



Are antiretrovirals prescribed according to the recommended prescribed daily doses in the private healthcare sector in South Africa

Authors:

Norah L. Katende-Kyenda¹
Martie Lubbe²
Juan H.P. Serfontein²
Ilse Truter³

Affiliations:

¹Department of
Pharmacology, Walter Sisulu
University, South Africa

²Pharmacy Practice, North-
West University, South Africa

³Pharmacy Practice, Nelson
Mandela Metropolitan
University, South Africa

Correspondence to:

Norah Katende-Kyenda

Email:

nkyenda1@gmail.com

Postal address:

Private Bag X1, Mthatha,
Eastern Cape, South Africa

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Current antiretroviral treatment (ART) guidelines recommend different combinations that have led to major improvements in the management of HIV and AIDS in the developed and developing world. With the rapid approval of many agents, health care providers may not be able to familiarise themselves with them all. This lack of knowledge leads to increased risk of dose-prescribing errors, especially by non-HIV and AIDS specialists. The purpose of this retrospective non-experimental, quantitative drug utilisation study was to evaluate if antiretrovirals (ARVs) are prescribed according to the recommended prescribed daily doses (PDDs) in a section of the private health care sector in South Africa (SA). Analysed ARV prescriptions (49995, 81096 and 88988) for HIV and AIDS patients were claimed from a national medicine claims database for the period 1 January 2005 through to 31 December 2007. ARV prescriptions prescribed by general practitioners (GPs) with PDDs not according to the recommended ARV dosing increased dramatically, from 12.33% in 2005 to 24.26% in 2007. Those prescribed by specialists (SPs) increased from 15.46% in 2005 to 35.20% in 2006 and decreased to 33.16% in 2007. The highest percentage of ARV prescriptions with PDDs not according to recommended ARV dosing guidelines was identified in ARV regimens with lopinavir-ritonavir at a PDD of 1066.4/264 mg and efavirenz at a PDD of 600 mg prescribed to patients in the age group of Group 3 (19 years > age ≤ 45 years). These regimens were mostly prescribed by GPs rather than SPs. There is a need for more education for all health care professionals and/or providers in the private health care sector in SA on recommended ARV doses, to avoid treatment failures, development of resistance, drug-related adverse effects and drug interactions.

Huidige riglyne vir behandeling met antiretrovirale middels beveel verskillende kombinasies aan wat tot groot verbetering in die beheer van MIV en VIGS in die ontwikkelde en ontwikkelende wêreld gelei het. Met die vinnige goedkeuring van talle nuwe middels kan dit gebeur dat verskaffers van gesondheidsorg nie kan bybly om hulle hiermee op hoogte te hou nie. Hierdie gebrek aan kennis lei tot 'n hoër risiko vir foute in die voorgeskrewe dosis en veral deur persone wat nie spesialiste in MIV en VIGS is nie. Die doel van hierdie nie-eksperimentele, retrospektiewe, kwantitatiewe studie van die gebruik van geneesmiddels was om te bepaal of antiretrovirale middels in 'n deel van die privaat gesondheidsorgsektor in Suid-Afrika (SA) volgens die aanbevole voorgeskrewe daaglikse dosisse (VDD) voorgeskryf word. Voorskrifte van antiretrovirale middels (49995, 81096 en 88988) aan pasiënte met MIV en VIGS wat in die periode van 1 Januarie 2005 tot 31 Desember 2007 van 'n nasionale medisyne databasis geëis is, is ontleed. Voorskrifte van antiretrovirale middels deur algemene praktisyns (APs) met VDDs wat nie volgens die aanbevole dosisse vir antiretrovirale middels was nie, het dramaties van 12.33% in 2005 tot 24.26% in 2007 toegeneem. Die wat deur spesialiste (SPs) voorgeskryf is, het van 15.46% in 2005 tot 35.20% in 2006 toegeneem en in 2007 tot 33.16% gedaal. Die hoogste persentasie van voorskrifte vir antiretrovirale middels met VDDs wat nie volgens die riglyne was nie, was in die regimens met lopinavir-ritonavir met 'n VDD van 1066.4/264 mg en efavirens met 'n VDD van 600 mg wat aan pasiënte in die ouderdomsgroep van ouer as 19 tot en met 45 jaar voorgeskryf is. Hierdie regimens is meer deur APs as deur SPs voorgeskryf. Daar is 'n behoefte aan nog opleiding van alle gesondheidsprofessies en/of voersieners in die privaat gesondheidsorgsektor in SA oor die aanbevole antiretrovirale middel-dosisse om mislukking van behandeling, ontwikkeling van weerstand, nadelige effekte vanweë geneesmiddels en geneesmiddel interaksies te voorkom.

Introduction

Background

HIV and AIDS (human immunodeficiency virus and acquired immune deficiency syndrome) is a disease progression continuum, from testing HIV positive to having AIDS-defining illnesses such as pneumocystis *carinii*, opportunistic infections and 'signs of wasting syndrome' (Ward &



Kim 1999:50–51). The causative organism of AIDS is HIV that belongs to a group of retroviruses, a subgroup of lentoviruses that replicate slowly whilst they destroy the victim's CD4 lymphocytes, making the person susceptible to opportunistic infections (Ward & Kim 1999:50–51). Antiretroviral (ARV) drugs have revolutionised HIV-infected patients' prognosis. ARVs do not cure HIV and AIDS but are used to suppress the replication of HIV to levels undetectable in the blood, and also help to increase the number of CD4 cells in the blood (Ward & Kim 1999:68–69).

Although there have been numerous beneficial effects of antiretroviral therapy (ART), new problems have emerged which include poor patient adherence to their ARV regimens, drug interactions, drug-related adverse effects and virus resistance (Tourret *et al.* 2007:779). As a result of ART, HIV-infected patients live longer. ARV prescriptions have become increasingly complex, leading to a number of prescription errors. In one study the rate of prescription error increased from 2% to 12% in infected hospitalised patients as new classes of ARVs became available, the most common errors being overdosing and underdosing (Purdy *et al.* 2000:833). DeLorenze, Follansbee and Nguyen (2005:63) in their study on ARV drug prescription errors amongst outpatients confirmed the incidence of dosing errors to be 9.8 errors per 100 prescriptions. It was further confirmed that patients in the age group of older than 19 years to 45 years were at a higher risk of receiving an erroneous dose compared to patients in other age groups.

The World Health Organisation (WHO) estimated that of the 38.6 million people living with HIV and AIDS worldwide (Johansson 2007:1614), the 4.7 million living in sub-Saharan Africa urgently needed ART (United Nations programme for HIV and AIDS (UNAIDS)/WHO 2007). In 2007 South Africa (SA) had about 5 million people infected with HIV and AIDS which, according to the UNAIDS, was the highest number in any country (UNAIDS/WHO 2007). SA had prescribed minimum benefits for HIV and AIDS implemented in the private health care sector in 2005 (Erasmus 2007:777).

Despite the increased availability and affordability of ART, the proportion of HIV-positive people in SA eligible and receiving treatment is low (Johnson 2006). In mid-2005 an estimated 60 000 people were receiving ART through medical schemes and community treatment programmes (Johnson 2006).

Current ART guidelines recommend different combinations, that have led to major improvements in the management of HIV and AIDS in the developed and developing world (Arshad *et al.* 2009). With the rapid approval of many new agents, health care providers may not be able to familiarise themselves with them all, and this leads to increased risk of dose-prescribing errors, especially by non-HIV and AIDS specialists (Purdy *et al.* 2000: 834). These errors can also occur at levels of dispensing by pharmacists and nurses and/or

self-administration by patients themselves due to inadequate accessibility of prescriber's information, complicated regimens, and incorrect reporting by the patient (Heelon *et al.* 2007:2064). Medication-prescribing errors associated with highly active antiretroviral therapy (HAART) may lead to treatment failure and are multifactorial. Therefore health care professionals and providers caring for HIV-infected patients should be aware of dose-prescribing errors and employ strategies to prevent them.

Guidelines for the use of ARVs in adults and adolescents infected with HIV-1 were formulated by both the South African HIV Clinicians Society (SAHIVCS 2009) and the National Department of Health (NDoH) and Human Services expert panel (DHHS 2008). ART refers to the ARV doses, frequencies and food restrictions prescribed for individual patients. In this study we only looked at the ARV doses. In SA both public and private sector patients commence ART if their CD4 counts are below 350 cells/mm³ or at WHO stage 4 or if they have AIDS-defining illnesses such as wasting syndrome, recurrent severe bacterial infections, encephalopathy or tumours (Anabwani & Jimbo 2005:5).

The private health care environment recommends the Aid for Aids (AfA) ART guidelines (AfA 2009), which are similar to those of the SAHIVCS, as shown in Table 1.

Problem statement

Aims and objectives of the study

Despite increased availability and affordability of ART in SA patients might not achieve maximum therapeutic goals. Incorrect prescribed daily doses (PDDs) of ARVs could result in ART-resistant strains of HIV, leading to poorer therapeutic outcomes at vastly more expense and with more side-effects than those from the initial ART guidelines (Heelon *et al.* 2007:2064). According to the WHO, PDDs are defined as the average doses prescribed according to a representative sample of prescriptions (WHO 2003). Therefore correct PDDs are beneficial to the individual patients, their communities and the country at large.

In this study PDDs were evaluated to see if they were adhering to recommended AfA ARV dosing. It is important that the PDD be related to the diagnosis made for the prescribed medication. In this study the reference guides used to evaluate PDDs were according to the recommended ARV-dosing guidelines. The research problem was thus to evaluate whether ARV prescriptions were prescribed according to the recommended AfA ARV dosing guidelines.

The purpose of the study was to evaluate whether ARV prescriptions by general practitioners (GPs) and specialists (SPs) were according to the recommended AfA ARV dosing, and to identify which regimens presented the most incorrect PDDs and in which age group of patients. The research question was: Are antiretroviral drugs prescribed according to the recommended ARV-dosing AfA guidelines?



The above recommended ARV combinations and their PDDs according to AfA guidelines were for 2009 when the study was done. There are new AfA guidelines for 2010 and 2011.

To start ART the patient must be ready for treatment and have a WHO stage four or two CD4 blood counts lower than 350 cells/mm³ done at least six weeks apart (AfA 2009). Certain disease management programmes in the private sector in SA use the initiation criteria for ART in children as shown in Table 2. In this study CD4 cell and viral load counts were not analysed, due to their unavailability from the PBM company database.

The recommended ART regimens in children are as follows:

For infants: Either 2 nucleoside reverse transcriptase inhibitors (NRTIs) + 1 protease inhibitor (PI) (lopinavir-ritonavir) or 2 NRTIs + 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) (nevirapine) (not to be used if mother or infant received single-dose nevirapine as part of the strategy to prevent mother-to-child transmission).

For children: Either 2 NRTIs + PI (lopinavir-ritonavir) or NRTI + NNRTI (efavirenz or nevirapine) as recommended by the NDoH (2005).

Significance of the study

Advances and efforts made in treating HIV infection over the past years led to a decline in the morbidity and mortality associated with HIV and AIDS (Palella *et al.* 1998:853). ARVs have transformed HIV and AIDS from a life-threatening condition to a chronic disorder that can be effectively managed, resulting in delayed disease progression, improved survival and decreased hospitalisation for the HIV-infected patient (Wong 2008:117). Providing ART to HIV patients in SA might, however, have a limited impact on the development of the HIV and AIDS epidemic unless ARVs are prescribed and administered according to the recommended ARV dosing guidelines.

The influence of the prescriber on the prevalence of ARV prescriptions with incorrect PDDs has not been studied in the

private sector in SA. The study evaluated whether GPs' and SPs' ARV prescriptions were according to the recommended AfA ARV dosing. Addressing this challenge could help achieve patients' adherence to ARV regimens and impact on virus resistance, drug interactions and drug-related adverse effects.

Research methods and design

Design

A retrospective quantitative drug utilisation study was performed on data obtained from a South African PBM company which manages the medicine benefits of medical schemes in a section of the private health care sector. Data were selected for three years, from 1 January 2005 to 31 December 2007.

Population and sample

The total database consisted of 8 506 355 (2005), 9 029 912 (2006) and 8 015 538 (2007) prescriptions prescribed to 1 218 358 (2005), 1 259 099 (2006) and 911 212 (2007) patients. This study was performed on 49 995 (2005), 81 096 (2006) and 88 988 (2007) ARV prescriptions for 7664 (2005), 10 162 (2006) and 10 061 (2007) HIV and AIDS patients. There were five age groups assessed in this study: 0 years ≤ Group 1 ≤ 12 years; 12 years > Group 2 ≤ 19 years; 19 years > Group 3 ≤ 45 years; 45 years > Group 4 ≤ 59 years; and Group 5 > 59 years. Prescribers of ARV prescriptions were divided into GPs and SPs.

Data collection methods

Data were obtained directly from the central database of a South African PBM company; therefore there was no direct manipulation of the data during the data analysis process, it was assumed that all data obtained were correct and accurate.

Data analysis

Data were analysed using the Statistical Analysis System® SAS for Windows 9.1® (SAS Institute 2006–2007). Basic

TABLE 1: Recommended antiretrovirals combinations and their prescribed daily doses (AfA 2009).

PIs	Dose for PI-naïve†		Dose for PI-experienced‡	
	Nevirapine	Efavirenz	Nevirapine	Efavirenz
Atazanavir-ritonavir	Not recommended	400/100 mg once a day	Not recommended	400/100 mg
Darunavir-ritonavir	800/100 mg once a day	800/100 mg once a day	600/100 mg twice a day	600/100 mg twice a day
lopinavir-ritonavir	800/200 mg once a day	800/200 mg once a day	600/150 mg twice daily	600/150 mg twice daily
Saquinavir-ritonavir	500/100 mg twice a day	500/100 mg twice a day	1600/100 mg once a day	1600/100 mg once a day

Source: (AfA, 2009)

†, 'Protease inhibitor (PI)-naïve' is a term used to describe HIV-infected individuals who have never taken or who have not previously been exposed to anti-HIV drugs. 'PI-experienced' is a term used to describe HIV-infected individuals who are currently being treated with anti-HIV drugs or who have taken anti-HIV drugs in the past.

TABLE 2: CD4 criteria for initiation of antiretroviral treatment in children in the private sector (AfA 2009).

Criteria	Age group			
	< 12 months	12 - 35 months	36 - 59 months	5 years and over
CD4 (%)	All	< 20	< 20	<15
Absolute CD4 count (cells/mm ³)	-	< 750	< 500	< 350

Source: (AfA 2009)



descriptive statistics, i.e. frequencies, the arithmetic mean (average) and standard deviations were used to characterise the study sample and calculations.

Classification system used for ARVs

ARV drug names were classified according to the pharmacological groups as described in the *Monthly Index of Medical Specialities* (MIMS) (Snyman 2009:359) as well as in the Regulations to the Medicine and Related Substances Act (Act 101 of 1965). The study evaluated potential PDDs in ARV prescriptions that were not according to recommended ARV dosing, in relation to the total number of patients and the five age groups mentioned above.

Results

ARV prescriptions

ARV prescriptions represented 0.59% ($n = 49\ 995$) of all prescriptions claimed during 2005 ($N = 8\ 506\ 355$), 0.90% ($n = 81\ 096$) of ($N = 9\ 029\ 912$) claimed during 2006 and 1.11% ($n = 88\ 988$) of ($N = 8\ 015\ 535$) claimed for 2007. It was observed that in the three years studied, GPs prescribed more ARV prescriptions than SPs, and these increased from 2005 to 2007 (Table 3). The highest percentage of ARV prescriptions for both GPs and SPs was observed for those with three ARV items, followed by those with two ARV items. Drug item (medicine item) is defined according to the Medicines and Related Substances Control Act of 1965, Act 101 of 1965 as amended (1965) as a 'substance intended for use in the diagnosis, cure, mitigation, treatment, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man'. In this research the words 'drug items' are used interchangeably with the words 'medicine items'. In the South African context a prescription can consist of one or more medicine items (or drugs). No practical significant differences were found between the average numbers of ARV medicine items per prescription ($d < 0.8$) claimed per year for the different years.

ARV prescriptions with incorrect PDDs

Prescriptions by SPs and GPs with PDDs not according to the recommended ARV dosing according to patients' age for the three years of the study are shown in Tables 4 and 5. Of the total number of ARV prescriptions ($n = 778$) claimed during 2005, 12.72% ($n = 99$) had PDDs not according to the recommended ARV dosing (DHHS 2008; AfA 2009) for different age groups. In 2006 the total number of ARV prescriptions ($n = 1155$) with PDDs not according to the recommended ARV dosing

(DHHS 2008; AfA 2009) increased dramatically to 21.47% ($n = 248$). The same trend was experienced during 2007 (25.74%; $n = 1177$).

For 2005 a higher percentage (15.46%) of ARV prescriptions prescribed by SPs (15.46%; $n = 97$) had incorrect PDDs compared to those prescribed by GPs (12.33%, $n = 681$). For year 2006, of the total number of ARV prescriptions ($n = 976$) prescribed by GPs, 18.75% or 183 had incorrect PDDs. A much higher percentage (35.20%, $n = 63$) of ARV prescriptions prescribed by SPs ($n = 179$) had PDDs not according to the recommended ARV dosing. For 2007, of the total number of ARV prescriptions by GPs ($n = 981$), those with incorrect PDDs accounted for 24.26% ($n = 238$), compared to a higher prevalence of 33.16% ($n = 65$) of ARV prescriptions with PDDs prescribed by SPs ($n = 196$).

ARV combinations with incorrect PDDs

It should also be noted in Tables 4 and 5 that for the three years the highest numbers of incorrect PDDs were identified in ARV combinations of lopinavir-ritonavir at PDD 1066.4/264 mg, with efavirenz at PDD 600 mg and nevirapine at PDD 400 mg. This was followed by indinavir 1600 mg with ritonavir 800 mg; ritonavir 600 mg with efavirenz 600 mg; saquinavir 800 mg with efavirenz 800 mg for both GPs and SPs, with the highest number of prescriptions prescribed by GPs to patients in the age group of Group 3, followed by patients in age group of Group 4. The highest number of ARV prescriptions with PDDs not according to recommended ARV dosing were for patients in the age group older than 19 years up to and including 45 years.

Ethical considerations

No specific patient, medical practice, pharmacy or medical scheme could be identified; thus confidentiality of information was maintained throughout the study. Permission to conduct the study was granted by the PBM company and approval was obtained from the Research and Ethics Committees of North-West University, Potchefstroom campus (ethical number 07M01) and Walter Sisulu University Mthatha campus.

Reliability and validity

The data for the study were obtained directly from the database and there was thus no direct manipulation of the data by the researcher. Data were obtained for a three-year

TABLE 3: Comparison of number of antiretrovirals prescriptions with potential drug-drug interactions, antiretroviral prescriptions with drug-drug interactions and inappropriate prescribed daily doses.

Year	ARV prescriptions with potential DDIs (level 2)				ARV prescriptions with DDIs and PDDs not according to recommended ARV dosing			
	GPs		SPs		GPs		SPs	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
2005	681	25.8	97	20.6	84	16.6	15	10.5
2006	976	37.0	179	37.9	183	36.3	63	44.0
2007	981	37.2	196	41.5	238	47.1	65	45.5
Total	2638	-	472	-	505	-	143	-

Source: Author's original data
n, given as means of number; DDI, drug-drug interaction; GPs, general practitioners; SPs, specialists.



TABLE 4a: Number of antiretroviral prescriptions prescribed by specialists not according to the recommended antiretroviral dosing and age group.

Age group (years)	Number of prescriptions		
	2005 (n = 97)	2006 (n = 179)	2007 (n = 196)
Group 3	6	25	23
	2	-	-
	1	-	-
	2	16	16
	2	-	-
	1	-	-
	1	-	-
Group 4	-	22	22
	-	-	3
Group 5	-	-	1
Total	15	63	65

Source: Author's original data

n, given as means of number; Group 3, (19 years > age ≤ 45 years); Group 4, (45 years > age ≤ 59 years); Group 5, (59 years > age).

period thus limiting external validity, implying that the results can only be generalised to the specific database used as well as to the specific study population from 2005 to 2007.

Discussion

Outline of the results

The aim of the study was to evaluate ARV prescriptions and their PDDs with specific reference to prescriber and age group in a section of the private health care sector in SA.

From the results it is evident that the percentage of ARV prescriptions that were claimed increased from year 2005 to 2007. This is supported by a WHO/UNAIDS press release in 2006 that the number of HIV-infected receiving treatment in sub-Saharan Africa was steadily increasing (WHO/UNAIDS 2005). It was also observed that most of the ARV prescriptions by GPs and SPs had two and three ARV items, supported by the fact that combination ARV regimens (especially those containing HIV type-1 PIs) provide clinical benefits achieving long-term virus suppression. Furthermore, the clinical value of triple-combination ART has been established by a number of large randomised controlled trials, showing striking improvements in disease markers (e.g. viral load, CD4 cell count) and improved survival and diminished disease progression relative to single- and double-agent therapy

(Erasmus 2007:777). According to AfA clinical guidelines, monotherapy is not recommended; it should only be used for prophylaxis (AfA 2009).

It was also noted that patients in age group (Group 3) in all three years presented the highest number of ARV prescriptions followed by patients (Group 4). A study performed in rural SA, in KwaZulu-Natal, the province with highest HIV and AIDS prevalence confirmed that the prevalence of HIV in adults (15–54 years) had reached 23% in 2003/2004, with 27% of resident women (15–49 years) and 14% of resident men (15–54 years) (Welz *et al.*, 2007:1467).

It is noted that ARV regimens most identified with PDDs not according to the recommended ARV dosing were between lopinavir–ritonavir (PI) and efavirenz (NNRTI), lopinavir–ritonavir with nevirapine (NNRTI), ritonavir (PI) with efavirenz, indinavir (PI) with ritonavir, saquinavir (PI) with efavirenz and saquinavir with ritonavir.

Because the pharmacokinetic profiles, side-effects and therapeutic outcomes of patients were not reported, this is a major limitation of the PBM database. It could be assumed that prescribers were not aware that the two regimens: PIs and NNRTIs presenting drug-drug interactions are the major causes of adverse drug reactions, so this caused prescribers to adjust the PDDs that were inappropriate. Studies performed by Seden, Back and Khoo (2009:5), Miller *et al.* (2007:1379) and Malaty and Kuper (1999:147) stated that all PIs and NNRTIs are predicted to have numerous drug-drug interactions because these are metabolised by the cytochrome P450 system and are also inhibitors of CYP3A4.

As observed in Tables 4a, 4b and 5a, 5b, the most commonly prescribed ARV drug was co-formulated lopinavir–ritonavir, the first and only co-formulated HIV-1 PI. It was reported in a review that large clinical trials have demonstrated lopinavir–ritonavir clinical efficacy in both ARV-naïve and –experienced patients (De Maat *et al.*, 2003:223). The immunological and virological benefits of treatment with this agent have been proved in HIV-infected adults, adolescents and children (NDoH 2005).

TABLE 4b: Prescribed daily doses not according to the recommended antiretroviral dosing and age group as prescribed by specialists.

Age group (years)	Specialists			
	ARV combinations with average PDD		ARV combinations with average PDD	
	Medicine item	PDD	Medicine item	PDD
Group 3	Lopinavir–ritonavir	1066.4/264 mg	Efavirenz	600 mg
	-	1142.6/282 mg	-	600 mg
	-	3999/990 mg	-	1200 mg
	Lopinavir–ritonavir	1066.4/264 mg	Nevirapine	400 mg
	-	799.8/198 mg	-	500 mg
	Indinavir	800 mg	Ritonavir	1200 mg
	Indinavir	1600 mg	Efavirenz	1200 mg
Group 4	Lopinavir–ritonavir	1066.4/264 mg	Efavirenz	600 mg
	Lopinavir–ritonavir	1066.4/264 mg	Nevirapine	400 mg
Group 5	Lopinavir–ritonavir	3999.9/990 mg	Efavirenz	600 mg

Source: Author's original data

ARV, antiretroviral; PDD, prescribed daily doses; Group 3, (19 years > age ≤ 45 years); Group 4, (45 years > age ≤ 59 years); Group 5, (age > 59 years).



TABLE 5a: Number of antiretroviral prescriptions prescribed by general practitioners not according to the recommended antiretroviral dosing and age group.

Age group (years)	Number of prescriptions by years		
	2005 (n = 681)	2006 (n = 976)	2007 (n = 981)
Group 1	8	6	6
	-	-	9
	4	3	-
Group 3	30	101	145
	-	26	-
	1	-	-
	-	-	3
	15	-	8
	1	-	-
	-	1	-
	-	2	-
	-	-	9
	1	-	-
	-	3	-
	1	-	-
	2	-	-
	-	14	2
	1	-	-
	-	-	18
Group 4	16	11	17
	-	7	-
	1	-	-
	-	-	13
Group 5	3	-	-
	-	-	8
	-	9	-
	-	2	-
Total	84	185	238

Source: Author's original data
n, given as means of number; Group 1, (0 years > age ≤ 12 years) Group 3, (19 years > age ≤ 45 years); Group 4, (45 years > age ≤ 59 years); Group 5, (59 years > age).

Results obtained for the three years of study for both GPs and SPs prescribing ARV regimens with incorrect PDDs are shown in Tables 4 and 5. As observed for the three years, GPs prescribed lopinavir–ritonavir for patients in the age group of Group 1. One of the limitations of this study was that the weights of children were not available; therefore it was not clear to which patients' weight and specific age this co-formulation was prescribed. Otherwise the safety, efficacy and pharmacokinetic profiles of lopinavir–ritonavir in paediatric patients below the age of 6 months have not been established. It was assumed that patients were older than 6 months who received 20 prescriptions for lopinavir–ritonavir 800/200 mg and efavirenz 200 mg; lopinavir–ritonavir 320/80 mg and nevirapine 2600 mg (n = 7) and lopinavir–ritonavir 640/160 mg; with efavirenz 350 mg (n = 9).

According to the SA treatment guidelines for the management of HIV-infected children (NDoH 2005) the recommended paediatric dose for lopinavir–ritonavir is <15 kg + 12 mg lopinavir/kg and ≥15 kg = 10 mg lopinavir/kg twice daily. In this case lopinavir–ritonavir was prescribed in a higher PDD considering one capsule of lopinavir–ritonavir to be 133.3/33.3 mg, and the maximum dose should be three capsules (399.9/99.9 mg) (NDoH 2005). If given in higher PDDs the patient can experience side-effects like diarrhoea, nausea, vomiting, hyperlipidaemia and glucose intolerance. Neither details of change in doses of ARVs nor side-effects experienced by patients were provided in the database; this was a limitation of this study as key confounding variables were not available.

TABLE 5b: Prescribed daily doses not according to the recommended antiretroviral dosing and age group as prescribed by general practitioners.

Age group (years)	General practitioners			
	ARV combinations with average PDD		ARV combinations with average PDD	
	Medicine item	PDD	Medicine item	PDD
Group 1	Lopinavir–ritonavir	800/200 mg	Efavirenz	200 mg
	-	640/160 mg	Efavirenz	350 mg
	-	320/80 mg	Nevirapine	2600 mg
Group 3	Lopinavir–ritonavir	1066.4/264 mg	Efavirenz	600 mg
	-	1066.4/264 mg	-	400 mg
	-	4500/3999 mg	-	1800 mg
	-	1599.6/264 mg	-	600 mg
	Lopinavir–ritonavir	1066.4/264 mg	Nevirapine	400 mg
	-	1066.4/264 mg	-	500 mg
	-	1244/308 mg	-	400 mg
	-	799.8/198 mg	-	1600 mg
	-	799.8/198 mg	-	500 mg
	Ritonavir	300 mg	Efavirenz	1800 mg
	-	600 mg	-	600 mg
	Indinavir	2400 mg	Ritonavir	3000 mg
	-	800 mg	-	800 mg
-	1600 mg	-	800 mg	
Indinavir	2400 mg	Efavirenz	1800 mg	
Saquinavir	800 mg	Efavirenz	800 mg	
Group 4	Lopinavir–ritonavir	1066.4/264 mg	Efavirenz	600 mg
	-	1066.4/264 mg	Efavirenz	400 mg
	Lopinavir–ritonavir	1066.4/264 mg	Nevirapine	500 mg
	Saquinavir	800 mg	Ritonavir	800 mg
Group 5	Lopinavir–ritonavir	1066.4/264 mg	Nevirapine	400 mg
	-	-	-	500 mg
	Lopinavir–ritonavir	1066.4/264 mg	Efavirenz	400 mg
	-	1066.4/264 mg	-	500 mg

Source: Author's original data
ARV, antiretroviral; PDD, prescribed daily doses; Group 1, (0 years > age ≤ 12 years) Group 3, (19 years > age ≤ 45 years); Group 4, (45 years > age ≤ 59 years); Group 5, (age > 59 years).



In this study nevirapine was also prescribed at a higher dose of 2600 mg to patients in Group 1 for the years 2005 and 2006. The recommended paediatric dose for nevirapine is 10 mg/ml or 200 mg tablet as an initial dose and 4 mg/kg once daily for 14 days followed by a maintenance dose of 7 mg/kg twice daily for children <8 years old, or 4 mg/kg twice daily for children >8 years old (NDoH 2005). At such a high dose the patient may experience adverse effects like rash including Stevens-Johnson syndrome, and symptomatic hepatitis including fatal hepatic necrosis.

Results from this study demonstrated that GPs prescribed lopinavir-ritonavir at higher PDDs of 1066.4/264 mg; 4500/3999 mg; and 1599.6/264 mg to patients patients in Group 3 for the three years studied. The standard adult dose for lopinavir-ritonavir is 400/100 mg (two tablets or 5 ml) twice daily or 800/200 mg (four tablets or 10 ml) once daily. Another limitation of this study was that information about ARV-naïve or ARV-experienced patients was not available from the PBM database. Otherwise once-daily dosing for lopinavir-ritonavir is only recommended for treatment-naïve patients, not for those receiving efavirenz, nevirapine or nelfinavir.

When lopinavir-ritonavir is given with efavirenz or nevirapine the recommended dose for treatment-experienced patients is 600/150 mg (three oral tablets twice daily) or 533/133 mg (6.7 ml oral solution) twice daily with food (Purdy *et al.* 2009 & NDoH 2005).

It was also revealed that other ARV regimens with incorrect PDDs were ritonavir and indinavir, efavirenz, and saquinavir. Ritonavir, a PI, is used as a booster in ARV combination therapy. The concurrent administration of ritonavir markedly inhibits CYP3A4 with another PI like saquinavir substantially increasing plasma concentrations of saquinavir, thus reducing the adverse effects. This means there is less frequent and thus more convenient dosing, with fewer tablets and food restrictions which, in turn, may enhance patient adherence and higher plasma PI levels, with the potential to overcome viral resistance to the PI (Murphy *et al.* 2008:1).

It was observed in this study that ritonavir was given with other PIs in PDDs of 3000 mg, 1200 mg, 800 mg and 600 mg. The recommended dosages of 100 mg capsules or 600 mg/7.5 ml solutions in adults are 600 mg every 12 hours (when ritonavir is used as sole PI). As a pharmacokinetic booster for other PIs the recommended dosing is 100 - 400 mg per day in 1-2 divided doses (DHHS 2008). Review of the literature showed that boosted PI regimens that utilise a low dose of ritonavir (100 - 200 mg) appear to offer the best balance of efficacy and tolerability.

Results from this study revealed that ritonavir 800 mg was administered with saquinavir 800 mg. These PDDs are not acceptable according to the treatment guidelines (DHHS 2008), although it was reported that when administered

with saquinavir, ritonavir enhances the bioavailability and prolongs the elimination half-life of saquinavir such that its plasma-concentration time increased as much as 30- to 50-fold compared to saquinavir alone (Hsu *et al.* 1997:898). Therefore the recommended combination dosage of ritonavir and saquinavir was reported to be 400/400 mg since this appeared to have extremely potent ARV activity, judged on the basis of documented durable responses observed in patients (Cameron *et al.* 1999:214).

In this study indinavir was administered with ritonavir at PDDs of 2400 mg and 3000 mg respectively. These doses are considered to be high, considering that indinavir has a very short half-life because of the high systemic clearance; therefore the recommended dose is 800 mg every 8 hours (AfA 2009). Indinavir is administered with ritonavir to improve its bioavailability and to prolong the elimination half-life, thus reducing the total dose necessary to achieve a potent ARV plasma concentration. The recommended dose for 200 mg, 333 mg and 400 mg capsules of indinavir is 800 mg every 8 hours if given alone, but with ritonavir the dosages should be 800 mg for indinavir and 100 mg or 200 mg for ritonavir every 12 hours (DHHS 2008).

Practical implications

Patients who receive highly active ART have a better survival rate than those that do not. However, ARVs have to be prescribed and administered in their correct doses for patients to achieve an optimal therapy. Results from this study highlight the importance of correct ARV dosing to avoid patients' problems of non-adherence, virus resistance, drug-related adverse effects and drug interactions.

Contribution to current knowledge

Drug interactions as well as incorrect PDDs of ARVs in terms of overdosing and potential drug interactions lead to adverse effects that could result in non-adherence to ARVs in HIV and AIDS patients. This further complicates the long-term management of the disease, which requires life-long HAART. Yet sustained adherence is an essential tool of the long-term efficacy of ART (e.g. significant reductions in viral load, drug resistance, deterioration of health status and treatment failure) (Potcho *et al.* 2010:11).

Clinical and statistical significance of the study

With the introduction of HAART, ART has become increasingly complex, this leading to a certain number of prescription errors as new classes of ARVs become available. Incorrect dosing of ARV drugs, especially in patients with other chronic conditions like kidney disease who are undergoing haemodialysis, osteoporosis, heart disease, hypertension or abnormal hepatic function, leads to serious adverse events such as toxicity, viral resistance or treatment inefficacy (Tourret *et al.* 2007:779). This study emphasises the need for more education for health care professionals in SA on the recommended ARV doses to ensure effective use of ART.



Limitations of the study

Some limitations of this study were the non-availability of patient clinical data to do in-depth clinical evaluation of PDDs. The data were obtained directly from the medicine claims database, which does not capture these data. Information on ARV-naïve or –experienced patients, CD4 values and viral loads were unavailable. Furthermore, data related to ARV doses initiated, changes made to the doses for reasons best known to prescribers, records of changed doses, success of the treatment, pharmacokinetic profiles, side-effects and therapeutic outcomes of the patients were not available in the database. The clinical relevance of the identified PDDs was evaluated according to criteria stated in the literature. However, the results emphasised the possibility of PDDs that could have led to severe problems.

A further limitation of the study was that no differentiation could be made between the prescription patterns of dispensing doctors versus pharmacy-dispensed prescriptions. This result emphasises the important role of prescribers and retail pharmacists in ensuring the appropriate use of ARVs.

Recommendations

Appropriate use of ARVs is essential to avoid virological failure, development of resistance to ARVs and increased mortality rates (Marazzi *et al.* 2006:34). Therefore the following are recommended:

- There is a need for collaboration amongst the prescribers and retail pharmacists, for pharmacists to be able to detect and correct prescriptions with incorrect doses by the prescribers at the level of dispensing. This is one of the primary responsibilities of specific pharmacists.
- The importance of educating health care providers in the appropriate use of ARVs specifically in the private health care sector is of SA is emphasised.
- There is a need for continuous monitoring and evaluation tools when handling medicines that are prone to cause more negative consequences when used inappropriately, especially in cases of infectious diseases that are societal problems such as HIV and AIDS.
- Future studies need to be performed on in-depth clinical evaluation of PDDs using clinical data of patients.

Conclusion

In this study inappropriate PDDs were identified between ARV agents prescribed in different regimens according to prescriber and age groups. There were more GP prescriptions for ARVs than SP prescriptions. It was observed that for the three years 2005–2007 a higher percentage of ARV prescriptions prescribed by SPs had PDDs not according to the recommended ARV doses. It is therefore recommended that more education be provided, for example by SAHIVCS Guidelines (2009), to health care providers in the private health care sector in SA on the recommended ARV doses so as to achieve optimal therapy.

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Competing interest

The authors declare that they have no financial or personal relationship which may have inappropriately influenced them in writing this paper.

Authors' contributions

N.L.K-K. was responsible for the entire writing up of the manuscript, which involved the initial planning and designing of it, statistical analysis, interpretation of results and final write-up. M.L. was involved in the original planning and design of study, statistical analysis and guidance in the interpretation of results and reviewed the manuscript. J.H.P.S. was involved in the original planning and design of study, and provided guidance in the interpretation of results and reviewed the manuscript. I.T. was involved in the original planning and design of the manuscript, guidance in the interpretation of results and final review of the manuscript.

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