Prevalence of drug-drug interactions of antiretroviral agents in the private health care sector in South Africa

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Objectives. Human immunodeficiency virus (HIV) infection can be effectively treated with highly active antiretroviral therapy (HAART), requiring concomitant administration of three to four different agents, often with a high potential for drug-drug interactions (DDIs). This study aimed to determine the prevalence of possible DDIs between antiretrovirals (ARVs) themselves and other drugs.

Design. Retrospective drug utilisation study using data from a national medicine claims database for the period 1 January to 31 December 2004.

Setting. A section of the private health care sector in South Africa.

Subjects. All ARV prescriptions (*N*=43 482) claimed during 2004. The possible DDIs found were classified according to a clinical significance rating described by Tatro (2005) in his book *Drug Interaction Facts.*

Results. A total of 5 305 882 medicine items were prescribed; of these, 1.92% (*N*=101 938) were ARVs. Of the total number of 2 595 254 prescriptions, 1.68% (*N*=43 482) contained ARVs. A total number of 18 035 DDIs (81 different types) were identified; of these, 83.89% (*N*=15 130) were DDIs between ARVs and other drugs, while 16.11% (*N*=2 905) were DDIs between ARVs themselves. Possible DDIs with a clinical significance level of 1 (major, *N*=17) and 2 (moderate, *N*=1 436) represented 8.06% (*N*=1 453) of the total number of identified interactions.

Conclusions. Since concomitant use of ARVs and other drugs used to treat HIV complications is increasing, there is a need to understand and anticipate these DDIs and to overcome them by dose adjustments and patient education, so that they are not life threatening to HIV/AIDS patients.

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Human immunodeficiency virus (HIV) infection can now be effectively treated with the use of combination therapy, described as highly active antiretroviral therapy (HAART), requiring concomitant administration of three or four different agents, with a high potential for drug-drug interactions (DDIs)[1] and adverse drug reactions (ADRs).[2] HAART consists of a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one or two protease inhibitors (PIs), decreasing morbidity and mortality[3] from opportunistic infections and making HIV infection a chronic disease.

HIV-infected individuals usually have an impaired immune response, and frequently develop opportunistic infections, malignancies, co-morbidity such as drug dependence, psychiatric disorders, and neurological manifestations of HIV or hepatic diseases, treatment of which requires a wide variety of drugs.[4] Since both NNRTIs and PIs are extensively metabolised by the cytochrome P450 (CYP) system[5] there is considerable potential for pharmacokinetic interactions when these drugs are administered concomitantly with drugs metabolised via the same pathway.

The complexity of the drug regimen poses a significant challenge, in that there is a potential for a great number of DDIs. Antiretroviral (ARV) combinations can result in enhanced therapeutic efficacy, while others may augment the toxicity.[6] To help the patient safely and effectively navigate the array of doses and drugs, the HIV/AIDS care provider should therefore have a comprehensive understanding of the key issues affecting the pharmacokinetic and pharmacodynamic effects of drug therapy, thus minimising DDIs and ADRs.

The prevalence of DDIs in ARVs has not yet been investigated in depth in private health care settings in South Africa. The aim of this study was therefore to determine the prevalence of possible DDIs between ARVs themselves and other drugs on prescriptions claimed for the year 2004.

Methods

Study design

Permission to conduct the study was granted from Interpharm Datasystems and approved by the Research and Ethics Committees of North-West University, Potchefstroom campus, and Walter Sisulu University, Mthatha campus. This was a retrospective drug utilisation study done on ARVs claimed

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through a national medicine claims database for the period 1 January 2004 to 31 December 2004. During 2004, this medical scheme administrator administered data for 80 medical schemes. The focus of this study was on the prevalence of possible DDIs between ARVs themselves and other drugs on the same prescription. The possible DDIs found in this study were classified according to a clinical significance rating expressed as a number assigned to each DDI based on the severity and documentation of the interaction, as follows: 1 (major), 2 (moderate), 3 (minor), 4 (major/moderate) and 5 (minor/any), as described by Tatro.[7]

Three degrees of severity were identified, namely major, moderate and minor:[7]

- **Major effects** are potentially life threatening, capable of causing permanent damage, and necessitating additional treatment, hospitalisation or extension of hospital stay.
- **Moderate effects** may cause deterioration of a patient's clinical status, requiring additional treatment, hospitalisation or extension of hospital stay.
- **Minor effects** are usually mild, having bothersome or unnoticeable consequences but not significantly affecting the therapeutic outcome. Additional treatment is usually not required.

The following documentation levels can be distinguished, namely established, probable, suspected, possible and unlikely. The scale represents an evaluation of the quality and clinical relevance of the primary literature supporting the occurrence of an interaction.[7] Drug interactions assigned documentation levels of established, probable, or suspected are considered to be well substantiated and have significance ratings of 1, 2 or 3. These interactions are considered probable, while interactions of significance ratings 4 or 5 are not substantiated, having documentation levels of possible or unlikely.

Study population

The study population consisted of all ARV prescriptions (*N*=43 482) claimed during 2004.

Study protocol

The data consisted of ARV drug names and others prescribed on the same prescription. The ARVs were classified according to pharmacological groups as described in the *Monthly Index of Medical Specialties* (*MIMS*).[8] Drug interactions were detected using a previously developed computerised drug interaction database system.

According to the Medicines Control Council of South Africa,[9] 14 ARVs (NRTIs, NNRTIs and PIs) were registered during the period 1989 - 2004.

Statistical analysis

The data were obtained directly from the Interpharm Datasystems and analysed using the Statistical Analysis System, SAS 9.1.[10] There was no direct manipulation of the data by the researcher. Research was conducted on the assumption that all data obtained from the medicine claims database were correct and accurate. Data for the analysis were obtained from one medicine claims database, thus limiting external validity, and implying that results can only be generalised to the specific database used, as well as to the specific study population. No specific patient, medical practice, pharmacy or medical scheme could be identified; confidentiality of information was thus maintained throughout the study.

Results

A total of 5 305 882 medicine items were prescribed; of these, 1.92% (*N*=1 01 938) were ARVs. Of the total number of 2 595 254 prescriptions, 1.68% (*N*=43 482) contained ARVs. A total number of 18 035 DDIs (81 different types) were identified; of these, 83.89% (*N*=15 130) were DDIs between ARVs and other medications, while 16.11% (*N*=2 905) were DDIs between ARVs themselves. Possible DDIs with a clinical significance level of 1 (major, *N*=17) and 2 (moderate, *N*=1 436) represented 8.06% (*N*=1 453) of the total number of identified interactions. The frequencies of level 3 to 5 interactions were: 3 – *N*=1 221; 6.77%, 4 – *N*=6 678; 37.03%, and 5 – *N*=8 683; 48.14%. Level 1 interactions were between: (*i*) indinavir and lanzoprazole (*N*=3; 17.65%), omeprazole (*N*=2; 11.76%) and simvastatin (*N*=1; 5.88%); (*ii*) ritonavir and simvastatin (*N*=4; 23.53%), digoxin (*N*=5; 29.41%) and fentanyl (*N*=1; 5.88%); and (*iii*) saquinavir and fentanyl (*N*=1; 5.88%). The most prevalent (more than 100) level 2 DDIs between ARVs themselves were: indinavir and ritonavir (*N*=490), efavirenz and ritonavir (*N*=274), efavirenz and indinavir (*N*=198), didanosine and indinavir (*N*=121) and efavirenz and lopinavir/ritonavir (*N*=118), as set out in Table I. Level 2 interactions between ARVs and other drugs are set out in Table II.

Discussion

The aim of this study was to determine the prevalence of possible DDIs between ARVs themselves and other drugs on prescriptions claimed in a section of the private health care sector in South Africa. This study indicated that the prescriptions of ARVs accounted for 1.68% (*N*=43 482) of the total number of prescriptions (*N*=2 595 254) claimed from the database. Eighty-one different types of DDIs were identified; of these 83.89% (*N*=15 130) were DDIs between ARVs and other medications, and 16.11% (*N*=2 905) were between ARVs themselves. HIV-infected individuals usually receive a wide variety of drugs in addition to their ARV drug regimen. Since both NNRTIs and PIs are extensively metabolised by the cytochrome P450 system, there is a considerable potential for pharmacokinetic drug interactions when they are administered concomitantly with other drugs metabolised via the same pathway. In addition, PIs are substrates as well as inhibitors of the drug transporter plasma membrane glycoprotein (P-

Table I. Frequency of level 2 interactions between ARVs themselves

ARVs interacting between themselves	*N*	%*
Indinavir (PI) and ritonavir (PI)	490	36.95
Efavirenz (NNRTI) and ritonavir (PI)	274	20.66
Efavirenz (NNRTI) and indinavir (PI)	198	14.93
Didanosine (NRTI) and indinavir (PI)	121	9.13
Efavirenz (NNRTI) and lopinavir/ritonavir (PI)	118	8.90
Efavirenz (NNRTI) and saquinavir (PI)	1	0.08
Efavirenz (NNRTI) and saquinavir (PI)	1	0.08
Nevirapine (NNRTI) and lopinavir/ritonavir PI)	49	3.70
Nelfinavir (PI) and nevirapine (NNRTI)	2	0.15
Nevirapine (NNRTI) and saquinavir (PI)	5	0.38
Nevirapine (NNRTI) and ritonavir (PI)	3.39	
Indinavir (PI) and lopinavir/ritonavir (PI)	9	0.68
Indinavir (PI) and nevirapine (NNRTI)	13	0.98
Total	1 326	100.00

*Percentages were calculated according to the total number of interactions presented.
NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Table II. Frequency of level 2 interactions between ARVs and the other drugs

Interacting ARVs and other drugs	*N*	%*
Didanosine + ketoconazole	1	0.91
Didanosine + ofloxacin	1	0.91
Didanosine + ciprofloxacin	2	1.82
Didanosine + iraconazole	3	2.73
Didanosine + ketoconazole	2	1.82
Efavirenz + alprazolam	6	5.45
Efavirenz + methadone	4	3.64
Efavirenz + triazolam	4	3.64
Indinavir + fluconazole	7	6.36
Indinavir + itraconazole	7	6.36
Indinavir + ketoconazole	4	3.64
Lopinavir + fluconazole	2	1.82
Lopinavir + itraconazole	2	1.82
Lopinavir/ritonavir + alprazolam	1	0.91
Lopinavir/ritonavir + chlordiazepoxide	3	2.73
Lopinavir/ritonavir + diazepam	1	0.91
Lopinavir/ritonavir + fluconazole	15	13.64
Lopinavir/ritonavir + itraconazole	2	1.82
Ritonavir + alprazolam	3	2.73
Ritonavir + chlordiazepoxide	3	2.73
Ritonavir + diazepam	1	0.91
Ritonavir + fluconazole	16	14.55
Ritonavir + itraconazole	2	1.82
Ritonavir + fluoxetine	2	1.82
Ritonavir + piroxicam	2	1.82
Ritonavir + pravastatin	2	1.82
Ritonavir + zolpidem hemitartate	3	2.73
Saquinavir + chlordiazepoxide	2	1.82
Saquinavir + diazepam	1	0.91
Saquinavir + fluconazole	2	1.82
Saquinavir mesylate + fluconazole	2	1.82
Saquinavir mesylate + alprazolam	2	1.82
Total	110	100.00

*Percentages were calculated according to the total number of interactions presented.

gp) that can result in pharmacokinetic drug interactions. The NRTIs are predominantly excreted by the renal system and may give rise to interactions.[4]

Possible DDIs with a clinical significance level of 1 (*N*=17) and 2 (*N*=1 436) represented 8.06% (*N*=1 453) of the total number of possible interactions identified in this study. Level 1 interactions were between (*i*) indinavir and lanzoprazole, omeprazole and simvastatin; (*ii*) ritonavir and simvastatin, digoxin and fentanyl; and (*iii*) saquinavir and fentanyl.

Indinavir and ritonavir are PIs, inhibitors of the CYP 3A4 enzyme that is important for the metabolism of several drugs, which increases the probability of pharmacokinetic interactions between PIs and drugs taken concomitantly. The interaction between ritonavir and simvastatin is supported by Clotet and Negredo,[11] who report that PI administration may be associated with alterations in plasma lipids and insulin levels, placing some PI-treated patients at increased risk for coronary heart disease. Statins are an important component of pharmacotherapy for PI-associated dyslipidaemia, but, because all except pravastatin are metabolised by the CYP450 enzyme system, concomitant use of these agents produces a substantial risk of drug interactions and statin-induced hepatotoxicity and myopathy.[1] Fortunately new PIs are available that do not adversely affect plasma lipid levels.

Interactions between ritonavir and digoxin accounted for 29.41% (*N*=5) of possible level 1 DDIs in this study. Ritonavir has been reported to decrease total digoxin clearance at renal and non-renal levels,[12] and therapeutic doses of ritonavir also inhibits drug transport and metabolism in humans. Concomitant use of ritonavir with digoxin, a P-gp substrate, therefore requires major dose adjustments.

In this study interaction of ritonavir with fentanyl accounted for 5.88% (*N*=1) of possible level 1 reactions. Among HIV PIs, ritonavir is the most potent inhibitor of CYP3A4. Fentanyl, a synthetic opioid analgesic is metabolised mainly by CYP3A4. A study[13] revealed that ritonavir profoundly affected the pharmacokinetics of fentanyl, reducing its clearance by 67% and increasing and prolonging fentanyl-induced respiratory depression. It is therefore advisable to maintain respiratory monitoring for longer than usual in patients on these two drugs.

Combinations of ARVs are being used to augment and prolong their virological and immunological benefits, and also to delay the emergence of resistance. ARVs, especially the PIs, have a strong potential to interact with each other. In particular, the NNRTIs metabolised by CYP3A4 have shown to interact with PIs, which are inhibitors of CYP3A4, especially ritonavir, a potent inhibitor. In our study interactions between indinavir and ritonavir accounted for 36.95% (*N*=490) of possible level 2 DDIs between ARVs themselves. Administration of ritonavir improves the bioavailability and prolongs the elimination half-life of indinavir, reducing the total dose necessary to achieve a potent ARV plasma concentration. It is therefore recommended that patients be closely monitored so that the dose can be adjusted when necessary.

This study revealed a possible DDI between ritonavir and efavirenz, with a prevalence of 20.66% (*N*=274) of possible level 2 DDIs between ARVs themselves. An interaction between ritonavir and efavirenz has been reported[13] in 20 healthy volunteers who received efavirenz 200 mg daily and ritonavir up to 600 mg twice daily. With this combination, the area under the curve (AUC) for efavirenz increased by 21% and that for ritonavir by 17%, leading to the conclusion that if patients experience intolerance to ritonavir while on efavirenz, the ritonavir dosage could be reduced to 500 mg twice daily.

Interactions between efavirenz and indinavir accounted for 14.93% (*N*=198) of possible level 2 DDIs between ARVs themselves in our study. This finding is supported by a study[14] reporting that the addition of efavirenz to a combination of 800 mg indinavir and 100 mg ritonavir twice daily resulted in significant decreases in AUC, C_{max}, and especially C_{min} of indinavir. Efavirenz is a potent inducer of CYP3A4, suggesting a potential interaction between this NNRTI and PIs that inhibit CYP3A4. It is recommended that the dose of indinavir or ritonavir be increased to maintain indinavir drug levels when efavirenz is added to the indinavir-ritonavir combination.

Interactions of didanosine with indinavir accounted for 9.13% (*N*=121) of possible level 2 DDIs between ARVs themselves in our study. Various combinations of NRTIs and PIs are acceptable as HAART: to overcome the induction of PI metabolism by the NRTIs, administration of indinavir and didanosine separately at least 1 hour apart on an empty stomach is therefore recommended.

Drugs used to treat opportunistic infections could influence the occurrence of ADRs to ARVs. In this study the azoles (ketoconazole, fluconazole and itraconazole), used to treat fungal infections, interacted with PIs at level 2. A patient taking ritonavir 600 mg twice daily and saquinavir 400 mg twice daily is reported to have developed symptoms of PI toxicity 1 week after itraconozole was increased from 100 mg to 200 mg twice daily,[15] and 2 of 4 patients receiving indinavir developed hyperbilirubinaemia and slightly elevated transaminase levels while on itraconazole. Levels returned to pretreatment values after discontinuing itraconazole. Fluconazole is a less potent inhibitor of CYP3A4, so may be a better tolerated alternative.

The PIs in this study interacted with benzodiazepines at level 2. Large increases in serum concentrations of benzodiazepines undergoing oxidative metabolism due to inhibition of hepatic metabolism (CYP3A4) may cause severe sedation and respiratory depression. Prolonged sedation was reported in a 32-year-old patient receiving intravenous midazolam for bronchoscopy after administration of saquinavir but not after midazolam alone.[16] Co-administration of PIs with benzodiazepines is therefore contraindicated.

Conclusion

In this study DDIs have been identified between ARVs themselves and between ARVs and other drugs. Managing these DDIs is one of the major challenges associated with the multidrug regimens used for HIV therapy. Some of these DDIs can be overcome by dose adjustments and by advising the patient to take some drugs separately. Other DDIs are not considered clinically life threatening.

Limitations of the study

The followings should be taken into consideration when evaluating these results.

- Only the prescription data were available to the researchers. It was not possible to gain any demographic or clinical information on the patients.
- The clinical relevance of the identified DDIs was evaluated according to criteria stated in the literature. No clinical evaluation of the real effects of these interactions was possible. However, the results emphasised the possibility of DDIs that could have led to severe problems. Further research into the usage of ARVs in the private health care sector should therefore be conducted in South Africa.
- Various combinations of NNRTIs and PIs are acceptable as HAART, with dosage adjustments of PIs, but in this study dosage adjustments were not investigated; we therefore recommend that further studies be done.

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