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Acceptability of dihydroartemisinin-piperaquine as malaria intermittent preventive treatment for pregnant women living with HIV in Southern Mozambique

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Abstract

Background HIV-infected pregnant women (HIVPW) are especially susceptible to malaria infection. However, HIVPW cannot receive the recommended malaria Intermittent Preventive Treatment (IPTp) with sulphadoxine-pyrimethamine due to potential adverse reactions with cotrimoxazole, which is given to HIV-infected individuals to prevent opportunistic infections. Within the scope of a clinical trial to evaluate the safety and efficacy of dihydroartemisinin-piperaquine (DHA-PPQ) as IPTp in HIVPW, we aimed to explore pregnant women's acceptability of DHA-PPQ in the Manhiça District Hospital, Mozambique.

Methods A qualitative study was conducted from December-2019 to October-2020 including 44 HIVPW participating in the clinical trial, 35 HIV-uninfected pregnant women attending the antenatal care clinic and eight health care providers (HCPs). Information was obtained through semi-structured and in-depth interviews. The interviews were recorded, transcribed, coded, and a combination of content and thematic analysis was performed.

Results All the HIVPW took monthly doses of DHA-PPQ until delivery. They stated that the main motivation for accepting DHA-PPQ was the belief that guidance from healthcare providers should not be refused. Despite some HIVPW reporting vertigo, vomiting, and malaise after taking DHA-PPQ, they expressed willingness to use it in a future pregnancy, believing it contributed to a healthy outcome. Pregnant women and HCPs indicated that factors supporting DHA-PPQ acceptability include information on the benefits of IPTp, testimonials from women who have previously taken DHA-PPQ, and home delivery of DHA-PPQ by HCPs. The perception that home dispensing of DHA-PPQ (a medication administered only for HIVPW) could affect measures taken to ensure HIV-infection confidentiality was not found to be a potential barrier to DHA-PPQ acceptability when delivered in HIVPW's homes.

Conclusion The acceptability of DHA-PPQ among HIVPW appears to be influenced more by trust in healthcare providers rather than by the perceived benefits of the medication itself. Leveraging this trust to enhance awareness

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and understanding of DHA-PPQ's benefits could further improve its acceptability. Moreover, further implementation research focused on acceptability in a real-world environment is essential to deepen the understanding of DHA-PPQ acceptability beyond the clinical trial setting, and inform policy decisions accordingly.

Keywords Pregnant women, Dihydroartemisinin-piperaquine, Acceptability, Malaria, Prevention, Mozambique

Introduction

HIV and malaria are two of the major public health problems faced by the Mozambican population. The national HIV prevalence in adults is approximately 12.5% [1] and women are disproportionately affected, being three times more likely to be infected when compared to their male counterparts. As a consequence, in some areas, the prevalence of HIV in pregnant women reaches up to 30% [2, 3]. Concerning malaria, the country reported an increasing trend since 2015, with over 10 million cases (95% confidence interval [95% CI]: 7 172 000—14 230 000) and 22 291 deaths (95% CI: 13 900- 37 800) in 2021 [4, 5]. Malaria prevalence based on rapid diagnostic test results was estimated to be 39% [6]. Moreover, many individuals in Mozambique are co-infected with HIV and malaria, and the interaction between the two infections is particularly deleterious during pregnancy [7, 8].

In order to improve the management and reduce the impact of HIV and malaria among pregnant women, one of the most vulnerable groups to both infections, Mozambique has adopted the corresponding WHO strategies [9, 10]. At the antenatal care (ANC) clinic HIVPW receive ferrous sulfate combined with folic acid for prevention and treatment of anaemia and fetal malformations, lifelong antiretroviral therapy (ART), isoniazid and cotrimoxazole prophylaxis (CTXp) for prevention of tuberculosis [TB] and opportunistic infections. This fact involves the daily self-administration of an average of four to five different medications during the pregnancy course, which can lead to errors in drug administration and lack of treatment adherence [11, 12]. In addition, HIVPW may receive other drugs depending on the occurrence of other diseases such as urinary infections, sexually transmitted diseases (STDs) and non-communicable diseases. For malaria prevention during pregnancy, the WHO guidelines recommend a package of interventions which includes the use of insecticide-treated nets, administration of intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP), and appropriate case management through prompt diagnosis and effective treatment of malaria [13]. However, although HIVPW are especially susceptible to malaria infection, they cannot receive SP due to potential drug interactions with CTXp [14].

In this context, the evaluation of the safety and efficacy of an alternative and effective antimalarial drug such as dihydroartemisinin-piperaquine (DHA-PPQ), for malaria IPTp in HIVPW receiving CTXp may help to improve the control of malaria infection in this population. With this aim, the MAMAH clinical trial, a multicenter double blind randomized study funded by the European & Developing Countries Clinical Trials Partnership (EDCTP),

was conducted in Gabon and Mozambique during 2019–2022 [15]. As part of the MAMAH clinical trial, HIVPW were required to take DHA-PPQ or placebo on a monthly basis from the second trimester of gestation, resulting in the uptake of 9–12 additional tablets over three consecutive days. Yet, evidence suggests that poor adherence to ART regimens is common, partly due to the need for additional medications, which further burdens individuals [16]. Furthermore, participating in a clinical trial specifically designed for women living with HIV would have implications for HIV confidentiality and contribute to HIV-related stigmatization. This could impact not only the acceptability of the DHA-PPQ but also adherence to the drugs related to HIV infection [17]. Therefore, within the context of the MAMAH clinical trial in Mozambique, it was considered relevant to assess DHA-PPQ acceptability and understand facilitators and barriers DHA-PPQ acceptability, including how trial participation could affect adherence to ongoing health interventions and the strategies HIVPW use to maintain HIV confidentiality. Beyond its clinical efficacy, the success of DHA-PPQ will relies on multiple factors, including the attitudes, behaviors, and knowledge of pregnant women, all of which are influenced by social and cultural contexts [18]. We hypothesize that limited awareness of malaria during pregnancy and the purpose of routine antenatal care (ANC) interventions may hinder compliance and, consequently, their overall effectiveness. Therefore, understanding malaria knowledge is a crucial step in identifying barriers that may impact the effectiveness of DHA-PPQ on malaria prevention during pregnancy.

This study aimed to address the above gaps by firstly, exploring pregnant women's knowledge about malaria infection (causes, clinical manifestations and prevention measures); secondly, assessing DHA-PPQ acceptability as IPTp in HIVPW; thirdly identifying barriers and facilitators to DHA-PPQ acceptability; and finally, understanding the influence of participating in the MAMAH clinical trial on strategies employed by HIVPW to ensure HIV

confidentiality and adhere to the on-going HIV treatment. To the best of the authors'knowledge, no studies have examined the acceptability of DHA-PPQ as an alternative for IPTp in HIV-positive pregnant women (HIVPW), gathering insights simultaneously from HIVPW enrolled in the clinical trial, HIV-uninfected pregnant women attending antenatal care, and healthcare providers involved in both ANC and the clinical trial.

Methods

Study design

This is a qualitative descriptive study, which included in-depth and semi-structured exit interviews with HIVPW participating in the MAMAH clinical trial, HIV-uninfected pregnant women (NoHIVPW) attending routine ANC and semi-structured interviews with health care providers (HCPs) at the Manhiça District Hospital (MDH), in southern Mozambique. The study was conducted from December- 2019 to October- 2020. In this study, the acceptability of DHA-PPQ for malaria prevention in pregnancy was conceptualized based on the Health Belief Model due to its proven track record in predicting various health-related conditions [19]. According to this model, two main factors influence the likelihood that a person will adopt a recommended preventive action. First, a person must feel susceptible by disease. Secondly, the person must believe that the benefits of practicing prevention outweigh the perceived barriers to the preventive action. Therefore, four constructs can be obtained from this model: perceived susceptibility, perceived severity, perceived benefits and perceived barriers.

The MAMAH clinical trial

The MAMAH clinical trial enrolled 664 HIV-positive pregnant women, with 444 participants from Mozambique and 220 from Gabon. Participants received daily CTXp and ART and a long-lasting insecticide treated net (LLITN) starting from their enrolment, which coincided with the first ANC contact as part of the trial interventions. Additionally, participating HIVPW received DHA-PPQ or placebo monthly over three consecutive days from the second trimester of gestation, implying 9–12 more tablets (depending on the woman's weight). The first dose was administered by nurses at the health facilities while the remaining two doses were administered at home by duly trained field workers.

Study setting

The Manhiça District is located 80 km north from the capital city, Maputo. The Manhiça Health Research Centre (CISM) runs a demographic surveillance system (DSS) since 1996, involving intensive and regular monitoring of a population of about 216,000 inhabitants covering the entire district, an area of around 2891.1 km2 [20, 21]. There are 21 healthcare centers, including a rural hospital, Xinavane Rural Hospital and a referral district hospital, Manhiça District Hospital (MDH). Overall, 90–93% of pregnant women in the district attend at least on ANC visit. However, many start these visits later in pregnancy, and attendance decreases in subsequent visits [22]. Pregnant women are managed according to Mozambican national guidelines adapted from WHO guidelines [23, 24]. The area is endemic for malaria and the community prevalence of HIV is very high, reaching as high as 30% [25, 26]. Retention on HIV care and treatment is a challenge. At the end of 2019, the country reported that among the 97% of all HIVPW receiving ART at ANC clinics, only 77% and 83% were retained in care at 33 days and 99 days, respectively [22]. The completion of this study coincided with the start of the COVID- 19 pandemic in Mozambique [27]. The country adopted COVID- 19 mitigation strategies that included, among others, the scheduling of ANC visits every three months instead of monthly, and the quarterly dispensing of all drugs recommended in the ANC, as well as ART [27]. Each day before ANC visits begin, health professionals hold health education sessions in the waiting room for all individuals seeking care. Topics included malaria, HIV, nutrition, COVID- 19, and other health conditions, as well as various research activities conducted at the hospital.

Sampling and recruitment strategies

Study participants were identified through an intentional non-probabilistic sampling strategy. HIVPW already enrolled in the MAMAH clinical trial were identified and invited to participate in the study by the nurses working at the ANC. Trial participants that agreed to participate were provided with a separate informed consent form. Although the determination of sample size in qualitative studies does not necessarily follow probabilistic sampling models as in quantitative research, the sample size was decided following the sampling approach of previous similar studies (i.e. framed within a broader clinical trial), where 10–30% of clinical trial participants was considered the minimum required sample size for the qualitative sub-study [28]. Thus, a sample size calculation of 10% of the number of HIVPW expected to be enrolled in the on-going clinical trial in Mozambique (444 participants) was used. For each HIVPW participating in the clinical trial and recruited into the qualitative study, a NoHIVPW attending the routine ANC at the MDH was identified and invited to the study, yet the saturation point was reached after 35 interviews in this group. Using a standardized guideline developed by the research team, the semi-structured exit interviews

were conducted among 79 pregnant women including 44 HIVPW and 35 NoHIVPW (Fig. 1), as soon as they left the ANC visit room. Ten women from each group (HIVPW and NoHIVPW) who agreed to participate in the semi-structured interviews and demonstrated extroverted tendencies during the interviews were purposely invited to participate in the in-depth interviews. We conducted eight semi-structured interviews with the eight randomly selected HCPs (seven nurses and one counsellor) directly involved in ANC and clinical trial procedures. Study participants were not offered any monetary or in-kind compensation for participating in the qualitative study. However, women enrolled in the clinical trial received a snack one hour after taking the research product (DHA-PPQ or placebo).

Data collection and analysis

Figure 2 presents the thematic areas explored with the study participants through interviews. Semi-structured exit interviews were conducted at the ANC of the MDH and explored the following thematic areas: i) knowledge about malaria causes, clinical manifestations and prevention measures among HIVPW and NoHIVPW and ii) HIVPW's ability to distinguish the DHA-PPQ tablet by showing them the drug, without any label as shown in Fig. 3. The in-depth interviews were conducted at places that participants considered more convenient, preferably outside the context of health facilities to minimize respondent bias. The thematic areas included iii) HIVPW's perceptions and acceptability of DHA-PPQ, and NoHIVPW's perceptions and acceptability of DHA-PPQ considering a hypothetical HIV infection; iv) aspects that could increase or reduce the acceptability of DHA-PPQ by HIVPW (facilitators and barriers); v) the influence of participating in the MAMAH clinical trial and being administrated a medication aimed only for HIVPW on strategies carried out by HIVPW to ensure HIV confidentiality and vi) the influence of an additional pill (DHA-PPQ) on adherence to the already taken medications. Finally, thematic areas explored through semi-structured interviews with HCPs conducted at MDH included: i) perceptions and acceptability of DHA-PPQ as a malaria IPTp for HIVPW and ii) facilitators and barriers for DHA-PPQ acceptability. Trained social scientists conducted the interviews in the preferred language of the participants. The interviews were recorded using digital voice recorders, after participants' permission. Subsequently the interviews were transcribed verbatim in MS Word, by the same team members who collected the data. The interviews performed in local language (Xangana) were translated into Portuguese. The social sciences research coordinator and team leader performed the data quality checks by reviewing the transcripts while listening to the audio recording. The transcripts were then imported to NVivo version 12 (QSR International Pty. Ltd. 2015) software. A combination of content and

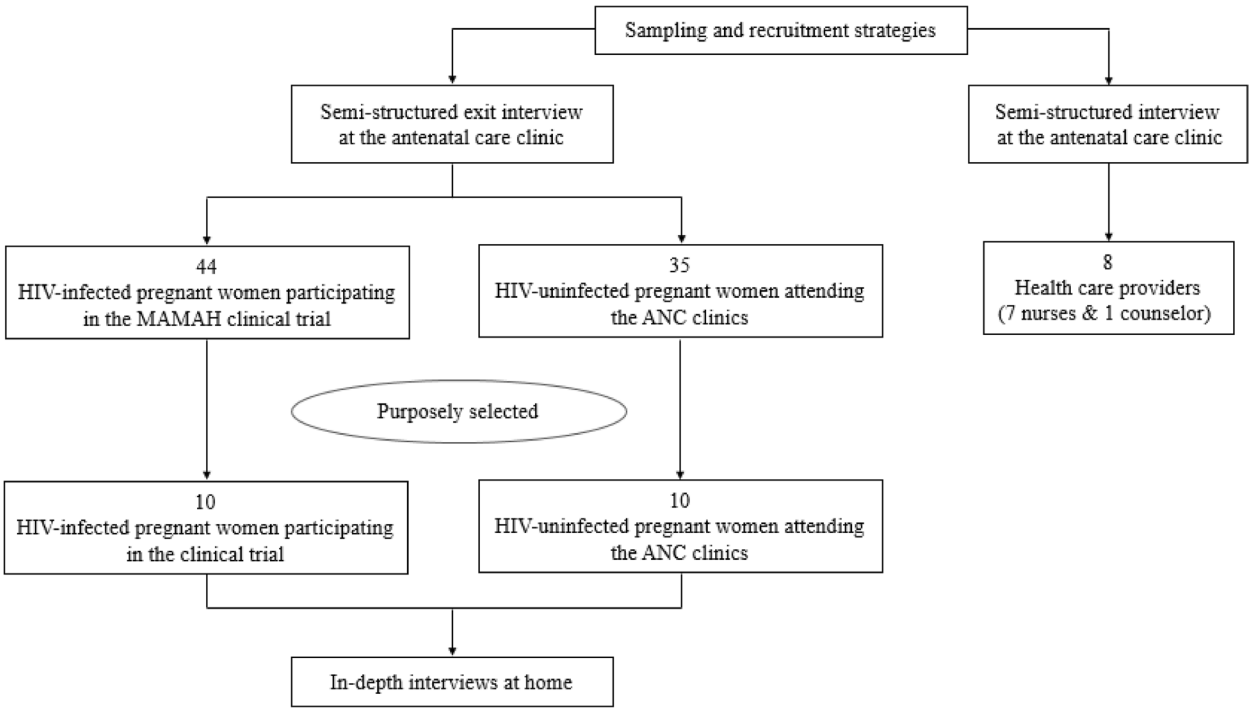

Fig. 1 Sampling and recruitment strategies

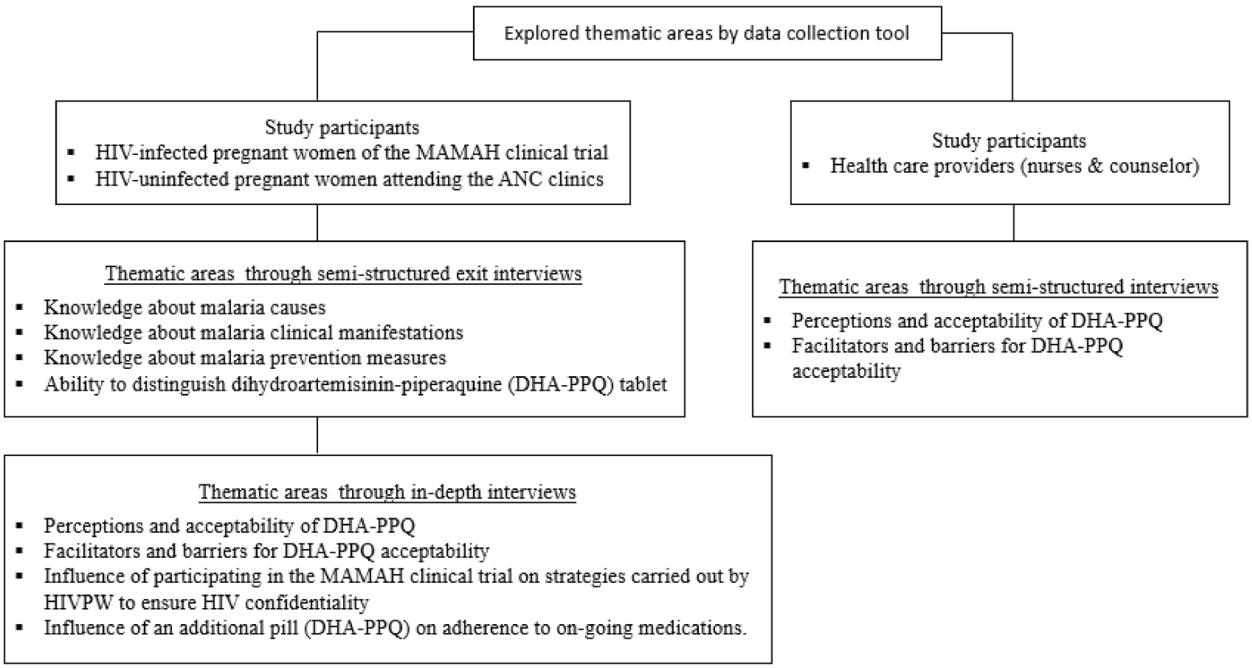

Fig. 2 Thematic areas explored in the study participants through the semi-structured and in-depth interviews

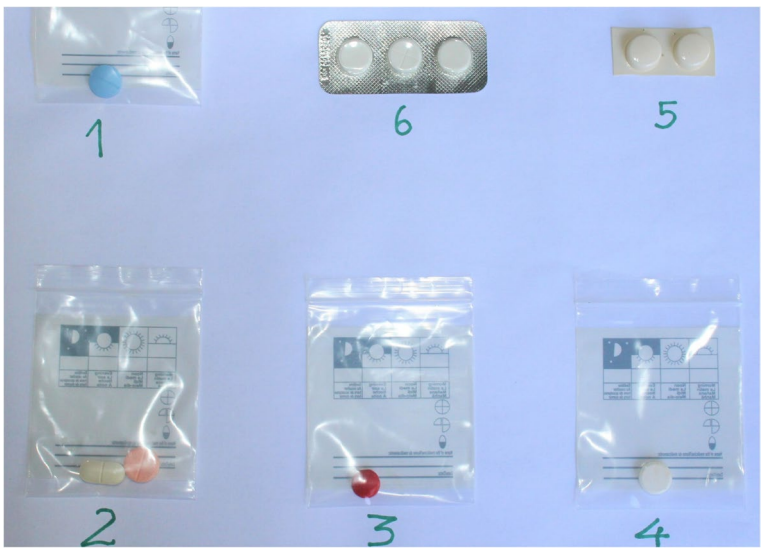

Fig. 3 Tray containing medication provided to pregnant women attending ANC, based on their HIV infection status. Unlabeled tablets were presented to study participants to test their ability to identify them (dihydroartemisinin-piperaquine included only for women participating in the clinical trial)

thematic analysis was performed through the following steps: i) generating categories based on the thematic areas structuring the question guides, according to the Health Belief Model; ii) coding text according to each category; iii) annotating emerging themes and patterns and readjusting the categories and relationships between them [29]. Then, consensus on codes and emerging themes was reached between the social scientist and the team leader.

Results

In this section, apart from presenting the socio-demographic and clinical characteristics of the study population, we present the study results in seven main themes.

The themes are i) pregnant women's knowledge about malaria transmission and clinical manifestations, ii) pregnant women's knowledge about malaria prevention measures during pregnancy, iii) practices of malaria prevention measures in pregnancy; iv) Perceptions and acceptability of DHA-PPQ; v) facilitators and barriers to DHA-PPQ acceptability; vi) the influence of participating in the MAMAH clinical trial and being administrated a medication aimed only for HIVPW on strategies carried out by HIVPW to ensure HIV confidentiality and vii) the influence of an additional pill (DHA-PPQ) on adherence to the already taken medications.

Socio-demographic and clinical characteristics of the study population

The socio-demographic and clinical characteristics of the 44 HIVPW participating in the MAMAH clinical trial and 35 NoHIVPW attending ANC included in the study are shown in Table 1. The median age of the women was 27 years (IQR: interquartile range [IQT] 21–32). Fifty-two women (65.8%) were unofficially married and Christian-Zion was the predominant religion among the participants. The median gestational age at recruitment was sixteen weeks (IQT 13–19) and the median of live children per women was four (IQT 4–5). Fifty-six women (71%) were housewives and 13% had no formal school education (no education or did not complete primary education). Regarding the eight HCP, seven were nurses and one a counselor.

Pregnant women's knowledge about malaria transmission and clinical manifestations

All pregnant women had heard about malaria in the past. Concerning malaria transmission mode and cause, the mosquito bite was the most reported, however, other causes were mentioned as shown in Table 2.

> *"Malaria is caught with a mosquito bite... Eating something like mangoes and oranges without washing you will catch malaria...Foods such as salads."(HIVPW, 31 years old).*

Only a few women (2/79) were able to explain the sequence from still water to mosquito breeding, and they were young NoHIVPW.

> *"Hmm, we can prevent ourselves from getting dirty.... avoid leaving dirty water.....because if we leave dirty water, the mosquitoes will come."(NoHIVPW, 21 years old).*

Table 1 Basic characteristics of the interviewed pregnant women at the enrolment

Variable		*N* = 79 n (%)
Age (years): median (IQR)		27 (21–32)
Age group	< 20	11 (14)
	20–24	20 (25)
	25–34	35 (44)
	> 35	13 (17)
Education	No formal education	10 (13)
	Primary	46 (58)
	Secondary	22 (28)
	University	1 (1)
Religion	Christian (Zion)	34 (43)
	Christian (Assembly of God)	16 (20)
	Christian (Others)	26 (33)
	Atheist	3 (4)
Marital status	Married (legally and in facto union)	51 (65)
	Single	28 (35)
Occupation	Housewife/Unemployed	56 (71)
	Self-employed (saleswoman)	16 (20)
	Formally employed	6 (9)
Gestacional age (months): median (IQR)		4 (4–5)
Children currently alive: median (IQR)		4 (4–5)
HIV infection	Yes	44 (58)
	No	35 (42)

N/n: number

Table 2 Most known causes and clinical manifestation of malaria

	HIV infection	
	HIV + *N* = 44 n (%)	HIV- *N* = 35 n (%)
Malaria causes		
Mosquito bites	18 (41)	21 (60)
Backyard and dirty environment	3 (7)	3 (9)
Still water	2 (5)	2 (6)
Bad food hygiene	4 (1)	1 (3)
Don't know/mentioned nothing	5 (11)	3 (9)
Malaria clinical manifestations		
Headache	20 (46)	20 (57)
Chill	20 (46)	9 (26)
Fever	19 (43)	13 (37)
Arthromyalgia	11 (25)	5 (14)
Vomiting/nausea	7 (16)	11 (31)
Weakness	7 (16)	6 (17)
Anorexia	4 (9)	2 (6)
Abdominal pain	2 (5)	4 (11)
Diarrhea	0	3 (9)
Cough	3 (7)	0
Mouth bitterness	2 (5)	0
Other	2 (5)	2 (6)
Don't know/mentioned nothing	5 (11)	1 (3)

N/n: number

"Malaria is only caused by water, mosquitoes..... dirty water.....Sometimes your house is near a river.....and it has dirty water.....or sometimes if a person doesn't have mosquito nets..... maybe."(NoHIVPW, 19 years old).

Headache, fever, chill, vomiting/nausea and arthromyalgia were the most reported malaria symptoms. Though, it is noted that up to 10% of HIVPW did not know any malaria symptom (Table 2).

Pregnant women's knowledge about malaria prevention measures during pregnancy

The most frequently reported malaria prevention measures by both HIVPW and NoHIVPW were the use of mosquito nets, elimination of mosquito breeders, use of burnet spatial repellents and hygienic habits. None of the women mentioned the need of mosquito nets to be a long lasting insecticide-treated net.

"You have to sleep inside a mosquito net."(HIVPW, 31 years old)

"I always have to control my backyard as to order the grass to be burnt and everything else to be kept in a clean place." (HIVPW, 29 years old)

Only two women reported indoor residual spraying as a way to prevent malaria. And no women mentioned the uptake of IPTp as malaria prevention method.

"Sometimes people pass by and put medicine in the houses [refers to spraying] ...so that the mosquito that ...causes malaria dies." (NoHIVPW, 38 years old)

Practices of malaria prevention measures in current pregnancy

The malaria prevention measures implemented by pregnant women in their current pregnancy were also explored. The use of mosquito nets, personal hygiene, elimination of mosquito breeders and use of burnet spatial repellents were the preventive measures taken during the current pregnancy by both groups of pregnant women.

"In my house, it's just cleaning, and when we sleep use a mosquito nets ..." (NoHIVPW, 26 years old)

"I have to sleep inside a mosquito net, I have to always clean what...wash my hands...

...I always have to control my backyard as it is, have the grass burn, everything else stay in a clean place." (HIVPW, 29 years old)

When asked about the ease of implementing prevention measures during their current pregnancy, mosquito nets were considered the easiest to implement. However, one HIVPW perceived them to be difficult to use due to a sensation of suffocation. The use of insecticides was reported as difficult to implement due to smoke, bad smell and perception that it may cause intoxication.

"It's lighting the dragon (referring to burnet spatial repellents).... cause cough."(HIVPW, 35 years old)

"It's dragon, because for me dragon brings me flu."(NoHIVPW, 18 years old)

"Because the net hahhhh [worry], suffocates me in there."(HIVPW, 33 years old)

Perceptions and acceptability of DHA-PPQ

During the interviews, none of the HIVPW included in the clinical trial was able to identify the DHA-PPQ by

their real name and some called them Fansidar (a commercial name for sulphadoxine-pyrimethamine). DHA-PPQ tablets were recognized by the container and color. Some of the women mentioned that they were unaware of DHA-PPQ usefulness.

"Hmm, when they give me to take it, inside my heart, I think I'm protecting my son so he doesn't get sick.... Hmm, I don't know what it protects."(HIVPW, 20 years old)

"...These I can't lie, I don't know what they are for."(HIVPW, 38 years old)

"I don't know. When they gave me pills and told me to take and I didn't ask what they were for. But that these pills are to do what when you take them, I don't know. I just took pills and took it." (HIVPW, 22 years old)

All the HIVPW participating in the clinical trial included in this qualitative study complied with monthly doses until delivery. When responding to the open-ended question about the motivation to be part of the study and take DHA-PPQ, HIVPW stated firstly that they accepted taking DHA-PPQ due to the belief that they cannot refuse any guidance from HCPs, and only then did they consider disease prevention during pregnancy and protecting their unborn child.

"When I get here, they say that pills like that came out for you pregnant, I don't deny it, I accepted because there's nothing I can deny, there's nothing I trust, I don't know what situation I'm in, if they say there's something like that, I don't deny it, I accept it, because there is nothing that I can discover alone in my body,..... aaah ..... if they say I have something like this I don't deny I accept it maybe I can be saved from other things..."(HIVPW, 23 years old)

"Hahhh, when they give you, you can't deny it. You can only take."(HIVPW, 35 years old)

Furthermore, HIVPW stated that other HIVPW not included in the clinical trial would accept taking DHA-PPQ as malaria IPTp in the future.

"They [referring to HIVPW not include in the clinical trial] can accept it because they don't know what will happen to them if they don't take pills. They do not know." (HIVPW, 38 years old)

"Because the pills prevent malaria. Because malaria is also a disease that kills". (HIVPW, 23 years old)

"Yes, they can accept it because they don't know what will happen to them if they know they have to prevent the child." (HIVPW, 32 years old)

In addition, the NoHIVPW stated that they would take DHA-PPQ if they become infected by HIV despite the fear of never having heard about DHA-PPQ.

"I would accept it but with fear because I don't even know it." (NoHIVPW, 26 years old)

"Because even if I don't take it, haaa it's not their health, it's my health." (NoHIVPW, 26 years old)

"To prevent me from malaria. Because malaria is also a disease that kills". (NoHIVPW, 23 years old)

"For the health...., for the health of my baby and mine too."(NoHIVPW, 21 years old)

Facilitators and barriers of DHA-PPQ acceptability

Pregnant women and HCP reported that facilitators for DHA-PPQ acceptability would be the information provided about the benefits of IPTp, the testimony of women who have already taken DHA-PPQ and home dispensing of DHA-PPQ by health providers.

"Huh, women want you to explain to them first. As daily first of all, we have morning sections there [referring to the waiting room at the hospital] ... where it is explained that in there [referring to the visiting room], we have more medication to be taken. And when they get in the visit room, pregnant women receive explanation of everything and give consent ...and the one who accepts it is because she knows that it is for her good." (Nurse 3)

"For people to accept taking these pills, we must be the ones who have already taken the pills to encourage them (referring to other HIVPW) to take the pills. Because the person gains strength when they see others." (HIVPW, 24 years old)

"Well, okay, accepting to come three consecutive days to the health unit, this can make it difficult. It's just that it's a bit like that, if we deliver medicine to take at home... we won't know if they took it or not. That is why it is very imperative for a healthcare provider to go to women's house... take the pills while he is present, stay a while to see what the reaction is before saying goodbye (health provider)." (Nurse 1)

While most HIVPW participating in the study did not report any side effects after DHA-PPQ administration,

those who did mentioned experiencing vertigo, vomiting, and malaise.

"The ones I felt like I'm not well after taking it are the ones in the box (referring to DHA-PPQ). Only this one was causing problems. It made me feel uncomfortable. Sometimes when I took it I felt like I have vertigo. Can't catch anything. But after two hours of time passed." (HIVPW, 38 years old)

"The ones that sometimes made me dizzy are those of malaria prevention, but after an hour of time, yes, but then it passed." (HIVPW, 29 years old)

"I felt bad. Sometimes I vomited." (HIVPW, 20 years old)

Despite these side effects after DHA-PPQ administration, HIVPW stated that they would take DHA-PPQ in a subsequent pregnancy, as they believe that it has contributed to a healthy pregnancy.

"Yes, I was going to take it because it protected the child from diseases inside my belly. And I don't know if I hadn't take what would have happened." (HIVPW, 38 years old)

"If something had happened, and I didn't feel well, I would say that I'm not taking it because of that"."(HIVPW, 24 years old)

Influence of participating in the MAMAH clinical trial on HIV confidentiality

To explore how participating in the MAMAH clinical trial and receiving medication specifically intended for HIVPW could influence their strategies to ensure HIV confidentiality, participants were firstly asked about disclosing their HIV infection status to their family.

Most HIVPW reported that they live with their husband and children and that all the family members were aware of their HIV infection status before the start of clinical trial interventions.

"Because I didn't hide it for my kids." (HIVPW, 38 years old)

"You know; I can almost say that everyone here at home knows. Even the mother-in-law know. There is no one who does not know. Everybody knows." (HIVPW, 24 years old)

"My husband and my kids know (referring to be HIV infected). You have to tell your family, even if it's just one person." (HIVPW, 33 years old)

When asked about the importance of disclosing their HIV status, women stated that it facilitates family support if they are unable to collect medicines at the hospital, allows them to take medicines without further questions or providing additional information, and helps them feel comfortable taking the drugs prescribed at the ANC.

"My husband and my kids know (referring to be HIV infected). You have to tell your family, even if it's just one person. For when I get sick and I can't go to the hospital, I'll tell them to go to the hospital and get pills." (HIVPW, 33 years old)

"…almost every family knows. They help me, motivate me… that this is nothing." (HIVPW, 23 years old)

"I'm not afraid anymore, I'm not scared anymore, there's no one who's afraid anymore. What made me tell them is because of tomorrow's things… because you don't know what will happen to you as time goes by… you could catch a relapse." (HIVPW, 29 years old)

With the exception of one woman, who was bothered by having received the DHA-PPQ at home for fear of neighbors realizing that she was HIV-infected, all other interviewed HIV-infected pregnant women stated that they did not mind having received DHA-PPQ at home from field workers during pregnancy.

"I didn't hide it because I'm not afraid, that's not up to them. Even if the person sees it or does not see it, it's not up to him. It's me, I'm protecting my life." (HIVPW, 24 years old)

"Well, I don't care about that...; what I deal with here in my house is with me."(HIVPW, 23 years old)

"…no. My neighbors all take pills" [Referring to ARVs]. (HIVPW, 33 years old)

"I don't think they can be suspicious because they know that there are always people who go from house to house doing surveys." (HIVPW, 28 years old)

"Even if they get to know [noise], I have nothing to do with it. The person can stop and laugh… Sometimes they [field workers]) brought me pills while I'm sitting with them (the people). So, I took the chair and sat in a place like there… while we talked, I went to fetch water. And I already knew that as soon as they arrived I didn't wait for them to charge me for water,

I would put water in a cup and took the pills while people were seeing it." (HIVPW, 24 years old)

Influence of an additional pill (DHA-PPQ) on adherence to the already taken medications

The addition of 9–12 more pills (of DHA-PPQ as IPTp) was perceived by the HCP and NoHIVPW as an important increase in the number of tablets to be taken by HIVPW.

"The reaction I can see is …Oops, there's no way I have to do it! Hmm, I have to do it for my own good and for the good of my son." (Nurse 1, referring to HIVPW reaction after receiving all medication at ANC)

"They ([HIVPW]) think there are too many. Especially now that we have to give it every three months. So when she takes 90 pills of ARVs, takes 90 of isoniazid, takes 180 of cotrimoxazole and goes to take 90 of ferrous salt, you can practically see the facial situation that there is a restlessness here. Many even say, they are many tablets…" (Nurse 2)

However, the NoHIVPW stated that the increase in the number of tablets would not affect adherence to the already taken medications, and that HIVPW would take all medication received at the ANC due to specific benefit of each of the medications.

"If someone really needs the cure, it's (referring to an increased number of tablets) not much."(NoHIVPW, 18 years old)

"There would be many (referring to an increased number of tablets) but with, with different utility." (NoHIVPW, 26 years old)

"It's (referring to an increased number of tablets) normal, it depends on the person's illness." (NoHIVPW, 21 years old)

On the other hand, HIVPW considered the increased number of tablets as manageable (acceptable) because they were able to take them and also due to the specific benefits of each medication.

"I can take all the time I'm told to. I can comply and take." (HIVPW, 38 years old)

"I don't give importance to the quantity, I prefer to understand that each one (referring to each medication) is doing their job. It costs me when I gather them all at once and I start to think of how many. But the way they are, in scale… I see it's good for me." (HIVPW, 29 years old)

Discussion

Patient knowledge of the causes of malaria and its clinical manifestation is key to promote universal access to effective malaria preventive interventions [30]. Therefore, in this study we aimed firstly at exploring pregnant women's knowledge about malaria transmission, clinical manifestations and prevention measures. Then we assessed the acceptability of DHA-PPQ as an alternative for IPTp in HIVPW among pregnant women and health providers. According to the findings of the present study, pregnant women attending the ANC in Manhiça district, revealed high knowledge of transmission and symptoms of malaria but a limited knowledge of malaria prevention measures such as indoor residual spraying and IPTp. In addition, the results suggest that DHA-PPQ was generally accepted despite its perceived usefulness and effectiveness being unclear to study participants.

Pregnant women's knowledge about malaria transmission and its clinical manifestations

We found that both HIVPW and No-HIVPW were aware that malaria could be transmitted through a mosquito bite. Moreover, we found accurate knowledge of the most common symptoms of malaria, suggesting that the occurrence of these symptoms leads pregnant women to seek assistance for suspected malaria. However, attention is drawn to the fact that there are still important proportions (almost 10%) of pregnant women who are unaware of the causes and symptoms of malaria. In fact, some women reported wrongly, that bad food hygiene conditions might cause malaria. Additionally, despite Mozambique being a malaria-endemic country, with long-term implementation of malaria awareness campaigns, only two of the 79 women interviewed were able to explain the sequence from still water to mosquito breeding. These results are similar to those found in previous studies in pregnant women in Manhiça district [31, 32] and calls for alternative health education approaches such as formative community engagement interventions to improve pregnant women's knowledge on malaria etiology, prevention and treatment measures [33].

Pregnant women's knowledge about malaria prevention measures during pregnancy

The use of mosquito nets was the most known and used prevention method mentioned by pregnant women, which is consistent with findings from other parts of the country [34–37]. Indoor residual spraying, a key tool for controlling and eliminating malaria by targeting vectors

was only reported by two pregnant women as a malaria prevention measure. This demonstrates that the contribution of indoor residual spraying to malaria and mosquito control continues to be poorly understood [38, 39]. Moreover, as found by Arnaldo et al., (2019), IPTp was not mentioned as measure of preventing malaria [40]. This finding suggests that pregnant women perceive that IPTp is only used to treat existing malaria infection in pregnant women and consequently preventing in-utero transmission of plasmodia to the fetus [41, 42]. The effect of protecting against new infections for several weeks after pregnant women administration is not known or taken into consideration [43].

Perceptions and acceptability of HIV-infected pregnant women in relation to the administration of DHA-PPQ

We observed that none of HIVPW included in the clinical trial was able to identify DHA-PPQ by its name. DHA-PPQ is not routinely used in Mozambique and this may have contributed to its poor recognition and consequently the lack of knowledge about its usefulness. Despite this, the results show that DHA-PPQ is generally accepted as suggested by the following findings: firstly, most of the HIVPW participating in the clinical trial and included in this qualitative study complied with monthly doses until delivery. Secondly, HIVPW included in the clinical trial indicated that other HIVPW would accept DHA-PPQ as malaria IPTp in future. Finally, NoHIVPW stated that they would take DHA-PPQ if they become HIV positive despite the fear of never having heard the name DHA-PPQ. Nevertheless, we acknowledge that our findings are primarily based on participants enrolled in the trial or attended in a conventional healthcare settings setting, further research outside the clinical setting is needed to nuance these findings and provide a broader understanding of DHA-PPQ acceptability in other contexts.

The acceptability of DHA-PPQ among HIVPW seemed to be associated with the belief that pregnant women cannot refuse any guidance from healthcare professionals, rather than being driven by the perceived benefits of DHA-PPQ in preventing malaria during pregnancy. This is in line with previous works pointing at the relevance of building trusting relationships with health providers as a factor contributing to the acceptability of health interventions such as vaccines [44, 45]. Therefore, there is a need to make better use of this advantage and treat patient-provider interactions as opportunities to raise awareness and clarity on the administration of DHA-PPQ while promoting health. Although DHA-PPQ, like SP in a previous study, was understood to play a role in general disease-prevention during pregnancy, it cannot be overlooked that some women referred to DHA-PPQ as Fansidar (SP), indicating they recognize DHA-PPQ as serving a similar purpose to SP [40].

In Mozambique, traditional medicine is deeply rooted in the local culture and remains an integral part of healthcare. Many residents turn to traditional healers and remedies for various health concerns. A study found that traditional healers often serve as the primary healthcare providers, particularly in rural areas where access to formal medical facilities is limited [46]. These healers employ a combination of plant-based treatments and spiritual practices to manage illnesses. However, this study did not gather information on alternative care-seeking practices. Consequently, the specific traditional medicines used for malaria prevention during pregnancy, along with their potential interactions and implications on DHA-PPQ acceptability, remain unexplored. We recommend that future research bridge this gap by examining acceptance beyond conventional healthcare settings.

Facilitators and barriers of DHA-PPQ acceptability

Since DHA-PPQ has to be taken over three consecutive days for maximum effectiveness, which would imply returning to the hospital with the same frequency, HCPs reported that home dispensing of DHA-PPQ could increase DHA-PPQ uptake. Taking into account that the efficient communication and understanding between healthcare workers and their patients and communities was widely deemed essential in acceptance of strategies to prevent malaria [47–49], the involvement of community healthcare workers in home administration should be considered. As others, we suggest a review of the current policy on malaria prevention in pregnancy to allow provision of IPTp through community structures that are feasible, practical and acceptable [50, 51].

Interestingly, known barriers for drug acceptability, such as stigmatization resulting from HIV status disclosure, the burden of taking multiple pills, and potential DHA_PPQ side effects [11, 52] were not found to influence DHA-PPQ acceptability in the present study. The hypothesis that taking DHA-PPQ could affect measures taken to ensure confidentiality of HIV-infection was counterbalanced by the disclosure of HIV infection status to the family, which seemed to lead pregnant women to feel comfortable taking DHA-PPQ. These results reinforce the importance that HIV status disclosure might have in improving adherence to therapy, good clinical outcomes, and reduction in the risk of HIV transmission [53–55]. However, it should be noted that some of the women included in the clinical trial were not clear of the purpose of the DHA-PPQ (malaria IPTp for HIVPW only), and it may have led women to not linking it to the possibility of affecting the HIV confidentiality. Therefore, although fear of being stigmatized was not identified as a

barrier in this study, it is important to acknowledge that the stigma remains an important and persistent obstacle faced by women living with HIV due to strong gender inequality in Mozambique, among other factors [56, 57]. Thus, continuous monitoring of the influence of DHA-PPQ on strategies carried out by pregnant women to ensure HIV confidentiality, must be considered if DHA_PPQ is approved as an alternative for IPTp in HIVPW in the future.

It was also expected that the increase in the number of pills taken by women could be a barrier to DHA-PPD acceptability. However, both HIVPW included in the clinical trial study and NoHIVPW mentioned that this would not be a barrier due to the specific benefits of each medication received at the ANC. Still, one cannot rule out the point of view of healthcare providers who deal daily with different challenges when assisting HIVPW, including the perceived restlessness of pregnant women after receiving numerous tablets.

Studies on patient compliance often highlight a strong link between perceived side effects and reduced acceptance of medications. However, in this study, side effects were not perceived as a potential barrier to DHA-PPQ acceptability. Participants who experienced side effects, such as vertigo, vomiting, and malaise, expressed a willingness to take DHA-PPQ during subsequent due to their trust in the medicine's capacity to promote and contribute to a healthy pregnancy. The temporary nature of the reported side effects likely contributed to their perceived manageability. Additionally, effective communication about potential side effects—facilitated during the informed consent process—may have further mitigated concerns. Proper labeling and clear risk communication play a crucial role in addressing side effects and building patient trust. To ensure the successful acceptability and adoption of DHA-PPQ, it is essential to address patients' fears related to side effects. Establishing a strong, trust-based relationship between HCPs and patients can foster open dialogue, enhance understanding, and support informed decision-making.

Policy implications

The policy implications of our findings include bringing together global and Mozambican policy makers and program managers in charge of malaria control in pregnancy to revise malaria prevention package based on these findings. If DHA-PPQ is adopted by the World Health Organization (WHO) as IPTp for HIV-positive pregnant women to advance global malaria eradication goals, our findings contribute to strengthen the evidence base to support the updated implementation of global guidelines in settings similar to Mozambique. The revised strategies will have to address the perceived barriers especially the limited knowledge of malaria prevention methods such as indoor residual spraying and IPTp among pregnant women (regardless of their HIV status). In addition, HCPs should receive training on communication and counselling regarding the use of DHA-PPQ in pregnancy, including its benefits and potential side effects. Finally, the successful implementation of the policy on malaria prevention in pregnancy will depend on the acknowledgment of the involvement of community healthcare workers in home administration as a key action to improve acceptability and uptake within communities.

By other side, while an intervention may demonstrate high acceptability in a clinical trial, real-world implementation introduces additional challenges that can hinder its uptake. Understanding these differences is essential for developing strategies that effectively translate research into practice. In clinical trials, interventions are delivered under controlled conditions with close monitoring, structured follow-ups, and strong participant support, which may enhance trust in healthcare providers. In our study, although participants did not receive incentives, they IPTp or placebo was administrated by the HCPs or field workers. Moreover, intensive education and counseling during ANC visits and home IPTp administration may have alleviated concerns about side effects, pill burden, or stigma. However, in real-world settings, where such structured support is often lacking, perceived burdens—such as side effects, cost, stigma, or complex dosing—can negatively impact acceptability, leading to lower adherence. Additionally, factors such as social norms, misinformation, and distrust in the healthcare system can further reduce uptake. Therefore, recognizing and addressing these real-world challenges is critical for successfully implementing interventions beyond the controlled conditions of clinical trials.

Study limitations and strengths

The present study has other methodological limitations worth mentioning, beyonde the fact that the semi-structured exit interviews carried out in a hospital environment may have affected the participants'comfort in giving an honest and open opinion. On the other hand, their performance immediately after leaving the office minimized the occurrence of bias memory. Furthermore, this study was carried out in a period of national restrictions due to COVID- 19 which affected the data collection process. The interviews were carried out as quickly as possible and not having allowed the interviewers to confirm some of the preventive measures implemented by pregnant women in the current pregnancy. Additionally, desirability bias may also explain the responses from pregnant women participating in the study regarding the

acceptability of the increased number of tablets, which contrasts with the views of healthcare providers. Finally, for the in-depth interviews, women who demonstrated extroverted tendencies during the exit interviews were intentionally selected. This selection presents a limitation, as it may have excluded more introverted individuals who might offer less expressive but potentially divergent perspectives. Consequently, the findings in this paper predominantly reflect areas of consensus, potentially overlooking contrasting viewpoints. Nevertheless, it is worth noting that the "Lost to follow-up" rate among all HIVPW (both introverts and extroverts) enrolled in the MAMAH clinical trial was low (4.2% for women on placebo and 4.5% for those on DHA-PPQ arms), suggesting minimal impact of divergent perspectives overall shape [58] Limitations aside, this is the first qualitative study providing meaningful insights on DHA-PPQ acceptability as an alternative for IPTp for HIVPW in Mozambique. Further research outside the clinical setting to nuance the findings and provide a more comprehensive understanding is required. In addition, the study not only collected insights from the HIVPW enrolled in the clinical trial, but also interviewed health providers directly involved in ANC and in the clinical trial who had a good understanding of the trial interventions. Their experiences in the trial and their views and opinions highlight important factors to be considered if DHA_PPQ become national strategy.

Conclusion

With the exception of the insecticide-treated nets, the study results evidence that there is limited knowledge about of malaria prevention methods such as indoor residual spraying and IPTp among pregnant women. Likewise, the acceptability of DHA-PPQ appeared to be driven more by the belief that pregnant women cannot refuse any guidance from healthcare provider guidance rather than being driven by the perceived benefits of DHA-PPQ in preventing malaria during pregnancy. Leveraging the trust placed in healthcare providers to enhance awareness and provide clear guidance on DHA-PPQ administration is crucial and Engaging community health workers in home administration could further improve acceptability and uptake within communities. Moreover, further implementation research focused on acceptability in a real-world environment is essential to deepen the understanding of DHA-PPQ acceptability beyond the clinical trial setting, and inform policy decisions accordingly.

Abbreviations

ANC	Antenatal care
ART	Antiretroviral therapy
CIBERESP	Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública
CISM	*Centro de Investigação em Saúde de Manhiça*
CTXp	Cotrimoxazole prophylaxis
DHA-PPQ	Dihydroartemisinin-piperaquine
DSS	Demographic and Health Surveillance System
EDCTP	The European & Developing Countries Clinical Trials Partnership
HCP	Health care providers
HIVPW	HIV-infected pregnant woman
INS	Instituto Nacional de Saúde
ISGlobal	Barcelona Institute for Global Health
IPTp	Intermittent Preventive Treatment
LLITNs	Long lasting insecticide-treated mosquito nets
MAMAH	Improving Maternal heAlth by reducing Malaria in African HiV women
MDH	Manhiça District Hospital
NoHIVPW	HIV-uninfected pregnant woman
TB	Tuberculosis
STDs	Sexually transmitted diseases
UEM	Universidade Eduardo Mondlane

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Authors' contributions

Project conception and protocol design: TN, CM, KM Coordination of data collection: TN, CC, MC, MM, KM Data analysis and interpretation: TN, CC, CM, NT, KM, ES, YA, CE Contributed to the writing of the manuscript: TN, CC, MC, NT, RG, LG, AM, ES, KM, CM, YA, CE Reviewed the draft and approved the decision to submit the paper: all authors.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the National Bioethics Committee of Mozambique (311/CNBS/19). After informing the objectives and characteristics of the study and addressing theirs questions and doubts, a written informed consent was obtained from each participant. One copy of the consent form was left with the participating women. Those who were literate signed the form and those who could not read or write thumb printed in the presence of an independent witness able to read and understand the contents of the participant information sheet and informed consent form. Inclusion of legal minors followed national ethics guidelines, in which, before enrolment, written informed consent was obtained from the parents or legal guardians of the minors (who were also asked to give assent).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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