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Barriers experienced by patients in adhering to antiretroviral treatment in a mobile clinic in KwaZulu-Natal, South Africa

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Abstract

Antiretroviral treatment (ART) plays a significant role in the wellbeing of individuals living with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). Adherence to ART is vital for patients since it helps to prevent the virus from multiplying and spreading through the body. This study explored challenges that hinder patients' adherence to ART at a mobile clinic of KwaZulu-Natal municipality, South Africa. A qualitative research approach was utilised, using an exploratory and descriptive design. Purposive sampling was used to select five participants aged 18 years and older, receiving treatment at a mobile clinic. Data were collected through semi-structured interviews from patients who defaulted ART treatment and analysed thematically. The findings revealed barriers to adherence as socioeconomic factors, stigma, and discrimination. Addressing ART non-adherence requires a multifaceted approach involving healthcare providers, policymakers, and community support structures. Recommendations include improving patient education on treatment adherence, ensuring consistent availability of medication at mobile clinics, and implementing patient-centered care strategies to enhance healthcare provider-patient relationships. Strengthening support systems within families and communities can also play a critical role in reducing stigma and encouraging adherence. Future research should explore adherence challenges in diverse settings, including urban areas, to develop broader interventions. *(Afr J Reprod Health 2025; 29 [12]: 33-41).*

Keywords: Antiretroviral treatment; adherence; challenges; mobile clinic; municipality

Résumé

Le traitement antirétroviral (TAR) joue un rôle essentiel dans le bien-être des personnes vivant avec le VIH/SIDA. L'observance du TAR est vitale pour les patients, car elle contribue à empêcher la multiplication et la propagation du virus dans l'organisme. Cette étude a exploré les obstacles à l'observance du TAR chez les patients d'une clinique mobile de la municipalité de KwaZulu-Natal, en Afrique du Sud. Une approche qualitative, exploratoire et descriptive, a été utilisée. Un échantillonnage raisonné a permis de sélectionner cinq participants âgés de 18 ans et plus, recevant un traitement dans une clinique mobile. Les données ont été recueillies par le biais d'entretiens semi-structurés auprès de patients ayant interrompu leur traitement antirétroviral et analysées thématiquement. Les résultats ont révélé que les obstacles à l'observance sont des facteurs socio-économiques, la stigmatisation et la discrimination. Lutter contre la non-observance du TAR nécessite une approche multidimensionnelle impliquant les professionnels de santé, les décideurs politiques et les structures de soutien communautaires. Les recommandations incluent l'amélioration de l'éducation des patients sur l'observance du traitement, la garantie d'une disponibilité constante des médicaments dans les cliniques mobiles et la mise en œuvre de stratégies de soins centrées sur le patient afin d'améliorer la relation soignant-patient. Le renforcement des systèmes de soutien au sein des familles et des communautés peut également jouer un rôle essentiel dans la réduction de la stigmatisation et l'encouragement de l'adhésion au traitement. Les recherches futures devraient explorer les difficultés d'observance dans divers contextes, notamment urbains, afin de développer des interventions plus globales. *(Afr J Reprod Health 2025; 29 [12]: 33-41).*

Mots-clés : Traitement antirétroviral ; observance ; difficultés ; clinique mobile ; municipalité

Introduction

Mobile clinics in KwaZulu-Natal, South Africa, play important roles in healthcare services delivery for rural communities, particularly those affected by human immunodeficiency virus (HIV). They provide vital services to communities including testing, counselling, and antiretroviral therapy (ART) in areas that have no traditional healthcare facilities. Mobile clinics provide flexibility which allows them to reach marginalised populations, informal settlements, and rural areas, where stigma and transportation challenges usually delay or inhibit access to medical care. Among the HIV patients who default on their treatment within these mobile clinics are often individuals from rural backgrounds, including people living in poverty and young men and women.

Evidence suggests that up to 20% to 30% of patients on ART in KwaZulu-Natal may default on their treatment.[1] This shows the need for innovative interventions and continued support to patients living with HIV/AIDS to ensure they receive the care they need to manage their health efficiently.[1]

Antiretroviral treatment plays a significant role in the wellbeing of individuals living with HIV/AIDS. Adhering to ART is vital for these patients since it helps prevent the virus from multiplying and as a result, the amount of HIV in the body is reduced. However, adherence to ART is associated with some challenges and barriers that hinder the commitment of patients to ART. Barriers to adherence to ART include economic, social, health, therapeutic, patient-related, and cultural barriers.[1]

Economic barriers which include poverty and unemployment, lack of food and disability grants, and lack of money, interfere with patients' ability to adhere to ART. The author also mentions fear of unintended disclosure seen when interacting with HIV care providers as a social barrier to adhering to ART. Culturally, conservative patients may believe more in concoctions to cleanse their body than ART, but for some patients it is merely poor treatment literacy that hinders adherence to ART.[2]

We became interested in conducting the study after observing that mobile clinics receive several patients who are not registered in the mobile clinic to access their ART. They have registered themselves in clinics that are in urban areas whereas they stay in rural areas. When they run out of their treatment due to lack of taxi fare, they could not fetch the treatment.

Possible barriers to treatment include transport costs, the time needed for treatment, and logistical challenges, while stigma around HIV/AIDS and side effects associated with ART are also important. Patients go to clinics to ask for treatment but become lost to follow-up in the clinics where they are registered. Many patients are avoiding their community clinic due to stigma and lack of confidentiality in a mobile clinic setting then this defaulting creates the problem of high viral load.[3]

Furthermore, we noticed that mobile clinics would ensure more patients are put on treatment, as national guidelines have evolved towards initiating ART for all people living with HIV regardless of clinical and immunological status. Several studies have shown evidence that retention in care through mobile clinics was good.[4] Therefore, this study explored challenges that hinder patients' adherence to ART at a mobile clinic of KwaZulu-Natal municipality, South Africa.

Methods

A qualitative exploratory, descriptive, and contextual approach was used in this study to address the identified research objective.

Study design

An explorative mode of inquiry was used to explore a new topic or learn more about issues of which little is known. Exploratory research designs are used to begin the process of building knowledge about a problem or question and to investigate a phenomenon where little knowledge exists. Since the research purpose was to explore the challenges that hinder patients' adherence to ART at a mobile clinic, we used an explorative and descriptive design.[5]

Setting

The study was conducted at a mobile clinic point located in the Ray Nkonyeni Local Municipality of the Ugu District, KwaZulu-Natal Province in South Africa.

Study participants

The study participants were patients who were recruited and included in the study that have defaulted ART at a mobile clinic point.

Sampling method and sampling size

The sample composition was influenced by demographics in the district and defaulters who volunteered to take part aged between 22 and 43 years. As shown in Table 1, all black Africans; one

Table 1: Demographic profiles of the participants

Participant	Age (Years)	Gender	Marital status	Language
Participant 1	36	Male	Single	IsiXhosa
Participant 2	43	Female	Single	IsiZulu
Participant 3	24	Female	Single	IsiZulu
Participant 4	43	Female	Single	IsiZulu
Participant 5	22	Female	Single	IsiZulu

participant was a male and four participants were females. Four of the participants spoke isiZulu and one isiXhosa. Data saturation was reached from 5th participant as enough data were collected to draw necessary conclusions.

Data collection and analysis

Data were collected using semi-structured interviews as data collection methods to help gain a detailed understanding of patients’ challenges and barriers to adherence to ART. The language used was isiZulu and the researchers interpreted the interview questions into the isiZulu language for participants to understand.

Semi-structured interviews involve a flexible set of questions which allowed for open-ended responses and follow up questions.[6] The local clinic located in the Ray Nkonyeni Local Municipality of the Ugu District; KwaZulu-Natal province was used as an interview site. The audio recordings allowed the researchers to ensure the data’s credibility. Credibility was ensured engaging participants during the interview process and encouraging them to be open. The researcher collected data from the participants over the course of three days. There was one research assistant that was trained by the researchers on research ethics and confidentiality. This was arranged to assist with data collection, writing field notes and observing participants body gestures when responding.

Data analysis is defined as the process of developing answers to questions through the examination and interpretation of data.[6] Thematic analysis was used. Thematic analysis is a method for analysing qualitative data that entails searching across a data set to identify, analyse, and report repeated patterns.[7] Data from the audiotapes were transcribed verbatim and coded into themes and subthemes by the researchers. The emerging themes, categories, and patterns were then analysed. Tesch’s approach to data analysis was used and eight steps were involved.

Measures to ensure trustworthiness

Trustworthiness is an essential concept in qualitative research methodology which emphasizes the rigour and credibility of the research findings.[13] To ensure the trustworthiness of this study, the researcher used the five criteria for developing the trustworthiness of a qualitative inquiry: credibility, dependability, confirmability, transferability, and authenticity.

Credibility

Credibility of a study is determined when coresearchers or readers are confronted with the experience and can recognise it.[8] The credibility of research findings that are used to make policy recommendations is particularly important for ecosystem management; assessing the extent to which the reader believes the recommendations are credible has implications for the expected success of implementation.[8] Credibility was ensured through persistent observation and prolonged engagement with participants.

Dependability

Dependability refers to the stability of data over time. It involves participants’ evaluation of the findings, interpretation, and recommendations of the study such that all are supported by the data as received from participants of the study.[7] To ensure dependability, the researcher conducted pre-testing of a study with two participants meeting the inclusion criteria. The pre-test provided the opportunity to fine-tune the final study tool and questions and revealed unanticipated issues to ensure that the data collected were consistent and stable.

Confirmability

Confirmability is concerned with establishing that the researcher’s interpretations and findings are derived from the data, requiring the researcher to demonstrate how conclusions and interpretations have been reached.[8] The author states that to achieve confirmability researchers must demonstrate that the results are linked to the conclusions in a way that can be followed and using a process that can be replicated. Confirmability was ensured by keeping a record of the research path for accurate data and interpretations of the findings.

Transferability

Transferability refers to the degree to which the results of qualitative research can be transferred to other contexts or settings with other respondents.[7] The researchers facilitated transferability through thick descriptions of the data and the findings. Transferability can be critical to the application of research findings because policy and management can rely on data, conclusions, and recommendations from a single or small number of research projects, often relying on evidence from a range of contexts that can be different from the one in which applications would be made.[7] To ensure transferability, the researchers provided the evidence that the findings of the study could be applicable to other contexts.

Authenticity

Authenticity is the genuine representation of participants perspectives, experiences, and voices without misrepresentation.[9] For the study to be considered authentic, the five principles of the authenticity were employed, namely, fairness, educative authenticity, catalytic authenticity, tactical authenticity, and ontological authenticity.

Ethical approval and informed consent

- Rigour incorporates ethics in qualitative research. The authors declare that the study obtained ethical approval from the University of South Africa (UNISA) College of Human Sciences (CREC Reference#: 45793514_CREC_CHS_2022). This study promotes truth and abides by ethical norms to avoid fabricating, falsifying or misrepresenting research data. Participants were not forced to engage in the study. The participants were introduced to the topic and asked to provide consent and if they agreed they signed an informed consent form which is a contract between the researchers and participants. Participants were offered the option to drop out of the study if the need arises. During the study, participants were always protected, and the researchers did not assume the study had no risk or harm.

Results

The following sub-section explores the multifaceted factors influencing non-adherence to ART, delving into both personal and systemic themes that emerged from the research interviews. The first theme that emerged from data analysis was socioeconomic barriers to treatment and the subtheme thereof was nonadherence. The second theme was stigma and discrimination barriers and subthemes thereof were misconceptions and confidentiality.

Theme 1: Socioeconomic barriers to treatment

It is important to first understand ART and the role it has in the treatment of HIV. All the participants in this study acknowledged being HIV positive and on ART. HIV treatment involves taking medicine as prescribed by a health care provider after a patient has been confirmed to be HIV positive. The ART for HIV reduces the amount of HIV in a patients' body and helps them to stay healthy. There is no cure for HIV, but it can be controlled with HIV treatment and the treatment does not prevent transmission of other sexually transmitted infections. The participants described different barriers that prevented them from adhering to the ART as prescribed by the health professionals. Participants noted the lack of funds to travel to clinics for medication and healthcare services and the nature of their employment involves frequent travel, which makes it impossible for them to keep their clinic appointments.

The following views illustrate this socioeconomic barrier as one of the challenges participants come across leading to non-adherence to HIV ART. One participant indicated that:

Unemployment, but now I'm working as a general worker, I'm an assistant builder. The nature of my job requires me to move around a lot, from one place to another, and I end up being distracted, I can't keep up with time and appointments at the clinic. Sometimes when I manage to get time to be at clinic, I spend the whole day at clinic and miss a day at *work, if I miss a day, I get no pay.* (Participant 1, Age 36).

The participants justified the need for mobile clinics that will attend to people living with her condition as non-adherence stems from financial issues. This is because they had to travel for access to health services. A participant had to say:

Mobile clinic is good and commendable to us who do not have money to travel to other clinics to access healthcare services (Participant 2, Age 43).

One participant pointed out how employment and travelling are controlling factors that led to appointments at clinics not being attended to. A participant reported that:

Nurses at mobile clinic were friendly and I used to enjoy being around them, but I moved from home to another place; I got a job to take care of an elderly woman who is bedridden, so my schedule got very tight and I'm unable to go to the clinic to fetch my ARVs. There is no one I can leave the elderly person with while I go to the clinic to fetch my ARVs (Participant 4, Age 43).

It was evident from the research findings that employment and relocation are some of the major causes of non-adherence to ART.

Table 2: Themes and subthemes

Themes	Subthemes
1 .Socioeconomic barriers to treatment	1.1 Non-adherence consequences
2.Stigma and discrimination barriers	2.1 Misconceptions 2.2 Confidentiality

Sub-theme 1.1: Non-adherence consequences

During the research interviews, it was discovered that most participants did understand that non-adherence had negative outcomes which resulted in different types of sicknesses. This was interesting for the researchers because it demonstrated that participants were aware of the risks they were facing for defaulting ARV medication. The quote below illustrates this:

It is not a right thing to default your ARVs. The results of defaulting ARVs are not good, I'm always physically weak, I contract flu all the time (Participant 2, Age 43).

Another participant also pointed out that they were constantly sick due to their not taking ARV medication and would travel to another health facility for assistance. This is because of the fear that they had defaulted on their ARV treatment at their local clinics so they would rather go to a clinic that did not know their HIV status. Furthermore, some of the participants mentioned that they suffer from kidney infections and tuberculosis due to non-adherence to treatment.

A participant commented:

*I became unhealthy, I had flu most of the time. My legs got swollen. I would travel to another clinic where they do not know about my HIV status and consult with regards to my swollen legs, I did not want to consult about my swollen legs from a clinic where I used to collect my ARVs, because I knew they would say the cause of swollen legs is me defaulting ARVs. It's not right at all to default ARVs, you get sick a lot, you lose weight and I also got kidney infection (*Participant 3, Age 24).

Another participant illustrated:

*Most of the time I'm physically weak and sick. I ended up contracting tuberculosis infection. I am taking medication for TB and according to the doctor my CD4 count is very low (*Participant 1, Age 36).

The findings show that sicknesses and being physically weak can be considered as risks that some participants are prone to due to not adhering to the ARV treatment. This was evident as all participants state that they all get sick when they are not taking their medication after a period of time. However, some participants point out sicknesses as side effects of the HIV treatment medication. The participant below stated that:

From 2018 I experienced pill fatigue, and I stopped taking my ARVs (Participant 3, Age 24).

Another participant confirmed this finding:

I would get sick and vomit after taking ARVs. I was diagnosed with kidney infection. I was born HIV positive (Participant 5, Age 22).

Theme 2: Stigma and discrimination barriers

HIV stigma and discrimination have detrimental effects on the emotional wellbeing and mental health of people living with HIV. Participants emphasised how much the negative attitudes by family members and members of the community contributed to their non-adherence to ART. One of the participants feared disclosing their HIV status because they thought they would be discriminated against or judged negatively because of their HIV status, and they did not have a support system at home. During the interview process there were also misconceptions that were detected which promoted inaccurate information about the virus leading to some participants defaulting from taking antiretroviral medication.

Sub-theme 2.1: Misconceptions

The participants mentioned a variety of reasons that led them to default from taking HIV treatment medication. Some of the reasons were socially constructed misconceptions that were believed by some of the participants to be true. The most common misconception among participants was that when you take the ART for a certain period of time the virus dies completely in your system; as a result, they discontinue taking ARVs.

A participant had this to say:

I would also look up to people who were HIV positive around me that stopped taking ARVs and were looking fine, not sick, continuing with their lives as normal and I also did the same and stopped taking my ARVs (Participant 3, Age 24).

The above statement suggests that there are behaviours and misconceptions that are widely mistaken that can cause people to default and suffer from the virus. One participant mentioned how they believe they are "*strong*" and "*different*" which made them more resistant to the virus hence, the non-adherence to ARV treatment.

The following excerpt is an example of the above misconception:

Our bodies are made differently. I am strong because I was diagnosed with HIV in year 2007 but I initiated on ARVs in 2019. When it was time for test and treat, my CD4 count was still high and even now that I have defaulted my ARVs I'm not sick (Participant 4, Age 43).

The participant further stated:

*I wouldn't really call myself a defaulter because I sometimes access ARVs from my friends who get three months' supply from their clinics (*Participant 4, Age 43).

This was mostly interesting and intriguing to the researchers, that even though the participant states that he is strong and different he understands the importance of adhering to ART hence he seeks ARVs from friends who get three months' supply. Another fascinating finding was that apart from having a different, strong body the participant goes as far to request family members to collect medication on his behalf.

The quote below illustrates this:

I used to ask my family to fetch my ARVs on my behalf, but the challenge was they would not know which dates the mobile clinic will visit our area (Participant 4, Age 43).

Sub-theme 2.2: Confidentiality

During the interview some of the participants mentioned confidentiality as one of the reasons for non-adherence to ART. This was evident when participants were asked a question about whether they have disclosed their HIV status. Below is a participant's viewpoint:

No, because I have not disclosed my status at home, my mother is an alcoholic and my fear is, if I told her about my HIV status, she would tell everyone about it when she is intoxicated (Participant 2, Age 43).

This was an interesting finding because it also shows how non-adherence is influenced by lack of support and fear of disclosure by family members. Furthermore, the participant further stated that:

They should improve the setting. Nurses' stations should not be close to each other. Nurses must speak softly to maintain confidentiality. Community (patients) should not be seated close to nurses' stations. Withdrawal of blood should not be taken in front of other patients because if a nurse withdraws blood from you the community immediately knows that you are HIV positive. All the files in clinic should be the same in colour to avoid being stigmatised (Participant 2, Age 43).

Yet again, this finding demonstrates how health professionals (nurses) and the environmental setting have an impact on how people respond to the ART. It is worth noting that during the interview confidentiality was a vital factor that had an impact on ARV treatment adherence.

Discussion

During the study, it was discovered that HIV/AIDS is not merely a bio-medical phenomenon, but a disease that encompasses socioeconomic barriers that have direct correlations with non-adherence. Findings revealed that non-adherence can compromise the efficacy of ART and impact on healthcare outcomes adversely. This has an immense effect on HIV positive patient's health, as they default their treatment and become sick. The authors confirm these assertions in their study by stating that non-adherence to ART over a given period tends to be a contributory factor in opportunistic infections such as tuberculosis and pneumonia.[10]

Poverty and unemployment are some of the constraints affecting non-adherence to treatment. This was reported by a few participants, especially in relation to transport costs for collection of ARVs from the clinic. Economic factors have significant impact to non-adherence to HIV treatment as some patients reported that they were unemployed and experienced poverty.[10]

As a result, lack of income meant that most of the participants were unable to buy food or afford transportation costs to meet their clinic appointment dates. The findings of the study as well as the participants suggest that some secured employment far from their local vicinity where they collect ARV medication which becomes a contributing factor to non-adherence.[11]

Some HIV positive patients stay very far from the health facilities and are thus challenged to make follow-up clinic appointments, particularly in rainy seasons.[10] These are like results found in other studies[12] which also suggested that the nature of patients' employment at times affected their ability to adhere to HIV treatment, as they may have to travel, and the nature of some jobs was also such that their schedules were not regular.

According to[13] the HBM identifies perceived barriers as a potential negative consequence that may result in failing to take health action. As a result, barriers such as financial costs, side effects of medications, are factors that can deter individuals from adhering to HIV treatment. In this study the most reported consequence of non-adherence to HIV treatment was sickness.

This claim is supported by[14] stating that loss of weight and appetite, fatigue, oral thrush, diarrhea, and/or Kaposi's sarcoma (a cancer of the blood vessels affecting the mouth, skin, and lymph glands) are some of the symptoms that may be noted when there is non-compliance and non-adherence to HIV treatment. This was evident in the study as some participants reported that they would constantly get sick due to them not taking the HIV medication as prescribed by the health professionals.

Stigma was found to have provoked discrimination, rejection and the isolation of people living with HIV/AIDS leading to non-adherence. The finding of the study by[15] points out that stigma and discrimination have been reported to be important variables in many studies and greatly contribute to low rates of disclosure and poor adherence to HIV treatment. It was evident in this study that HIV stigma created emotional distress, resulting in some participants skipping doses and defaulting in taking HIV treatment medication. In addition, stigma results in misconceptions as some participants were not well informed about HIV/AIDS. For instance, feeling healthy for some participants were interpreted by them as meaning that they did not have to take their medication. This is usual, because of pre-existing stereotypes and prejudices associated with HIV/AIDS.

Feeling better for HIV positive patients is like a double-edged sword that positively and negatively influenced adherence in some patients; while some patients believed in the treatment because they were sure to regain their health after the treatment, others took advantage of the improvement in their health and deliberately stopped taking their treatment to carry on with their past risky social lifestyles.[16]

Pre-existing stereotypes and prejudice appear to be an existing barrier to non-adherence to HIV treatment. Most participants pointed out how stigma and discrimination played a role in them defaulting HIV/AIDS treatment. Furthermore, some of the participants pointed out that this was due to lack of support from family. Discrimination had been experienced by some of the patients in a form of rejection by their family members, employers, and community members, who pass derogatory remarks resulting in discontinued adherence to HIV treatment.[14]

According to[13], the HBM cues to action are events that motivate people to act in changing their habits and are crucial determinants of change. External factors such as advice from healthcare providers and support from family or peers may serve as cues to prompt individuals to adhere to treatment. Lack of relevant cues or insufficient support systems contribute to non-adherence to HIV treatment.

Confidentiality was discovered to be one of the contributing factors to non-adherence to HIV/AIDS treatment. It was evident from the previous chapter that some healthcare workers' attitudes towards patients with HIV/AIDS led to lack of adherence to treatment. Healthcare providers' negative attitude and absence of familial support impeded adherence to treatment.[17] Most participants were unwilling to disclose their HIV status to their family members as they feared that confidentiality would not be maintained, and the clinic setting exposes their HIV status to other patients.

Limitations

- Limited research data were available addressing patients’ non-adherence to ART.
- The target population was only limited to males and females aged 18 years and above, who attended the mobile clinic located in the Ray Nkonyeni Local Municipality of the Ugu District, KwaZulu-Natal province.
- Considering differences in terms of the biographical details of the participants (i.e. age, source of livelihood, length of treatment, and marital status), it cannot not be assumed that barriers from other race groups (i.e. Indians, Coloureds and Whites), or residents in other provinces, would be the same.
- The participants who were willing to cooperate in this study and share their difficulties with adherence to HIV/AIDS treatment were mostly women, although it should be noted that the interviews were conducted by a woman and that men might therefore have been unenthusiastic to discuss their personal experiences with a woman.
- An increased proportion of male participants in the research may have contributed to the emergence of additional themes and provided valuable understanding of gender-specific issues. Because of the high level of denial about the prevalence of HIV/AIDS and refusal to use condoms, this may have also created an educational platform among men.

Strengths

To curb non-adherence to ARV treatment, efforts from multiple sources are required, especially in poverty-stricken environments. A multifaceted intervention that will investigate the different barriers that hinder adherence has potential to enhance HIV/AIDS treatment adherence among patients.

Implications of the findings for policy and practice

Policy makers to closely monitor patients’ adherence to ARV treatment and their attendance at the mobile clinics. Human resources on duty should be able to contact the patients’ closest family members.

Conclusion

Even though HIV/AIDS treatment in South Africa is now freely available for the public the potential benefits are obstructed by non-adherence to the treatment. The findings show that participants did not adhere to the HIV/AIDS ART due to multifaceted underlying barriers.

Consent for publication

All the authors have read and agreed to the published version of the manuscript.

Data availability

The data supporting the findings of the study are available from the authors upon reasonable request.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing the manuscript.

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Authors' contributions

A.S was responsible for the collection and analysis of data and drafting of the manuscript. DSK was responsible for supervising A.S and made conceptual contributions in the whole manuscript. All the authors contributed to the finalization of the manuscript.

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