therefore, alternative electronic databases, such as the Medscape Drug Interaction Checker⁷ and the Monthly Index of Medical Specialties Interaction Checker,⁸ that are available online for free use, may be sought. Although references may be helpful in identifying drug interactions, studies have shown that major conflicts exist among drug compendia on drug interaction information, particularly with regard to specific information such as severity and evidence ratings.^{9–11}

The main objective of this study was to identify the clinically significant DDI between ARV and co-prescribed drugs among HIV-infected children in Lagos, Nigeria, and to evaluate the consistencies of the drug information resources with regards to severity ratings and categorization of the DDIs.

Methods

Study design

We retrospectively analyzed the clinical records of HIV-infected children who were receiving treatment at the AIDS Prevention Initiative in Nigeria clinic at the Lagos University Teaching Hospital in Nigeria, between January 2005 and December 2010. The AIDS Prevention Initiative in Nigeria clinic at the Lagos State University Teaching Hospital is one of the United States' Presidential Emergency Plan for AIDS Relief-funded centers for the HIV relief program. The clinic is held every Monday through Friday, between 8 am and 4 pm.

On average, about 350 returning and new patients (adults and children) are seen each day at the AIDS Prevention

Initiative in Nigeria (APIN) clinic. All HIV-infected children, including those who had progressed to full-blown acquired immunodeficiency syndrome (AIDS) (according to the World Health Organization's criteria),³ as well as meeting the other inclusion criteria, were included in this study. These included children younger than 15 years old and those who had been initiated on highly active ARV therapy. Patients must have completely documented demographic information and prescribed medications in the case files. Also, they must have used ARV drugs, at least once, after enrollment.

Data abstraction

Eligible cases were identified through the main register obtained from the medical record of the APIN clinic. One of the researchers (SL) reviewed each case file, and – using a standard form purposely designed for the study – extracted data on sex, mode of contracting HIV, comorbid diseases and concurrent infections at presentation and follow-up, co-prescribed drugs, and the highly active ARV therapy regimen prescribed for each patient.

Prescribed highly active ARV therapy (HAART) regimen

The national guidelines for HIV treatment in Nigeria¹² recommended first-line ARV drugs for children such as zidovudine and lamivudine, plus nevirapine or efavirenz; substitution with stavudine or abacavir was allowed for toxicity. Second-line ARV drugs included any of the first-line drugs – didanosine and abacavir or didanosine and zidovudine (AZT) or didanosine (ddI) and efavirenz/nevirapine – in combination with the protease inhibitors lopinavir/ritonavir or saquinavir/ritonavir.

Identification of potential interactions between co-prescribed and ARV drugs

The entire co-prescribed and ARV drug pairs were screened for potential interactions using the Medscape Reference Online Drug Interaction Checker⁷ and the Monthly Index of Medical Specialties (MIMS) Interaction Checker.⁸ The potential DDIs not identified by the two databases or those with the severity rated as contraindicated (category X) or unknown (category A) by any of the two databases were searched from a third database, the Liverpool HIV Pharmacology Group website.¹³ This is to ensure that important DDIs were not missed out of the total potential DDIs.

Classification of potential interactions between co-prescribed and ARV drugs

The severity and category of interactions were based on the method of Armahizer et al,¹⁴ which utilized MICROMEDEX^{®5} and Lexicomp^{®6} method of severity and category classification. The details of the severity rating scale (A to D and X) are presented in Table 1. Interactions relating solely to overlapping toxicities, or between co-prescribed ARV drugs, such as protease inhibitor boosting, or involving topical applications, were excluded. In addition, we excluded from our analysis the potential interactions between lamivudine and cotrimoxazole, due to limited clinical significance suggested by controlled data.² If a given drug interaction was listed more than once with different risk ratings, the most-severe risk rating was used to determine the severity grade. Interaction between ritonavir in the lopinavir/ritonavir combination and the sulfamethoxazole/trimethoprim were excluded from analysis, since these drug combinations are generally used together intentionally and result in a beneficial interaction.

Results

Demographics of the patients

A total of 417 patients were enrolled for HAART over the study period, but only 310 (74.3%) met the inclusion criteria. The majority of those excluded had incomplete demographic information or missing details of the ARV or co-prescribed drugs. The case files of all the 310 patients were reviewed in this study. Females (172; 55.5%) were more affected than males (138; 44.5%). Their median age was 3 (range 1–15) years. Mother-to-child transmission (182; 58.8%) and blood transfusion (10; 3.2%) were the most common routes of transmitting HIV-infection in the study. However, the route

of transmission was unknown in 31 (10.0%) cases and not documented in 87 (28.1%) cases.

Prescribed HAART regimen

A total of 306 patients (98.7%) were enrolled on first-line ARV therapy, comprising of zidovudine–lamivudine–(NVP) (279; 91.2%) and zidovudine–lamivudine–efavirenz (27; 8.8%). Four (1.3%) patients were enrolled on a second-line treatment (zidovudine–lamivudine–abacavir (ABC)–lopinavir/ritonavir [LPV/r]). The first-line ARV therapies were changed for 66 (21.6%) patients after an initial enrolment. Nearly all the patients (64/66; 97%) who switched their HAART regimen did so after a year of commencing the first-line treatment. Poor adherence and therapeutic failure (60/66; 90.9%), therapeutic failure only (4; 6.1%), and an adverse drug event (2; 3.0%) were the reasons for changing the HAART regimen. ABC–lamivudine (3TC)–LPV/r, (20/66; 30.3%); AZT–3TC–ABC–LPV/r (16/66; 24.2%); AZT–3TC–ABC–ddI–LPV/r, (10/66; 15.2%); ABC–3TC–NVP, (8/66; 12.1%); AZT–ABC–LPV/r (6/66; 9.1%); and AZT–3TC–LPV/r (6/66; 9.1%) were the types of second-line regimens prescribed.

Co-medications for HIV-infected children on ARV drugs

A wide range of medications were co-prescribed for the patients while on HAART regimen. The drugs were used to treat comorbid conditions, opportunistic infections, or concurrent infections. Tuberculosis (35; 11.3%) was the most common opportunistic infection treated in the patients. It was treated with a combination of rifampicin–isoniazid–pyrazinamide for an average of six months either before or during ARV treatment. Presumptively diagnosed malaria (208; 67.1%), pneumonia (70; 22.6%), and sepsis (4; 1.3%) were the concurrent infections frequently treated in the patients.

Table 1 Drug–drug interaction rating scale

| Rating | Category | Action | Explanation |
|--------|-----------------|-------------------------------|---|
| X | Contraindicated | Avoid combination | The drugs are contraindicated for concurrent use |
| D | Major | Consider therapy modification | The interaction may be life threatening and/or require medical intervention to minimize or prevent serious adverse events |
| C | Moderate | Monitor therapy | The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy |
| B | Minor | No action needed | The interaction would have limited clinical effects. May include an increase in the frequency or severity of side effects but generally would not require a major alteration in therapy |
| A | Unknown | No known interaction | Unknown |

Note: Data from Lexicomp,⁶ MICROMEDEX^{®5} and Armahizer et al.¹⁴

Identified potential interactions between co-prescribed and ARV drugs

The first-line regimens, AZT–3TC–NVP (309; 67.1%) and AZT–3TC–EFV (66; 14.3%), were frequently associated with clinically significant drug interactions, followed by a second-line regimen, ABC–3TC–NVP (30; 6.6%). Other regimens associated with DDIs were ABC–3TC–EFV, (8; 1.7%); ABC–3TC–AZT–LPV/r, (9; 1.9%); ABC–3TC–LPV/r, (10; 2.2%); AZT–3TC–LPV/r, (12; 2.4%); and AZT–3TC–ddI–LPV/r, (17; 3.7%).

A total of 310 patients were included in the evaluation, and 596 potential DDIs were identified in 280 (67.1%) patients. Discrepancies between the databases were noted, with the Medscape⁷ electronic database identifying 504 (84.6%) and the MIMS database⁸ identifying 302 (50.7%) potential DDIs. Excluding category A interaction (unknown/no known interaction), simultaneous identification of DDIs by both databases, occurred for only 275 (46.1%) listed interactions. Table 2 shows the discrepancies in the severity rating and categorization of the interactions identified by the two databases. The Spearman’s rank correlation test result suggested a medium correlation between the Medscape database and the MIMS database on the severity rating ($r_s = 0.45$; $P < 0.001$).^{7,8} The DDIs most commonly identified by the databases were nevirapine (NVP) and artemisinin-based combination therapy (antimalarials), (170; 28.5%); NVP and fluconazole, (58; 9.7%); and zidovudine and fluconazole, (55; 9.2%) (Table 3). Interaction severity agreement differed between the databases, with Medscape and MIMS databases agreeing for 272 (45.6%) interactions.

An evaluation of contraindicated DDIs was conducted to determine their potential clinical relevance. A total of 189 (31.7%) contraindicated DDIs were discovered during the evaluation by the Medscape database only and involved NVP and artemisinin-based combination therapy (170; 28.5%) and efavirenz (EFV) and artemisinin-based combination

therapy (19; 3.2%). All the contraindicated DDIs were rated as category A (unknown/no known interaction) by the MIMS database, and as category C (moderate severity/monitor therapy) by the Liverpool HIV Pharmacology Group website,¹³ another database.

Discussion

Various databases^{5–8} and compendia^{15–17} are available to evaluate DDIs. The differences in their ratings of the severity and category make it complicated to have a uniform system of evaluating DDIs, especially with respect to severity assessment. The overall agreement between the two databases (Medscape and MIMS) in our study was 45.6%, which was similar to the frequency of agreement for physicians in their assessment of DDIs involving medications that were currently prescribed to patients in the adult cardiac intensive care unit.¹⁴ In contrast, a lower agreement rate (39.4%) has been reported for MICROMEDEX[®] and Lexicomp[®] databases in the ratings of the potential DDIs among currently used cardiovascular drugs for adult patients.¹⁴ Another study¹⁸ had reported a higher agreement rate (74.3%) of severity rating for oral anticancer and nonanticancer drugs between Drug Interaction Facts and MICROMEDEX[®].

Fulda et al¹⁰ have compared the inclusion of drug interactions for five drug classes in five American drug interactions compendia and found that individual interactions were rarely listed in more than one or two of the compendia. Chao and Maibach¹⁹ reported substantial discrepancies among four American drug compendia for the inclusion of drug interactions on selected at-risk dermatologic drugs. Abarca et al⁹ assessed the agreement of four American drug interaction compendia for major drug interactions and found a substantial disagreement. In an Australian study, 14%–44% of the drug interactions classified as major in any one compendium were not listed in the other compendia.¹¹ The previous comparisons of DDI severity between compendia, databases, or databases and clinicians involved medications frequently used in the adult cardiovascular intensive care units, oral anticancer and nonanticancer drugs, dermatologic drugs, and antihypertensive drugs.^{9–11,14,18} These were contrasting to the DDIs between ARV and co-prescribed drugs evaluated in our study.

Several studies have evaluated DDIs in HIV-infected patients, but – to our knowledge – this is the first study evaluating DDIs in HIV-infected children.^{1,2,20,21} Most of the previous studies relied on a single-drug interaction compendium to identify potential interactions between ARV and co-prescribed drugs. In the few studies where more than one compendium was used, none assessed the consistency

Table 2 Severity and category of the interactions between antiretroviral and co-prescribed drugs

| Severity | Category | Medscape database n (%) | MIMS database n (%) |
|----------|-----------------|-------------------------|---------------------|
| A | Unknown | 96 (16.1) | 303 (50.8) |
| B | Minor | 72 (12.1) | – |
| C | Moderate | 239 (40.1) | 293 (49.2) |
| D | Major | – | – |
| X | Contraindicated | 189 (31.7) | – |
| Total | | 596 (100.0%) | 596 (100.0%) |

Abbreviations: n, number; MIMS, Monthly Index of Medical Specialties.

Table 3 The most common antiretroviral and co-prescribed drugs interactions identified

| ARV and co-prescribed drug interaction | Number of DDI identified N = 596 (%) | Severity | |
|---|---|-------------------|---------------|
| | | Medscape database | MIMS database |
| Nevirapine + artemisinin combination therapy | 170 (28.5) | X | A |
| Nevirapine + fluconazole | 58 (9.7) | C | C |
| Zidovudine + fluconazole | 55 (9.2) | B | C |
| Zidovudine + rifampicin | 35 (5.9) | C | C |
| Nevirapine + prednisolone | 31 (5.2) | C | C |
| Zidovudine + ibuprofen | 27 (4.5) | A | C |
| Efavirenz + rifampicin | 27 (4.5) | C | C |
| Zidovudine + clarithromycin | 24 (4.0) | C | C |
| Nevirapine + clarithromycin | 19 (3.2) | C | C |
| Lamivudine + frusemide | 19 (3.2) | A | A |
| Nevirapine + frusemide | 15 (2.5) | A | A |
| Abacavir + metronidazole | 15 (2.5) | A | A |
| Lopinavir/ritonavir + artemisinin-based combination therapy | 15 (2.5) | C | A |
| Efavirenz + loratadine | 15 (2.5) | C | A |
| Efavirenz + artemisinin combination therapy | 14 (2.4) | X | A |
| Nevirapine + rifampicin | 8 (1.3) | B | D |
| Lamivudine + sulfadoxine/pyrimethamine | 8 (1.3) | A | A |
| Lopinavir/ritonavir + artemisinin/amodiaquine | 7 (1.2) | C | A |
| Efavirenz + artemisinin/amodiaquine | 5 (0.8) | C | D |
| Efavirenz + clarithromycin | 5 (0.8) | C | C |
| Nevirapine + ketoconazole | 4 (0.7) | C | C |
| Lopinavir/ritonavir + proguanil | 4 (0.7) | C | A |
| Lopinavir/ritonavir (solution) + metronidazole | 4 (0.7) | C | A |
| Lopinavir/ritonavir + loratadine | 4 (0.7) | A | A |
| Lopinavir/ritonavir + frusemide | 4 (0.7) | A | A |
| Lopinavir/ritonavir + prednisolone | 4 (0.7) | C | C |

Abbreviations: ARV, antiretroviral; DDI, drug–drug interaction; n, number; MIMS, Monthly Index of Medical Specialties.

of severity ratings using two or more databases for DDI check.^{20,21} Our study identified discrepancies between Medscape and MIMS databases with regard to DDI listings and severity ratings between ARV agents and drugs from other classes (Tables 2 and 3). Although this study was limited to only six ARV drugs (lamivudine, AZT, ABC, NVP, EFV, and LPVr), the results were consistent with those involving oral anticancer and nonanticancer drugs from another study, where a comparative assessment of two interaction compendia (Drug Interaction Facts and MICROMEDEX®) was done.¹⁸

The discrepancies in DDI listings between the databases seem to suggest that either MIMS is underreporting or Medscape is overreporting DDIs. One reason could be the difference in time between the data collection and the updating of the database online, as DDIs are continually identified in randomized controlled trials and published in journals. The inability to include the more recent and updated interactions could result in many DDIs being excluded from the MIMS.

Although both databases are available free online, the Medscape database appears to be updated continuously with practice-changing evidence culled daily from journal publications, which results in a shorter lag time between updating and publishing the data. Therefore, Medscape database could have included more recent DDIs involving artemisinin-based combination therapy (antimalarials) and loratadine that were not reported in the MIMS (Table 3). This would suggest a need for health care professionals to consult more than just one DDI information reference source to ensure that it is indeed safe to use certain drugs concomitantly.

Several factors could have contributed to the variations in the ratings of severity between the Medscape and the MIMS databases. Both databases might have obtained information from different sources, unpublished reports by drug companies, reports collated from postmarketing surveillance, and summaries of product characteristics.¹¹ Depending on which resource is used, the DDI information provided can be different. For instance, the ratings of DDI severity may be less

severe in the summary of product characteristics compared with postmarketing surveillance reports, or vice versa. The DDI reports in summaries of product characteristics were likely to be generated from randomized controlled trials and may not be completely representative of the general population. In contrast, a larger and more diverse segment of the general population is involved in postmarketing surveillance studies.^{22,23} Other contributory factors to the discrepancies are the possibility that both databases might have extrapolated the DDI of one co-prescribed drug to other drugs within the same class, based on different assumptions, and the nonstandardized method of classifying DDIs and assessing their clinical relevance.¹¹

The inconsistencies in the ratings of DDI severity by two different databases can result in several clinical implications. Health care professionals seeking information about a particular DDI may become confused upon their realization that there is a disagreement in the information provided by different databases. All databases or compendia should have similar DDI information to enable health care professionals to work more efficiently, without the need to search for additional information to clarify the discrepancies observed. This will save health care professionals time that could be spent with patients. Furthermore, the discrepancy in DDI listings can result in potential interactions occurring in patients if the DDIs are not identified in the particular database or compendium used by health care professionals. Such discrepancies may be detrimental, especially in HIV patients, because DDIs involving ARV drug and other drugs may result in increased risk of adverse drug toxicities. Therefore, it is very necessary to solve the problem of inconsistency on DDI listings and severity ratings among drug databases and compendia.

As a means of reducing discrepancies in the listing, categorization and severity rating of DDIs in various databases, Hazlet et al²⁴ have proposed precision analysis of the databases or compendia for sensitivity, specificity, positive, and negative predictive value. Other studies have suggested the use of user-friendly additional criteria to identify and classify DDIs,²⁵ and the use of a drug interaction probability scale to assess the DDIs and to assist health care professionals in the assessment of drug interaction-induced adverse outcomes.²⁶

The 189 (31.7%) DDIs rated as contraindications (category X) by the Medscape database (NVP + artemisinin-based combination therapy and EFV + artemisinin-based combination therapy), and the 45 (7.6%) DDIs rated as moderately significant interactions (LPVr + artemisinin/amodiaquine; LPVr + artemisinin-based combination therapy;

LPVr + proguanil; LPVr [solution] + metronidazole; and EFV + loratadine) that required therapy monitoring, were rated as category A by the MIMS database. However, a third database exclusively used for identifying drug interactions with ARV drugs (the Liverpool HIV Pharmacology Group website) corroborated the severity ratings of the category X and category C DDIs identified by the Medscape database. These findings therefore underscore the importance of using a third database where one of the two databases identifies a DDI as category A or X.

There are some limitations that characterized our study. Only two free drug online electronic databases were used to compile the DDI profiles. Although the results could have been different if other electronic software for DDI checking or compendia had been used, unfortunately, the widely used MICROMEDEX[®] and Lexicomp[®] software programs and the compendia were unavailable to us when the study was conducted. Relative to the wide range of ARV drugs available for HIV treatment, only a few ARV drugs were evaluated for DDIs in this study. This was as a result of the national treatment guideline that recommended the use of only the following ARV drugs: AZT; lamivudine; NVP; EFV; stavudine; ABC; ddI; LPVr; or saquinavir/ritonavir for children. Therefore, this study might not have captured the important potential DDIs that are associated with other ARV drugs.

Conclusion

Discrepancies occurred in DDI listings between the Medscape and the MIMS databases. Health care professionals may need to consult more than one DDI information database to ensure safe concomitant prescribing for HIV patients. Further studies should be conducted to create a standard evaluation tool or selection criteria to standardize the definitions and classifications of DDIs among databases commonly used to identify DDIs. As more ARV drugs are introduced into patients' therapy, clinically significant DDIs should be prevented or identified for the benefit of better care and medication safety for HIV patients.

Disclosure

The authors report no conflicts of interest in this work.

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