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ORIGINAL STUDY

Clinical Outcomes of Isoniazid Preventive Therapy Amongst Persons Living with HIV Attending a Referral Hospital: A Cross-sectional Study

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ABSTRACT

Tuberculosis (TB) is the most common opportunistic infection amongst persons living with HIV (Human Immunodeficiency Virus) (PLWHIV). World Health Organisation recommends tuberculosis preventive therapy (TPT) to avert the effects of TB/HIV co-infection. This study aimed at determining the incidence of active tuberculosis infection, assessing the burden of adverse drug events (ADEs) and identifying the associated factors. In this study, records of 379 patients who started isoniazid preventive therapy at Mbarara Regional Referral Hospital (MRRH) between 1st July, 2017 and 30th June, 2022 were retrospectively reviewed. Data was analyzed using a statistical software (SPSS version 20.0) and presented using descriptive statistics. Logistic regression was performed to explore the factors associated with adverse drug reactions during the course of isoniazid preventive therapy. The prevalence of ADEs was 20.3%. Fifty-five (71.4%) experienced at least one adverse drug event during the course of isoniazid preventive therapy while 22 (28.6%) had at least two. Elevated serum transaminases (23.7%), peripheral neuropathy (20.4%), skin rash/pruritis (15.1%) and musculoskeletal symptoms (10.8%) were the most frequently documented adverse drug events. Patients on at least two other drugs alongside their isoniazid preventive therapy (AOR = 2.23 (1.25, 3.97 at 95% CI); p value = 0.006) and those not prescribed prophylactic pyridoxine (AOR = 3.21 (1.34, 7.60 at 95% CI); p value = 0.008) were significantly likely to experience adverse drug events. Only one patient (0.28%) developed tuberculosis disease making the incidence of tuberculosis disease 0.1 per 100-person years. The study findings revealed that the prevalence of ADEs among PLWHIV who are on isoniazid preventive therapy was very low. Elevated serum transaminases, peripheral neuropathy, skin rash/pruritis and musculoskeletal symptoms were the most commonly reported adverse drug events. The incidence of ADEs can be reduced by providing pyridoxine prophylaxis therapy and limiting the number of concomitantly used medications.

Keywords: Clinical outcomes, Persons living with HIV, Isoniazid preventive therapy

1. Introduction

Despite the invention of highly active antiretroviral therapy (HAART), tuberculosis(TB) still commonly causes death and hospitalization among persons living with HIV(PLHIVs) [1]. In 2019 out of the 10 million people worldwide who were ailing because of TB 8.2% were PLHIVs [2]. Isoniazid preventive

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therapy (IPT) has been proven to diminish the risk of TB infection. It also reduces rate of deaths from TB among PLHIV by 52% [3, 4]. Ministry of Health (MoH) Uganda rolled out the accelerated scale-up of IPT to reduce the rate of TB infections and TB related deaths among PLHIVs. Insite of the relative safety attributed to IPT use as monotherapy, when used alongside other drugs it has been observed to be associated with severe adverse drug events (ADEs) [5].

The strategy for reducing TB infection rates among PLHIVs is to effectively screen for TB cases, promptly initiate isoniazid preventive therapy (IPT) and HAART [6]. IPT has globally been associated with some challenges like increase in pill burden, poor adherence, occurrence of ADEs and development of drug resistance. It has therefore been sparingly embraced for use among PLHIV worldwide [7].

The risk of occurrence of ADEs increases when IPT is used alongside HAART. This may result from toxicities that are common to both therapies like hepatotoxicity. Hepatotoxicity is associated with isoniazid, nevirapine [8], dolutegravir and efavirenz [9]. Gastrointestinal symptoms and fatigue may also occur due to both isoniazid and dolutegravir [10]. These ADEs can lead to poor adherence to IPT among PLHIV and increased death rates [11, 12]. They have also been observed to increase the cost of therapy [8].

Painful polyneuropathy (PN) is a complication commonly associated with isoniazid however it can be prevented with adequate pyridoxine supplementation. PN may also occur as a complication of with HIV infection or as a toxicity of HAART [13]. It is important that patients at risk for developing isoniazid associated PN, like alcoholics, malnourished patients, diabetics and PLHIV are adequately supplemented with daily pyridoxine [14].

Unfortunately, the clinical outcomes of IPT are understudied in Uganda, making it difficult to improve care among PLHIVs with regard to TB infection prevention. Over the past decade, Uganda has been identified by WHO as one of the 22 countries with the highest burden of TB in the whole world [15]. Despite the Ugandan Ministry of Health rolling out IPT program, its association with ADEs [5] has been associated with poor adherence among patients initiated on it. This study was conducted with the purpose of determining the burden of ADEs associated with IPT among PLHIV.

2. Methods

2.1. Study design and setting

A retrospective cross-sectional study design employing quantitative methods was used. The study was conducted from the Immune Suppression Syndrome (ISS) clinic of Mbarara Regional Referral Hospital. The hospital was founded in 1940 and is located in Mbarara city in South Western Uganda along Mbarara Kabale road 266k from Kampala Capital City. It serves a population of over four (4) million people in its catchment area comprising 15 districts of South Western Uganda (Mbarara, Mbarara City, Sheema, Bushenyi, Rwampara, Lyantonde, Rakai, Ntungamo, Kazo, Kiruhura, Ibanda, Buhweju, Rubirizi, Mitooma, Isingiro districts), and the neighboring countries including Burundi, DRC, Rwanda, and Tanzania. This Clinic serves a population of approximately 13,000 PLHIV with over 95% completion rates of Isoniazid Preventive Therapy.

2.2. Study population

Records of PLHIV (TPT register and patient files) at the ISS Clinic were. Patient files of all adult PLHIV on HAART and IPT between 1st July 2017 and 30th June, 2022 were included in the study whereas ineligible and incomplete patient medical files or records were excluded.

2.3. Sample size determination

The following formula by [16] was used in estimating the minimum sample size (Eq. (1)):

$$n = \frac{Z^2 p(1-p)}{d^2} \tag{1}$$

Where:

n = sample size

p = Prevalence of ADEs in PLHIV

Z = Value of the standard normal distribution corresponding to the significance level of 0.05 (type 1 error, where $p < 0.05$) = 1.96 (two-sided test) considering the confidence level of this study to be 95%,

d = acceptable error of 5%

1-p = (1 − 0.9 = 0.1) where *p* is 51% representing the prevalence of ADEs in PLHIV [17].

$$n = \frac{1.96^2 * 0.51(1-0.51)}{0.0025} = 359.85 \sim 360$$

Minimum sample size = 396

2.4. Sampling procedure

A random systematic selection of a TPT number of the patient records was performed at every 27th interval without replacement of the selected number.

Table 1. Characteristics of the patients who started Isoniazid Preventive Therapy.

Variable	Category	Frequency	Percentage (%)
Gender	Male	160	42.2
	Female	219	57.8
Age (years)	≤25	23	6.1
Mean = 42.79, SD = 11.49	26–59	327	86.3
	≥60	29	7.7
Marital status categories	Single	33	8.7
(N = 360)	Married	271	71.5
	Separated/divorced/widowed	56	14.8
Body Mass Index (N = 359,	Underweight	40	10.6
Mean = 23.6, SD = 4.98)	Normal weight	200	52.8
	Overweight	119	31.4
Presence of Chronic diseases	No HTN/DM	353	93.1
	Has HTN/DM or both	26	6.9
Total number of medications Prescribed.	<2	248	65.4
(Mean = 1.6, SD = ± 1.1, Range = 0–7)	≥2	131	34.6
Baseline CD4+ status-cells/μL	≤200	111	29.3
(N = 349, Mean = 349.06)	≥201	238	62.8
Viral Load status at the time of TPT	Suppressed	364	96.0
(N = 371)	Non-suppressed	7	1.8

SD: Standard Deviation; HTN: Hypertension; DM: Diabetes mellitus; TPT: Tuberculosis Prevention Therapy.

2.5. Data collection

In this study, adverse drug event was defined as any harmful and unwanted effect of drug that occurred after the initiation of IPT therapy but not necessarily associated with the IPT regimen itself. Accordingly, any adverse event recorded in the patient file that was in the list of ADR profile of IPT regimen and temporally related to IPT initiation was considered as ADE. A data extraction guide was used for data abstraction from the patient records. The guide was used to collect data on adverse drug events, TB disease status and factors associated with occurrence of adverse events among PLHIV on HAART and IPT.

2.6. Data management and analysis

Each data abstraction form was assigned a serial identification number (TPT number). The data from the completed abstraction forms was entered into Microsoft excel and imported into SPSS version 20.0; SPSS In., Chicago, IL, USA for analysis. The prevalence of ADEs and incidence of TB disease were analyzed using descriptive statistics. Logistic regression was performed to explore factors associated with occurrence of ADEs among PLHIV on IPT and are attending MRRH. All variables with p values < 0.25 during the univariate analysis were included in the multivariate analysis. A p value < 0.05 was considered as statistically significant.

3. Results and discussion

3.1. Patient characteristics

The study included records of 379 patients. The majority (219, 57.8%) were females and 193 (50.9%) were aged between 41–60. A total of 119 (31.4%) were overweight (mean ± SD = 23.60 ± 4.98). Approximately a third of patients (131, 34.6%) had two or more drugs prescribed (mean ± SD = 1.60 ± 1.1). Most patients (271, 71.5%) were married and 353 (93.1%) had no chronic disease. Almost one-third (111, 31.8%) had advanced HIV Disease (≤200 cells/μL) at the time of HAART initiation. Almost all (364, 98.1%) had virologic suppression at IPT initiation (Table 1).

3.2. Distribution of medications usage

Only 16 (12.9%) were discontinued from IPT due to loss to follow up and adverse events. The majority (344, 90.8%) of patients were prescribed pyridoxine, 332 (87.6%) had no prescription for cotrimoxazole and 312 (82.3%) were on a TDF based regimen during the time of IPT. The mean ± SD duration on ART before IPT initiation was 7.3 ± 4.7 years (Table 2).

3.3. Prevalence of adverse drugs events

The prevalence of documented ADEs was 20.3%. Out of 379 patient records reviewed, 77 (20.3%) indicated that the patients had experienced a total

Table 2. Medication information during IPT.

Variable	Category	Frequency	Percentage (%)
TPT Regimen	6H	379	100.0
Status of TB Preventive Therapy (N = 379)	Completed (≥6 months)	363	95.8
	Discontinuation (<6 months)	16	4.2
Reason for Discontinuation of IPT (N = 16)	Adverse Event	5	31.3
	Developed TB disease	1	6.3
	Lost to follow-up	10	62.4
ART regimen at the start of IPT (N = 372)	AZT backbone	60	16.1
	TDF backbone	312	83.9
Duration on ART before IPT initiation (years) (N = 358, Mean = 7.3)	<5	127	35.5
	5–10	117	32.7
	>10	114	31.8
Pyridoxine	No	35	9.2
	Yes	344	90.8
Cotrimoxazole	No	332	87.6
	Yes	47	12.4

TPT: Tuberculosis Prevention Therapy; ART: Antiretroviral Therapy; IPT: Isoniazid Preventive Therapy; H: Isoniazid.

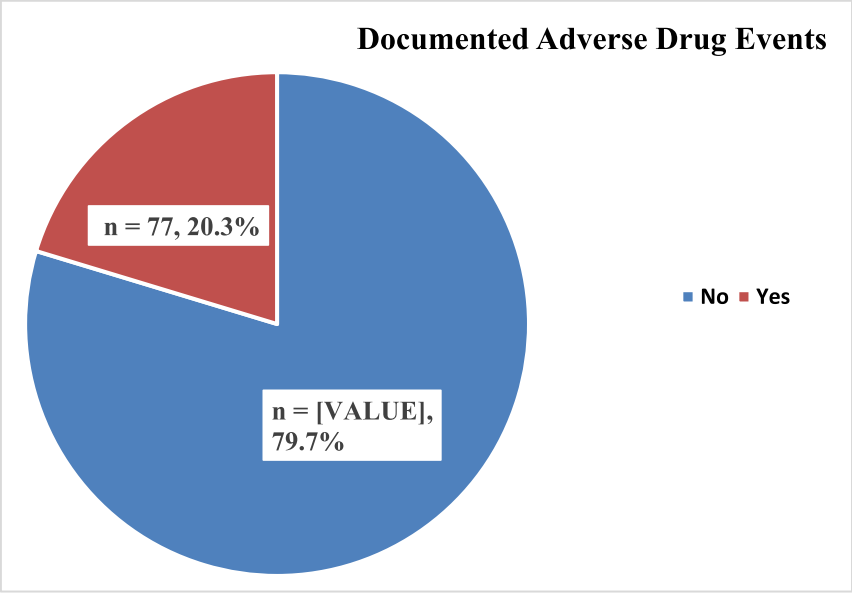

Fig. 1. Prevalence of ADEs amongst PLHIV.

of 93 ADEs (mean = 1.2 ADEs per patient). A total of 55 (71.4%) records had only one documented ADE while 22 (28.6%) had more than one documented ADE (Fig. 1). The current prevalence is quite low compared to 51% which was reported from a cross-sectional study done at three regional referral hospitals in central Uganda [18]. It is also lower compared to 79% reported from a prospective study from Malawi [19]. This could be explained by the fact that the current study was retrospective while the others interfaced with participants in real time. The current study was therefore prone to being affected by errors in patient records unlike the prospective ones. Another study conducted in Ethiopia a higher prevalence of 31% [20]. However, the study from Ethiopia was primarily designed to assess adherence of PLHIV to IPT while the primary outcome in the current study was clinical outcomes of PLHIV and are on IPT.

The prevalence from the current study are comparable to findings from some studies conducted in the middle east, that is Malaysia and India which reported prevalences of 18% [21] and 19.7% [22]. The settings of these studies are in middle- or low-income countries which are faced with health challenges like difficulty in monitoring and follow up of chronically ill patients. Due to the fact that medical record keeping is largely manual as opposed to computerized, there could be data that is not captured [23].

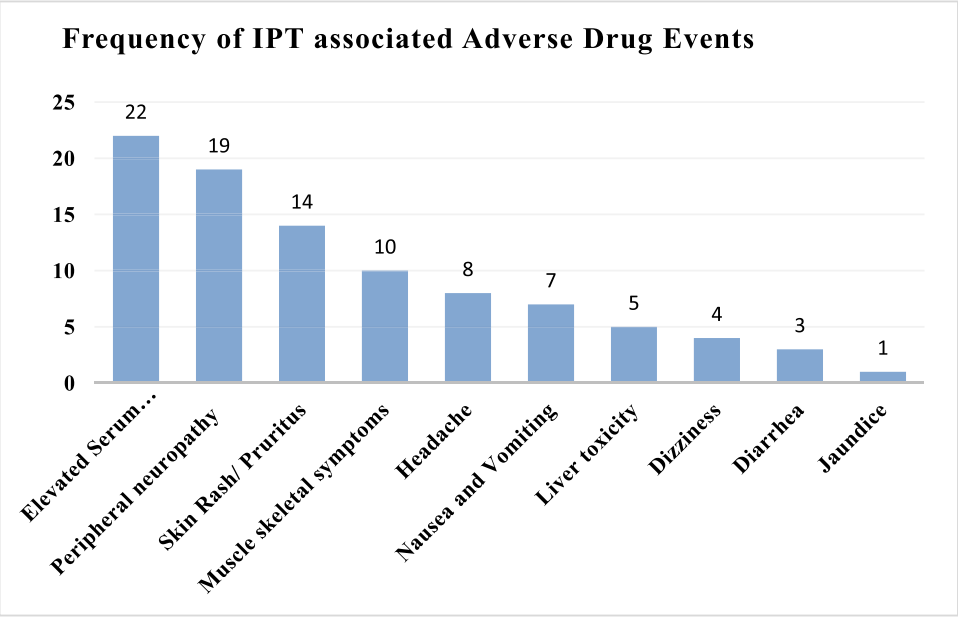

Fig. 2. Frequency of IPT related Adverse Drug events.

The most reported ADEs were elevated transaminases (22, 23.7%), peripheral neuropathy (19, 20.4%) and skin rash/pruritis (14, 1 5.1%) (Fig. 2). Elevated serum transaminase (5.8%) was the most documented adverse drug event. This finding is consistent with that from a study from India which reported the same ADE to be prevalent at 5.5% [24]. Peripheral neuropathy (5.01%), skin rash (3.69%) and musculoskeletal symptoms (2.64%), were also among most reported adverse drug events related to IPT in this study. Similarly, these ADEs were observed in other studies in various settings [11, 18, 19]. This demonstrates that elevation in serum transaminases, peripheral neuropathy, skin rash and musculoskeletal symptoms are ADEs that may need close monitoring among PLHIVs and are on IPT as they tend to occur frequently. These studies are cross sectional by design and have been carried out with relatively small sample sizes. They are inadequate to establish a concrete relationship between IPT and these ADEs however the above observed ADEs have been established as adverse drug reactions of isoniazid. This could explain why they occur in numerous studies irrespective of the setting.

3.4. Incidence of TB disease in PLHIV

Out of 362 patients with documented completion of the IPT course, only one (0.28%) patient developed TB disease. The incidence rate in the current study is 0.1 per 100-person years. This finding was lower than those observed in some studies within sub–Saharan Africa and the middle east. For instance, from Zimbabwe (1.06 per 100 person years), South Africa (2.3 per 100 person years), Botswana (0.8 cases per 100 person years) and Indonesia (1.09 per 100 person years) [25–28]. TB incidence in this study was also lower than a similar study in Ethiopia (0.21 per 100 person years) and another in Tanzania (2.7 per 100 person years) [29, 30]. However, it is important to note that the study from Ethiopia included both pre-and post-HAART PLHIVs and the one from Tanzania considered both IPT exposed and non-exposed PLHIVs. This could possibly explain the higher TB incidence in both the previous studies. It is plausible to argue that these differences likely result from individual variances among PLHIVs on ART such as adherence levels, socioeconomic gradients and country specific TB endemicity [31]. The low TB incidence in this study could be attributed to good adherence to IPT as evidenced by a high completion rate of 95.8%. This underscores the importance of adherence among PLHIVs and have been initiated on IPT.

3.5. Factors associated with the occurrence of adverse drug events

On performing logistic regression, the outcomes showed that having a prescription without pyridoxine and having a prescription of more than one medicine were significantly associated with occurrence of ADEs; (AOR = 3.21 (1.34,7.60 95% CI); p value = 0.008) and (AOR = 2.23 (1.25,3.97 at 95% CI); p value = 0.006) respectively. Patients who were

Table 3. Factors associated with Adverse Drug Events among PLHIV.

Variable	Category	COR (95% CI)	P-value	AOR (95% CI)	P-value
Baseline CD4+ (cells/L)	≤200	1			
	>201	1.41 (0.78,2.55)	0.26		
ART Backbone	AZT based	1.31 (0.67, 2.53)	0.43		
	TDF based	1			
Gender	No	1.10 (0.67, 1.83)	0.70		
	Yes	1			
Cotrimoxazole	No	1			
	Yes	1.41 (0.69, 2.86)	0.34		
Pyridoxine	No	2.29 (1.06, 4.73)	0.04*	3.21 (1.34,7.60)	**0.008**
	Yes	1			
Total number of prescribed medications	≤1 medication	1			
	≥2 medications	1.91 (1.15, 1.18)	0.13*	2.23 (1.25,3.97)	**0.006**
Presence of Chronic Diseases	No	1			
	Yes	2.22 (0.95, 5.19)	0.07*	2.09 (0.77, 5.82)	0.150
Body Mass Index	Under weight	1			
	Normal BMI	1.41 (0.54, 2.86)	0.16*	0.68 (0.25,1.89)	0.460
	Obese	1.62 (0.50, 5.12)	0.42		
Marital status	Single	1.47 (0.52, 4.20)	0.47		
	Married	1.15 (0.54, 2.41)	0.72		
	Separated	1			
Age Category	≤25 years	1			
	26–59 years	0.68 (0.26, 1.78)	0.43		
	≥60 years	1.079 (0.31, 3.72)	0.08		

Included in multivariate analysis*; ***Bold:* *statistically significant.*

not prescribed pyridoxine were over three times more likely to experience an ADE compared to their counterparts with a prescription of pyridoxine. Having a prescription with more than one drug gave the patients over two times the risk of experiencing ADEs compared to those on only one drug (Table 3).

Taking other medications alongside isoniazid (excluding ARVs, pyridoxine and cotrimoxazole) and not being prescribed pyridoxine were significantly associated with occurrence of ADEs related to IPT. Patients being on multiple medications increases risk of ADEs and this can possibly be due to drug-drug interactions between isoniazid and other drugs. Isoniazid is a known enzyme inhibitor. Some of the established clinically relevant drug-drug interactions are between isoniazid and CYP2C19 substrates like omeprazole, diazepam, citalopram; CYP3A4 substrates like carbamazepine; CYP2E1 substrates (acetaminophen) [32]. The risk of ADEs also increases as a result of exposure to multiple drugs [33]. Each drug that is prescribed to the patient has potential to cause ADEs and that calls for caution when making prescriptions for these patients. The benefit of including a drug on the prescriptions of PLHIVs should outweigh the risks associated with using them. PLHIVs already have a compromised quality of life because of HIV/AIDS and it is on these grounds that deprescribing should be considered in scenarios where there is no clinical benefit of keeping the patient on a drug.

Not being prescribed pyridoxine was significantly associated with occurrence of ADEs in the current study. In a qualitative study conducted in Ethiopia it was reported that unavailability of pyridoxine was associated with increased reports of peripheral neuropathy [7]. Pyridoxine is prescribed to patients on prolonged isoniazid therapy as prophylaxis for peripheral neuropathy and other neurotoxic effects. It is important to note that some patient categories are at a higher risk of experiencing peripheral neuropathy than others. High risk categories include slow acetylators and malnourished patients [34]. Patients of older age, current protease inhibitor use and history of diabetes also stand a high chance of experiencing peripheral neuropathy [35]. Ensuring optimum pyridoxine supplementation is vital in preventing onset of peripheral neuropathy.

4. Conclusions

The study findings revealed that the prevalence ADEs was relatively low at 20.3%. Elevated serum transaminases, peripheral neuropathy, skin rash/pruritis and musculoskeletal symptoms were the most commonly reported ADEs among PLHIVs on IPT attending MRRH. The incidence of TB disease was low at 0.1 per 100-person years. and taking two or more drugs while on IPT. Patients who were not prescribed

pyridoxine were over three times more likely to experience an ADE compared to their counterparts with a prescription of pyridoxine. Having a prescription with more than one drug gave the patients over two times the risk of experiencing ADEs compared to those on only one drug. This study demonstrated that adherence to IPT significantly reduces the incidence of TB among PLHIVs. Adequate supply and adherence to pyridoxine supplementation also plays a vital role in preventing peripheral neuropathy, one of the common ADRs of isoniazid, that would otherwise prevent some patients from completing their course of IPT.

However, the conclusions of this study should be carefully interpreted by understanding the limitation of the study. Being a retrospective study, some data could have been missed as a result of omission during documentation, for instance ADEs observed but not documented, ADEs that may require laboratory tests or physical assessments.

List of abbreviations

ADE: Adverse Drug Event, ADR: Adverse Drug Reaction, AIDS: Acquired Immuno-deficiency Syndrome, ALT: Alanine Transaminase, ART: Anti-Retroviral Therapy, AST: Aspartate Aminotransferase, BMI: Body Mass Index, CNS: Central Nervous System, DM: Diabetes Mellitus, HIV: Human Immunodeficiency Virus, HP: Rifapentine and Isoniazid, HTN: Hypertension, ICF: Intensified Case Finding, INH: Isoniazid, IPT: Isoniazid Preventive Therapy, MoH: Ministry of Health, MRRH: Mbarara Regional Referral Hospital, OI: Opportunistic Infection, PI: Protease Inhibitor, PLHIV: Persons Living with HIV,PN: Peripheral Neuropathy, SE: Side Effects, TB: Tuberculosis, TPT: TB Preventive Therapy, WHO: World Health Organization

Ethics approval and consent to participate

A waiver of informed consent was obtained from the ethics committee of department of Pharmacy of Mbarara University of Science and Technology. The management of Mbarara Regional Referral Hospital granted permission for research to be done using the medical records of PLHIV attending the HAART clinic.

Consent for publication

All the authors agreed that this article is published in its current form.

Availability of data and materials

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

Conflicts of interest

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by DCM, BAA, MDO, WB, ML, NCF, MC. Data analysis was performed by SO and TMY. The first draft of the manuscript was written by MDO, WB, ML, NCF, MC, DCM, BAA, SO and TMY provided critical review of the subsequent versions of the manuscript. All authors read and approved the final manuscript.

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