Original Article

Evaluation of concomitant use of prescribed antimicrobial medicines with traditional medicines in iLembe District, South Africa: A medical chart review

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Abstract

Background: Antimicrobial resistance in South Africa is driven by many factors, such as the careless use of prescribed antimicrobial medicines and the use of traditional medicines, with the result that there is always the danger of misadministration, interaction, and toxicity. This study was conducted in two different public healthcare facilities in iLembe District, KwaZulu-Natal Province, South Africa to determine whether any interaction occurred among patients attending outpatient departments in selected healthcare facilities in terms of the concurrent use of traditional medicines and prescribed antimicrobial medicines.

Methods: This study was a cross-sectional descriptive study using medical chart reviews. Antimicrobials prescribed alone or in association with traditional medicines were assessed and reported using descriptive statistics. Where applicable, associations were carried out; a p-value <0.05 was estimated as statistically significant.

Results: A total of 400 outpatients' medical records were documented from two different municipalities, revealing that many participants had viral infections (194/400, 48.5%). Overall, 12% of participants (48/400) had documented adverse effects (30/48) and interactions (18/48). A few participants (15/400) used traditional medicines in conjunction with prescribed medicines. After adjustment, negative clinical outcomes namely adverse effects and interactions were significantly more likely due to the use of traditional medicines (AOR=0.01, 95% CI:0.001-0.05) and (AOR=0.21, 95% CI: 0.37-1.23), respectively.

Conclusions: Traditional medicine was used sparingly in conjunction with prescribed antimicrobials for infectious diseases. However, adverse effects and interactions, such as herbal intoxication, persistent rashes, and treatment failure, were documented in a few medical records. Further studies are needed to investigate the effects of the concurrent use of traditional medicine with antimicrobials or other prescribed medicines from the perspectives of traditional healers and biomedically healthcare professionals. [*Ethiop. J. Health Dev.* 2021; 35(1):58-71]

Key words: Concomitant use, prescribed antimicrobials, traditional medicine, antimicrobial resistance, treatment failure, adverse effects

Background

Antimicrobial resistance (AMR) is the ability of a microorganism to withstand the effects of antimicrobials, such that AMR reduces the potential human health benefit derived from antibiotics and/or antiviral medicines (1). Some microorganisms have become resistant to multiple antimicrobial classes, which means that infectious diseases caused by resistant bacteria are now common (2). A report from the World Health Organization (WHO) has shown that 30% of bacteria are resistant to common antibiotics used to treat bacterial infectious diseases (3). AMR is a serious burden, with some bacteria and/or viruses becoming so resistant that there is either only 'last resort' antimicrobials or infections cannot be treated (4).

AMR is a leading cause of treatment failure and is largely responsible for the reduction in infectious disease extermination rates worldwide (5). Infectious and non-infectious disease conditions are mostly treated with antibiotics, which leads to the indiscriminate use of antimicrobials (6). Viruses and bacteria cause a large proportion of infectious diseases; bacterial infections account for 45% of deaths in Africa and South-East Asia (3). Actually, due to antiretroviral therapy (ART), the incidence of HIV infection has decreased from 0.40 per 1,000 people non-infected with HIV/AIDS in 2005 to 0.26 per 1,000 people non-infected with HIV/AIDS worldwide in 2016 (7). Similarly, from 2000 to 2016, the incidence of tuberculosis (TB) decreased by 19%, from 173 cases per 100,000 population to 140 per 100,000 population. Despite the increase in the incidence of TB infection, drug-resistant TB remains a global menace; as a result, of 600,000 registered new cases of TB resistant to rifampicin, 490,000 cases were multidrug-resistant (8).

South Africa is not an exception to widespread AMR; it confronts a triple AMR burden: drug-resistant tuberculosis, drug-resistant HIV and antibiotic resistance (1). People living with HIV/AIDS (PLWA) increased from 6.8 million in 2014 (9) to 7.52 million in 2018 (10). AMR is driven by many factors in South Africa, such as the careless use of prescribed antimicrobial medicines and the use of traditional medicine (TM), with the result that there is always a risk misadministration, interaction, and toxicity (11).

Plants are considered as one of the most promising sources for the discovery of new antimicrobial medicines; hundreds of plants in the world are used in TM for the treatment of viral and bacterial infections and other disease conditions by up to 80% of the population in Asia, Africa, Latin America, and the Middle East (12). In the European Union, 100 million people believe in the use of TM (13). It is estimated that approximatively 27 million South Africans, including PLWA, depend on TM for their primary health care

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needs (14). This is due to good access to plants, affordability, and confidentiality of health information between patients and traditional health practitioners, and the high cost of synthetic medicines (15). Medicinal plants are also believed to combat the specific symptoms of diseases, such as weight loss, skin disorders, lack of energy, and digestive problems, including a lack of appetite, diarrhea, nausea, vomiting, and treatment for side effects from antiretroviral medicines, as well as dizziness, fungal infections, pain and stomach upsets (16,17). Studies from around the world have shown that people have used TN concurrently with different prescribed medicines. A study in north-east Scotland showed that women have the potential to increase the risk of postpartum hemorrhage, alter maternal hemodynamic and increase the depression of the central nervous system between mothers and fetus (18). In addition, another study showed that less than 20% of participants co-used TM and antiviral medicines; however, nearly 80% of participants used TM before contracting HIV infection (19). Furthermore, 45% of study participants were co-users of conventional drugs and herbs, while a significant proportion of general health practitioners who co-used herbs with conventional drugs for their patients reported potential interactions or adverse effects due to the concomitant use of anticoagulants and garlic (20). TM is commonly used in combination with conventional medicines, mainly with satisfactory results, but in some cases, the effect of the two treatments can be increased, interacted and/or opposed (21). Different patient groups are known to use herbal remedies and conventional drugs concomitantly (co-use). This poses a potential risk of interactions between herbal drugs by changing the pharmacokinetics or pharmacodynamics of the drug. A study using a broth microdilution method suggested the concurrent use of some classes of antibiotics with some medicinal plant extracts against infectious diseases caused by *Escherichia coli* (*E. coli*). However, in the same study other medicinal extracts were tested concomitantly with some other classes of antibiotics that resulted in resistance to *E. coli* (22). Little is known about AMR among patients who co-use prescribed medicines, antibiotics or antiviral medicines with TM. Individuals may consult both traditional health practitioners (THPs) and biomedically trained healthcare professionals (BHPs) in relation to bacterial and viral infections. However, there is a limited knowledge of interactions about the concurrent use of TM and prescribed medicines for bacterial and viral infections. A study done among HIV patients who used concurrently herbal drugs and antiretroviral medicines reported that patients were at risk of developing viral resistance, treatment failure, and drug toxicity (23).

This study aimed at determining whether any interaction could occur among patients attending outpatient departments (OPDs) in selected healthcare facilities and who used concurrently TM with prescribed antimicrobial medicines in iLembe District, KwaZulu-Natal.

Methods

Study design: This study was a cross-sectional descriptive study using medical chart review among patients attending OPDs in two public healthcare facilities in iLembe District, KwaZulu-Natal Province, South Africa.

Study setting: This study was carried out in iLembe District, one of 11 districts in the province of KwaZulu-Natal in South Africa. iLembe is the smallest district municipality in the province with a surface area of 3,269 km^2; it is approximately 75km from Durban with a population of 630,464 inhabitants (90.8%) were natives, (2.4%) white population and (6.8%) were others. The majority of the population in the district consists of native isiZulu speakers (82%), followed by native English speakers (9.6%), native Xhosa speakers (3.3%) and others (5.5%) (24). It is located in KwaDukuza on the east coast of the province, bordering the Indian Ocean, and comprises four municipalities: Mandeni, Ndwedwe, KwaDukuza, and Maphumulo.

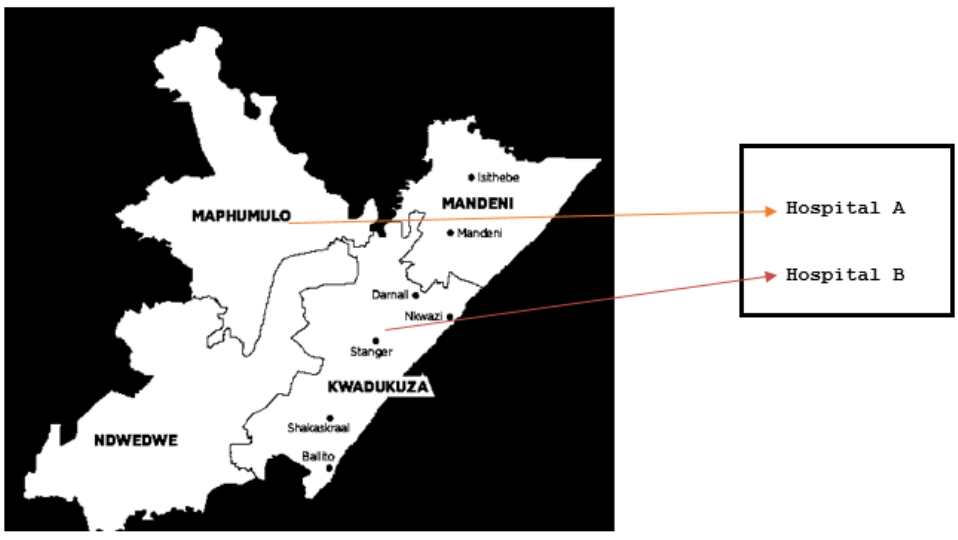

Figure 1: Map of the study area (www.municipalities.co.za)

There are four hospitals in the iLembe Health District, namely Montebello District Hospital, Stanger Provincial Hospital, Umphumulo District Hospital, and Untunjambili District Hospital. This study involved two hospitals: the Stanger Provincial Hospital in the municipality of KwaDukuza and the Umphumulo District Hospital in the municipality of Maphumulo. Both hospitals belong to the iLembe health department in the public sector.

Figure 1 shows the area where data were collected for this study. The map contains two different arrows that show the two hospitals (Hospital A and B) where the study was conducted.

Sample size calculation assumption: Records or medical charts of patients aged 18 years and older were systematically sampled from January 2018 to March 2018. In general, a margin of precision of ±10% requires a sample size of approximatively 100, which increases to approximatively 400 for a margin of precision of ±5% and 10,000 for a margin of precision of ±1%, for an expected prevalence of approximately 50% for the outcome variable (25). The sample size was determined in respect of the calculation method (26), which stipulated that the sample size would be 377 for a sizeable population of 20,000, with a margin of precision of ±5%, 95% CI and within 50% as an equal distribution. Accordingly, iLembe District has a population size of 630,464. The researcher assumed that the sample size for a large population of 630,464 was at least 384 (27). The study was oversampled by a maximum sample to include 400 medical chart reviews.

Recruitment process and selection of participants: Medical chart records of adult patients, aged 18 years and above, irrespective of gender, were selected at the OPDs of the two selected healthcare facilities, as well as at their respective TB and HIV clinics, during clinic visiting hours. Patients' medical records from January 2017 to January 2018 were assessed and selected according to the study's inclusion and exclusion criteria during the data collection period, February to March 2018. Records of patients who used concurrently TM and prescribed antimicrobials, as well as those who developed side effects and/or interactions, were reviewed in detail.

Data collection technique and instruments: A medical chart review was conducted over four weeks between February and March 2018. Data from 400 outpatients were collected manually by the researcher, since there were no computerized records in the OPDs. A data extraction form specifically developed specifically for the study. The form included the following information: patient's address, age, gender, marital status, educational level, language spoken, occupation, as well as viral infectious diseases, bacterial and/or fungal infectious diseases. Moreover, the details of any antimicrobials prescribed alone (antiretroviral, antibiotics and/or antifungals) or in association with other prescribed medicines, the use of traditional medicine, any adverse effects, and interactions registered were assessed. The data extraction form was prepared in the English language. Thus, all the patient information needed for this study was recorded for every eligible outpatient in both hospitals.

Statistical analysis: Descriptive statistics using frequencies and percentages were used to describe the socio-demographic characteristics of study participants. Data deriving from medical records using medical chart reviews were transferred into Excel spreadsheets, and then later analyzed using Statistical Package for Social Sciences (SPSS) software, version 25. Categorical data were presented as Tables. The prevalence of HIV infection, tuberculosis (TB) infections, and other respiratory infectious disease were reported as percentages, with 95% confidence intervals (95% CIs). The prevalence of the use of TM and prescribed antimicrobial medicines were also reported as percentages, with 95% CIs. Associations between variables were carried out using Pearson's chi-squared tests. For multivariate analysis, a binary logistic regression analysis (adjusted odds ratio, AOR) was used. In addition, a separate multivariate logistic regression model was built to determine the association between the use of TM and clinical outcomes. A p-value ≤ 0.05 was considered as statistically significant. Logistic regression analyses were used to calculate odds ratios for adverse effects and interactions regarding TMs used.

Ethical considerations

Ethical approval to undertake the study was granted by the Biomedical Research Ethics Committee of the University of KwaZulu - Natal (Reference BE476/17). In this the study, no contact was made with participants. Medical chart records were reviewed. The findings of this study have been reported anonymously – no names, no personal identifiers or file numbers have been reported to protect the privacy of, and maintain confidentiality about, the study participants.

Results

This study reviewed 400 documented patients' medical records in two different municipalities in iLembe District, KwaZulu-Natal, South Africa.

Socio-demographic characteristics of study participants: Table 1 presents the socio-demographic characteristics of the study participants. Overall, the majority of participants were black African, female gender, and unmarried. Most of the participants were employed and had attended at least primary school. The median age was 33 years old with a standard deviation of 16.42 (33 years old ± 16.42), range 18-93 years.

Table 1: Socio-demographic characteristics of participants

Category	Sub-category	N (%) [95% CI]
iLembe District	Municipality A	200 (50.0) [45-55]
	Municipality B	200 (50.0) [45-55]
	Total	**400 (100)**
Gender	Female	218 (54.50) [50-60]
	Male	182 (45.50) [41-51]
	Total	**400 (100)**
Race	Black African	339 (84.75) [81-89]
	Indian	31 (7.75) [5-10]
	Mixed race	18 (4.50) [3-7]
	White	12 (3.0) [2-5]
	Total	**400 (100)**
Occupation	Employed	228 (57.0) [52-62]
	Unemployed	172 (43.0) [38-48]
	Total	**400 (100)**
Marital status	Married	62 (15.50) [12-20]
	Unmarried	314 (78.50) [74-82]
	Widowed	24 (6.0) [4-8]
	Total	**400 (100)**
Educational level	Illiterate	23 (5.75) [4-8]
	Primary school	193 (48.25) [43-53]
	Secondary school	174 (43.50) [39-49]
	Tertiary	10 (2.5) [1-4]
	Total	**400 (100)**
Language spoken	English and Afrikaans	43 (10.75) [8-14]
	IsiZulu	340 (85.0) [81-88]
	IsiZulu and English	17 (4.25) [2-6]
	Total	**400 (100)**

Prevalence of infectious diseases associated with HIV and TB among study participants: Table 2 presents the prevalence of HIV, TB and other associated diseases or comorbidities among study participants. The majority of participants had either HIV infection alone, a co-infection of HIV and TB, or HIV with other diseases. TB was documented either alone or in combination with other infections, excluding HIV infection reported above. Overall, 17% of participants had other respiratory infections excluding TB. Besides HIV infection, TB either alone or associated with other comorbidities or other infectious diseases were documented in almost 7.5% of cases, while the remainder of participants had non-communicable diseases.

Table 2: Frequency of communicable and non-communicable infectious diseases associated with HIV and TB

Category	Sub-category	Frequency of documented diseases (%)	p-value, AOR (95% CI)
HIV infection	HIV infection alone	49 (12.25)	
	HIV with tuberculosis	61 (15.25)	
	HIV with other bacterial infectious diseases (pneumonia (3), meningitis (2) and other (12))	21 (5.25)	
	HIV with fungal infectious diseases non-identified	6 (1.5)	$p < 0.001$
	HIV with other sexually transmitted diseases (10) and three viral infectious diseases (shingles (1), genital warts (2))	13 (3.25)	0.073 (0.039-0.14)
	HIV with non-communicable diseases (hypertension (6), assault (injury) (5), renal failure (5) and other (28))	44 (11)	
Subtotal		**194**	
Tuberculosis infection	Tuberculosis infection alone	35	8.75 (6.1-11.4)
	Tuberculosis with other bacterial infectious diseases (pneumonia (3), meningitis (2), one fungal infection (candidiasis) and one viral infectious disease (hepatitis B), and with two others)	9	2.25 (0.88-3.62)
	Tuberculosis with non-communicable diseases (acute gastroenteritis (2), asthma (1) and two other diseases)	5	1.25 (0.27-2.23)
Subtotal		**49**	
Respiratory infection	Respiratory infection alone (pneumonia (3), upper respiratory tract infection (3), pharyngitis (2) and other (6))	14	3.5 (1.83-5.17)
	Respiratory infection with other infectious diseases: pneumonia with lower respiratory tract infection (1), upper respiratory tract infection with diarrhea (1), upper respiratory tract infection with tinea pedis (1) and other diseases (4)	7	1.75 (0.79-2.71)
	Respiratory infection with non-communicable diseases (lower respiratory tract infection with acute gastroenteritis (4), pneumonia with asthma (4) and other diseases (35))	43	10.75 (7.69-13.81)
Subtotal		**64**	
Other infectious diseases alone (urinary tract infection (3), one herpes simplex, and other infectious diseases alone (26))		30	7.5 (5.01-9.99)
Non-communicable diseases (hypertension (11), diabetes (5) and other diseases (47))		63	15.75 (12.26-19.24)
Total		**400**	**100%**

AOR: Adjusted odds ratio that is obtained from binary logistic regression; CI: confidence interval; HIV: human immunodeficiency virus.

Documented medicines prescribed (antimicrobial and non-antimicrobials) by biomedically trained healthcare professionals: Table 3 presents the frequency of documented antimicrobial medicines prescribed by BHPs. Most of the medical records reviewed for study participants contained prescribed antimicrobials, while the remainder had prescribed medicines other than antimicrobials.

Overall, 1,497 medicines were identified within study participants' medical chart records. Although the majority of medical records referred to cases of infectious diseases and the appropriate antimicrobial treatment, non-antimicrobial medicines were predominantly prescribed in conjunction with antimicrobials. Those non-antimicrobials consisted mainly of paracetamol in combination with other painkillers (paracetamol +codeine + potassium sorbate), which accounted for at least 16%. Antimicrobial medicines were mainly common antibiotics or antifungals, such as Augmentin® (amoxicillin +

clavulanate), Bactrim® (sulfamethoxazole + trimethoprim), Flagyl® (metronidazole), and fluconazole. These were followed by antiretroviral medicines in a fixed-dose combination of antiretrovirals containing either tenofovir + emtricitabine + efavirenz, or abacavir + lamivudine + lopinavir; and finally followed by anti-TB medicines consisting of a fixed-dose combination of Rifafour®, comprising rifampicin + ethambutol + isoniazid + pyrazinamide.

Table 3: **Documented medicines prescribed (antimicrobials and non-antimicrobials) by BHPs**

Frequency of participants (N=400, %)			**Frequency of prescribed medicines used (N=1,497, %)**	
Prescribed antiretroviral fixed-dose combination (FDC) tenofovir + emtricitabine + efavirenz, or abacavir + lamivudine + lopinavir)	FDC (alone)	31 (7.75)	FDC (alone)	31 (2.07)
	FDC with Rifafour®, consisting of a fixed-dose combination (rifampicin + ethambutol + isoniazid + pyrazinamide)	31 (7.75)	FDC (31) with Rifafour® consisting of a fixed-dose combination (rifampicin + ethambutol + isoniazid + pyrazinamide) (31)	62 (4.14)
	FDC with other prescribed antibiotics (Augmentin® (amoxicillin + clavulanate) (9) and to other medicines (74))	83 (20.75)	FDC (83) with other prescribed antibiotics (Augmentin® (amoxicillin + clavulanate) (9) and to other medicines (74))	166 (11.08)
	FDC with prescribed antifungals (clotrimazole (3), prescribed antibiotics and other prescribed medicines (23))	26 (6.5)	FDC (26) with prescribed antifungals (clotrimazole (3), prescribed antibiotics and other prescribed medicines (23))	75 (5.01)
	FDC with other prescribed medicines (amlodipine (3), hydrochlorothiazide (2) and other (14))	19 (4.75)	FDC with other prescribed medicines (amlodipine (3), hydrochlorothiazide (2) and other (14))	38 (2.53)
Other antiviral used (acyclovir) associated with 8 other prescribed medicines		4 (1)	Other antiviral used (acyclovir) associated with eight other prescribed medicines	12 (0.80)
Subtotal		**194 (48.5)**		**384 (25.62)**
Prescribed antibiotics	Rifafour® (rifampicin + ethambutol + isoniazid + pyrazinamide) with other prescribed antibiotics (Augmentin® (amoxicillin + clavulanate) (10), Bactrim® (sulfamethoxazole + trimethoprim) (8) and others (61))	79 (19.75)	Rifafour® (rifampicin + ethambutol + isoniazid + pyrazinamide) with other prescribed antibiotics (Augmentin® (amoxicillin + clavulanate) (10), Bactrim® (sulfamethoxazole + trimethoprim) (8) and others (61))	158 (10.55)
	Other prescribed antibiotics used alone: Flagyl® (metronidazole) (4), praziquantel (2) and other (13)	19 (4.75)	Other prescribed antibiotics used alone: Flagyl® (metronidazole) (4), praziquantel (2) and other (13)	19 (1.27)
	Other combination between prescribed antibiotics (amoxicillin with metronidazole (8), clotrimazole with fluconazole (4) and other (52))	64 (16.0)	Other combination between prescribed antibiotics (amoxicillin with metronidazole (8), clotrimazole with fluconazole (4) and other (52))	128 (8.55)
Subtotal		**162 (40.5)**		**305 (20.37)**
Other prescribed medicines: Panado®: (paracetamol + codeine + potassium sorbate) (131), pyridoxine (113), multivitamin (49), Brufen® (ibuprofen (43)) and other (472)		44 (11)	Other prescribed medicines: Panado®: (paracetamol + codeine + potassium sorbate) (131), pyridoxine (113), multivitamin (49), Brufen® (ibuprofen (43)) and other (472)	808 (53.97)
Total		**400 (100)**		**1,497 (100)**

Documented clinical outcomes of the concurrent use of traditional medicines and prescribed medicines among study participants: Table 4 presents the documented concurrent use of TM and prescribed medicines among study participants. Overall, very few participants used TM with their prescribed medicines had clinical outcomes were documented in their medical chart records. Seven out of 15 cases of the co-use of TM and conventional antibiotics/antiviral drugs were interactions consisting mainly of treatment failure and drug resistance to the first line ARV treatment and a persistent rash to conventional treatment, while loss of scrotum pigmentation, diarrhea, nausea, vomiting, body pain, headache, and renal impairment were the main documented adverse effects. Twelve cases were documented of drug resistance and treatment failure, either from the first line or the second line of ART, severe renal impairment, rashes, kidney pain, jaundice, painful lower limbs, weakness, and vomiting.

Table 4: **Documented clinical outcomes of the concurrent use of TM and prescribed medicines**

Use of TM (N=15)				**Non-use of TM (N=385)**			
Conditions	**Prescribed medicines used**	**Documented interactions**	**Documented adverse effects**	**Conditions**	**Prescribed medicines used**	**Documented interactions**	**Documented adverse effects**
HIV infection disease	FDC, aminophylline, Bactrim® (co-trimoxazole or sulfamethoxazole + trimethoprim), Panado® (paracetamol + codeine + potassium sorbate)	Herbal intoxication (1), treatment failure (to the first line)	Unconsciousness due to overdose (1), nausea (1) and headache (1)	**HIV infection alone**	FDC, Bactrim® (co-trimoxazole or sulfamethoxazole + trimethoprim), fluconazole, clotrimazole, multivitamin	Drug resistance and treatment failure (7), either of the first line or the second line of FDC	Missed period (1), shingles, and sores (1), genital warts (1), vomiting (2), dizziness (2), loss of balance, headache (1), weakness (1), stomach cramps
HIV with TB and/or other disease	FDC, Rifafour® (rifampicin + ethambutol + isoniazid + pyrazinamide), Bactrim® (co-trimoxazole or sulfamethoxazole + trimethoprim), Augmentin® (amoxicillin + clavulanate potassium), multivitamin, fluconazole, Venofer® (iron sucrose), Rocephin® (ceftriaxone), azithromycin, Clexane® (enoxaparin), FeSO4, Paracold® (paracetamol + codeine phosphate), Voltaren® (diclofenac sodium), betamethasone, Brufen® (ibuprofen), Allergex®, Sorol Citrate ®, ampicillin, prednisolone, clotrimazole cream, Flucox® (flucloxacillin), acyclovir	Herbal intoxication (1), treatment failure (3) and drug resistance (to the first line ARV regimen) (1), and persistent rashes to conventional treatment	Loss of scrotum pigmentation (1), diarrhea (2), rash resistant (2), nausea (1), diarrhea (1), body pain (1), headache (1), rashes(2), renal impairment (2)	**HIV with tuberculosis infection**	FDC, Rifafour® (rifampicin + ethambutol + isoniazid + pyrazinamide), Augmentin® (amoxicillin + clavulanate potassium), Bactrim® (co-trimoxazole or sulfamethoxazole + trimethoprim), norfloxacin, pyridoxine, Panado® (paracetamol + codeine + potassium sorbate), dapsone, multivitamin, vitamin B Complex, vitamin C	Drug resistance (2) and treatment failure (1), either of the first line or the second line of FDC	Severe renal impairment (2), rashes (1), kidney pain (2), jaundice bloods (1), painful lower limbs (1), weakness (1) , diarrhea (1), vomiting (2)

Tuberculosis infection alone	Rifafour® (rifampicin + ethambutol + isoniazid + pyrazinamide), pyridoxine, Panado® (paracetamol + codeine + potassium sorbate), multivitamin	None	None	**HIV with mouth ulcer and other diseases**	FDC, Bactrim® (co-trimoxazole or sulfamethoxazole + trimethoprim), flucloxacillin, Flagyl® (metronidazole), Lansoloc® (lansoprazole), Brufen® (ibuprofen), Buscopan® (hyoscine butylbromide), fluconazole, clotrimazole	Drug resistance (1) and treatment failure, either of the first line or the second line of FDC	Diarrhea (1), vomiting (1), kidney failure (1)
Abdominal pain (renal impairment)	Buscopan® (hyoscine butylbromide), ringer lactate	Herbal intoxication (1)	Abdominal pain (1), vomiting (1), body weakness (1)	**TB with Acute Gastric Enteric**	Rifafour® (rifampicin + ethambutol + isoniazid + pyrazinamide), Augmentin® (amoxicillin + clavulanate potassium), Rocephin® (ceftriaxone), clotrimazole, nystatin, Maxolon® (metoclopramide), Sorol Citrate ®, Allergex®, pyridoxine, Panado® (paracetamol + codeine + potassium sorbate), multivitamin	None	Vomiting and abdominal pain (2)
Gastritis and sepsis	Augmentin® (amoxicillin + clavulanate potassium), Rocephin® (ceftriaxone), Flagyl® (metronidazole), Maxolon® (Metoclopramide)	None	Vomiting and weakness	**TB with pneumonia**	Rifafour® (rifampicin + ethambutol + isoniazid + pyrazinamide), Augmentin® (amoxicillin + clavulanate potassium), azythromycin, Rocephin® (ceftriaxone), pyridoxine, Panado® (paracetamol + codeine + potassium sorbate), vitamin C	None	Loss of energy and headache

Association between the use of traditional medicine and documented adverse effects and interactions: Table 5 presents associations between the use of TM and adverse effects and/or interactions. Overall, less than 10% of patients had documented adverse effects. A few participants had used TM in conjunction with prescribed medicines. Seven out of 15 of the co-uses of TM and conventional antibiotics/antiviral drugs were interactions consisting mainly of treatment failure and drug resistance to the first line ARV treatment, and a persistent rash to conventional treatment, while loss of scrotum pigmentation, diarrhea, nausea, vomiting, body pain headache, and renal impairment were the main documented adverse effects. Although there is a relatively small number of documented cases of interactions and adverse effects in this study, there is a risk of AMR and treatment failure among patients using TM and prescribed medicines concurrently. This result may suggest the need for BHPs to communicate properly with patients and document information accordingly to allow this type of study (medical chart review) to pick the information from medical chart records of patients in the absence of face-to-face interviews and self-reported use of TM by patients. Of the 15 participants, 60% were female, 73.33% had attended at least primary school, and were employed.

Documented interactions and adverse effects were significantly associated with the use of TM in combination with prescribed medicines using Pearson chi-square ($p< 0.001$). Using multiple logistic regression models, the risk estimate of using of TM alongside prescribed medicines was higher among females compared to males. After adjustment, documented adverse effects and interactions were significantly more likely due to the use of TM.

Table 5: **Association between the use of traditional medicine and documented adverse effects and interactions**

Variables (N=400)		**Use of TM (N=15)**			**p-value (χ^2)**	**AOR (95% CI)**
		No	**Yes**	**Total**		
Gender	Female	209 (52.25%)	9 (2.25%)	218 (54.5%)	0.886	1.07 (0.3-2.9)
	Male (Ref.)	176 (44%)	6 (1.5%)	182 (45.5%)		
Educational level	Illiterate	23 (5.75%)	0	23 (5.75%)	0.199	0.2 (0.02-2.1)
	Primary School	182 (45.5%)	11 (2.75%)	193 (48.25%)		
	Secondary School.	170 (42.5%)	4 (1%)	174 (43.5%)		
	Tertiary (Ref.)	9 (2.25%)	1 (0.25%)	10 (2.5%)		
Documented adverse effects	No	367 (91.75%)	3 (0.75%)	370 (92.5%)	0.000	0.01 (0.001-0.05)*
	Yes (Ref.)	18 (4.5%)	12 (3%)	30 (7.5%)		
Documented interactions	No	374 (93.5%)	8 (2%)	382 (95.5%)	0.000	0.21 (0.37-1.23)*
	Yes (Ref.)	11 (2.75%)	7 (1.75%)	18 (4.5%)		
	Total			**400**		

AOR: Adjusted odds ratio that is obtained from binary logistic regression, TM: traditional medicine.

Discussion

This study found that a few participants had a documented concurrent use of TM with prescribed medicines (15/400, 3.75%). TM was not commonly used by the study participants 385/400 (96.25%). This finding is in agreement with a study carried out in eThekwini municipality (28), which showed a quite low use of ARV in conjunction with TM (4.98%). A study done by Hughes *et al.* (2016) revealed that less than 20% of participants co-used TM and ARV(19, 29). In contrast, however, studies done in Nigeria (30) and in north-east Scotland (18) indicated a high prevalence (69.4% and 44.9%, respectively) of the concurrent use of both TM and prescribed medicines. According to the WHO (31), this trend may be attributed to accessibility, affordability, and the availability of TM. Regardless to the total number of those who used TM in this study (15/400, 3.75%), almost half of them (8/15, 53.33%) had documented adverse effects and interactions (8/15) versus 46.67% of those who also used TM but without any adverse effects or interactions (7/15). Documented cases of the concurrent use of TM and prescribed medicines (8/15) were associated with those patients who disclosed this concomitant use to BHPs and which resulted mainly in treatment failure, drug resistance to the first line ARV treatment, and renal impairment. The authors believe that numbers of documented adverse effects and interactions will increase if BHPs communicate consistently with their patients. In addition, the authors hold the view that there is a risk of AMR and treatment failure among patients using TM and prescribed medicines concurrently. This has been demonstrated in the relatively small number (15/400) of documented

cases. Therefore, the emphasis of authors on the need for BHPs to communicate properly with patients and document information accordingly to allow this type of study (medical chart review), to pick the information from medical chart records of patients in the absence of face-to-face interviews and self-reported use of TM by patients.

Another study where patients used TM (906/1,130, 80.2%) reported that only 9.6% of them (109/1130) felt confident to disclose the use of their TM to BHPs; they believed that their BHPs were more knowledgeable regarding the safe use of TM and the danger of adverse effects and interactions between TM and prescribed medicines, which could have been reduced (32). This difficulty is justified by other studies which indicate that patients do not disclose the use of TM remedies without direct questions. Similarly, another study where more than half of the study respondents (175/321, 54.6%) did not report to their BHPs the use of TM in conjunction with prescribed medicines, with the reason that BHPs did not ask or it was not important to disclose the information to the BHPs and only a small number of those who used TM (3/205, 1.5%) developed adverse effects, mainly rashes, gastric complications and pimples due to the use of TM (33). Communication between BHPs and patients on the use of TM is important in order to assess patient needs and, more importantly, in the assessment of any potential adverse effects and interactions.

In this study, there was no statistically significant association between use of TM and gender (p=0.886) and the use of TM and level of education (p=0.199). The majority of those who used TM were female participants (9/15, 60%). This was in agreement with other studies carried out in Iraq (34) and in Nigeria (35), which indicate that 52.9% and 72.4%, respectively, of female participants used more TM concurrently with their prescribed medicines than males. The preponderance of female use of TM in this study (9/15) is similar to other studies that report that female gender is a predictor of TM use among people living with AIDS (19,36).

This study found a few cases of documented adverse effects (30/400) and interactions (18/400) as clinical outcomes; among those who had adverse effects, 40% (12/30) used TM concurrently with prescribed medicines, while 38.89% (7/18) had interactions and used TM concurrently. After adjustment, documented adverse effects and interactions were significantly more likely due to the use of TM (AOR = 0.01, 95% CI: 0.001-0.05) and (AOR = 0.21, 95% CI: 0.37-1.23), respectively. This may suggest that there is a risk of having interactions and adverse effects with the concomitant use of TM and prescribed medicines. These results are in agreement with a similar study conducted in Norway (20), which showed that patients who used conventional medicines concurrently with TM had significantly ($p < 0.05$) increased odds of experiencing adverse effects (AOR 37.5); in the same way, McLay *et al.* (2017) show that pregnant women who co-use TM and conventional medicines had postpartum hemorrhage and altered maternal hemodynamic (18). Interactions between TM and prescribed medicines can occur and may lead to negative clinical consequences. However, the results of this study are in contrast to studies carried out in Portugal and around the world which show that antimicrobial compounds from plants can be synergistic enhancers, in that though they may not possess any antimicrobial properties alone, when used concurrently with prescribed medicines, they enhance the activity of the medicine and co-users of both TM and prescribed medicine feel improved quality of life (37,38).

This study found a high prevalence of HIV infection (47.5%, 190/400). This finding is in agreement with a published report on the high prevalence of HIV infection in KwaZulu-Natal, as well as the most prevalent province (approximatively 26.6%) among the top four provinces for HIV (10). Shah *et al.* (39) show that of 404 participants, 311 (77%) had HIV infection in KwaZulu-Natal. The South African government has highlighted that aspects of poverty in townships, such as inadequate sanitation and food, unemployment and poor education, violence, and crime, are associated with increased HIV transmission (40).

This study was a medical chart review; no direct contact was made with patients who reported using TM and prescribed medicines concurrently. One of the strengths of this study is the demonstration that, despite the relatively small number of documented cases, there is a risk of AMR and treatment failure among patients who use both TM and prescribed medicines – patients who had bacterial, viral and/or fungal infections developed adverse effects and interactions. Some more information could have been collected by talking directly to patients themselves. The findings of this study should be interpreted with caution. They cannot be generalized to the entire province of KwaZulu-Natal or to South Africa as a whole. Further studies are needed in other districts of KwaZulu-Natal and the rest of South Africa. There was a difficulty of finding data that revealed the type of TM used, since documented patient medical records do not highlight such information. Hence, studies involving direct interactions with patients, BHPs and THPs are warranted to gather more information on the problem under study.

Conclusions

The findings from the present study reveal a low documented use of TM in conjunction with prescribed antibiotic and/or antiviral medicines. In the healthcare facilities included in this study, few documented

adverse effects and interactions were documented among those who used TM and prescribed medicines concurrently. Further studies are needed to investigate the effects of concurrent use of TM and prescribed medicines on antimicrobial resistance and/or treatment failure in other parts of South Africa.

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Competing interests
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Authors' contributions
MN conceptualized the study and its design, revised the manuscript, and accepted the final version of this publication as the senior author. MGK collected data and wrote the first draft of the manuscript. All authors have read critically the manuscript for its substantial intellectual content and approved the final manuscript.

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