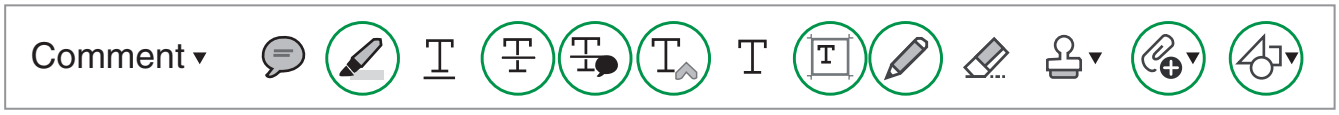
Page Proof Instructions and Queries

Journal Title: International Journal of STD & AIDS (STD)

Article Number: 809749

Thank you for choosing to publish with us. This is your final opportunity to ensure your article will be accurate at publication. Please review your proof carefully and respond to the queries using the circled tools in the image below, which are available **by clicking "Comment"** from the right-side menu in Adobe Reader DC.*

Please use *only* the tools circled in the image, as edits via other tools/methods can be lost during file conversion. For comments, questions, or formatting requests, please use T. Please do *not* use comment bubbles/sticky notes.



*If you do not see these tools, please ensure you have opened this file with Adobe Reader DC, available for free at get.adobe.com/reader or by going to Help > Check for Updates within other versions of Reader. For more detailed instructions, please see us.sagepub.com/ReaderXProofs.

No.	Query
	Please note, only ORCID iDs validated prior to acceptance will be authorized for publication; we are unable to add or amend ORCID iDs at this stage.
	Please confirm that all author information, including names, affiliations, sequence, and contact details, is correct.
	Please review the entire document for typographical errors, mathematical errors, and any other necessary corrections; check headings, tables, and figures.
	Please confirm that the Funding and Conflict of Interest statements are accurate.
	Please ensure that you have obtained and enclosed all necessary permissions for the reproduction of artistic works, (e.g. illustrations, photographs, charts, maps, other visual material, etc.) not owned by yourself. Please refer to your publishing agreement for further information.
	Please note that this proof represents your final opportunity to review your article prior to publication, so please do send all of your changes now.
AQ: 1	Please check whether the names of the countries are correct as given in the affiliations.
AQ: 2	To maintain consistency, 'persons living with human immunodeficiency virus' has been changed to 'people living with human immunodeficiency virus'. Please check.
AQ: 3	Per journal style, when trademarked equipment or software is used, the company, city, state (if in the US) and country details should be provided. Kindly check throughout this article and provide the details.
AQ: 4	Please provide author names, article title in Refs. 23 and 24, if applicable.
AQ: 5	Please provide volume number and page number in Ref. 30.

Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
0(0) 1–7

DOI: 10.1177/0956462418809749
journals.sagepub.com/home/std
SAGE

Widespread use of herbal medicines by people living with human immunodeficiency virus and contamination of herbal medicines with antiretrovirals in Nigeria

J Gini[1], A Amara[1], Sujan D Penchala[1], David J Back[1], L Else[1], D Egan[1], J Chiong[1], Bala I Harri[2], Elkanah D Kabilis[3], Paul P Pama[4], M Stephen[5] and and Saye H Khoo[1]

Abstract

Herbal medication use amongst people living with human immunodeficiency virus (PLWH) is widespread and understudied. [AQ2] This study aimed to evaluate the prevalence of herbal medicine use amongst PLWH and possible contamination with antiretrovirals (ARVs). Countrywide collection of herbal samples sold by street vendors in Nigeria for the following indications: human immunodeficiency virus (HIV), acquired immune deficiency syndrome, fever and general weakness. Samples were screened using a validated liquid chromatography-mass spectrometry/mass spectrometry method for the presence of the following ARVs: efavirenz, nevirapine, lopinavir, darunavir, ritonavir, atazanavir, emtricitabine, tenofovir and lamivudine. A survey was conducted among 742 PLWH attending four HIV clinics in Nigeria. Data were collected using a structured questionnaire and analysed using IBM SPSS statistics version 22.0 (IBM Corp., 2013). [AQ3] Of the 138 herbal medicine sampled, three (2%) contained detectable levels of tenofovir, emtricitabine and/or lamivudine. Additionally, of the 742 PLWH surveyed, 310 (41.8%) reported herbal medicine use. Among the users, 191 (61.6%) started taking herbals after commencing HIV therapy while herbal medicine use preceded ARV treatment in 119 (38.4%) PLWH. We found herbal use to be widespread among PLWH in Nigeria, with increasing use after commencing ARV. Three herbal preparations were also found to contain detectable levels of ARV. This is a concern and should be studied widely across the region and countries where herbal medicine use is prevalent and poorly regulated.

Keywords

Herbal medicines, antiretroviral therapy, human immunodeficiency virus, tenofovir, lamivudine, emtricitabine

Date received: 18 June 2018; accepted: 1 October 2018

Introduction

Prevalence of herbal medication use among people living with human immunodeficiency virus (PLWH) and contamination with medicinal products and certain pharmaceutical agents has previously been reported,[1] though understudied. Herbal contamination has not been described for antiretrovirals (ARVs), despite suspicion and poor regulations of herbal practices in sub-Saharan Africa (SSA).[2,3]

Globally, several studies have reported the use of herbal medicines among PLWH either as part of complimentary medicines or as a component for treating

[1]Institute of Translational Medicine, University of Liverpool, Liverpool, UK
[2]Dalhatu Araf Specialist Hospital, Lafia, North-central Nigeria [AQ1]
[3]State Specialist Hospital, Gombe, North-east Nigeria
[4]Federal Medical Centre, Katsina, North-west Nigeria
[5]Faith Alive Foundation Hospital and PMTCT Centre, Jos, Nigeria

Corresponding author:
J Gini, Institute of Translational Medicine, University of Liverpool, 70 Pembroke Place, Liverpool L69 3GF, UK.
Email: J.Gini@liverpool.ac.uk

other ailments[4] but few reports described the impact of herbal medication use on patient safety, adherence and health outcomes.[5,6] Widespread use of herbals among PLWH sabotages the intensified efforts to end human immunodeficiency virus (HIV) epidemic by 2030.[7] Use of herbal medicines could be associated with toxicities, reduced ARV adherence and poor health outcomes.[5,6,8] In a Ugandan study, 63.5% of PLWH reported herbal medicine use after HIV diagnosis and 32.8% use herbals concomitantly with other pharmaceutical products including ARV.[9] Similarly, a Nigerian study reported 27.5% herbal use among PLWH prior to starting ARV and 4.25% concomitant use with ARV.[9,10]

Nigeria and South Africa account for over 40% of the HIV burden in SSA and over three million PLWH in 2016 were living in Nigeria.[11,12] Poor access to healthcare, lack of qualified healthcare personnel, healthcare cost, economic status, education and cultural beliefs promote dissatisfaction with health services and use of herbal medicines even while taking ARV.[13–15] Other challenges of healthcare in Nigeria include: infrastructural, administrative and logistics challenges. Marked variability in ARV access across the country and complex peculiarities of the HIV programmes pose a significant challenge to PLWH and promote utilisation of herbal medicines by patients.[11]

Although conflicting information have previously been reported by some studies on the relationship between concomitant use of herbal medicines and ARV adherence,[10,14,16] herbal use in HIV treatment should be discouraged because of unknown constituents of the herbal and potential drug interactions with ARVs.[17]

Use of herbals in relation to timing of ARV initiation or safety is not well characterized.[9,18] Users and practitioners erroneously consider herbal medicines to be safe without any safety prior evaluation.[19,20] Furthermore, practitioners often have little or no understanding of the modern approaches to evaluate the safety of medicinal products.[19,21]

We sought to evaluate the prevalence of herbal medicine use by PLWH attending one rural and three urban HIV clinics in Nigeria, and related this to the time of ARV initiation. In addition, samples of traditional herbal medicines were collected from street vendors across Nigeria and were screened for the presence of ARVs using liquid chromatography-mass spectrometry (LC-MS).

Methods

Contamination of herbal medications with ARVs

Herbal medicines were collected across eight states in Nigeria between December 2014 and June 2015. The protocol for sample collection was as follows: (i) street vendors from both urban and rural settings were approached by study investigators or assigned personnel, (ii) herbal medicines were requested for the following indications: HIV, acquired immune deficiency syndrome, fevers or non-specific symptoms (e.g. weakness) known to be associated with HIV, (iii) herbal vendors were not informed that samples were to be used for research purposes to avoid any attempt by the vendors to modify the preparation, (iv) only herbals sold as powders or liquids were purchased, (v) instructions for use were recorded, as was the date and site.

A semi-quantitative screen for ARV contamination of herbal medicines was performed at the University of Liverpool by LC-MS for the following ARVs: efavirenz, nevirapine, lopinavir, darunavir, ritonavir, atazanavir, emtricitabine, tenofovir and lamivudine, using a method adapted from Else et al.[22] This method enabled the simultaneous measurement of nine ARVs and was modified based on the suspected solubility of the different ARVs.

Sample pre-treatment. Herbal powders were weighed and dissolved in both water and dimethyl sulfoxide in order to optimise recovery due to different solubility of possible contaminants, at a stock concentration of 10 mg/mL. Working solutions were prepared by further diluting the stock (1:1) with mobile phase. Control (drug-free) mobile phase and blank herbal extracts (herbal controls) were prepared to check the background response of the LC-MS assay. Reference standards spiked with nine ARVs (efavirenz, nevirapine, lopinavir, darunavir, ritonavir, atazanavir, emtricitabine, tenofovir and lamivudine) at two concentrations (50 ng/mL and 100 ng/mL) were prepared.

Semi-quantitative LC-MS/MS. Blanks, reference standards and unknown samples (sourced herbal extracts) were injected (10 μL) onto the LC column coupled to a triple quadrupole mass spectrometer (TSQ Ultra; Thermo Scientific, Hemel Hempstead, UK). Data acquisition and processing was performed using LC Quan™ software (Thermo Scientific, Hemel Hempstead, UK). Herbal contamination was determined by semi-quantitative LC-MS assay (no internal standard or calibrators were used). An estimate of the amount of drug within contaminated samples was derived by comparing chromatographic peak areas of the samples against peak areas of known concentrations of tenofovir, emticitabine and lamivudine spiked in water after correcting for background signal from a known negative herbal sample. Two rounds of analysis (initial screening using 10 mg/mL and confirmatory tests using 50 mg/mL) were performed before accepting the presence of ARV contamination in the sample. Detectable drug was confirmed if the response (chromatographic peak area; arbitrary units) of the unknown sample was at

least five times greater than the response of the blank herbal extract (assay background). A semi-quantitative value per milligram of herbal powder was calculated based on the response of the reference standards minus the assay background interference. For samples that showed presence of drug during screening, additional confirmatory experiments were performed using higher (50 mg/mL) concentrations of herbal extract.

Survey of herbal medication use among PLWH

A clinical survey of PLWH attending ARV facilities in one rural (Rural Hospital, Idong) and three urban HIV facilities (Specialist Hospital, Gombe, Faith Alive Foundation Clinic, Jos, and Dalhatu Araf Specialist Hospital, Lafia) was conducted. Using a non-probability sampling technique, 500 PLWH were surveyed from Faith Alive Foundation Clinic, 199 from Dalhatu Araf Specialist Hospital, 33 from Specialist Hospital Gombe and 10 from Rural Hospital, Idong, respectively. The national prevalence rate of HIV in Nigeria is 3.2%; Kaduna, Gombe, Plateau and Nassarawa states have HIV prevalence rate of 9.2%, 8.1%, 3.4% and 2.3%, respectively. These surveyed clinics attend to over 6000 PLWH and the Faith Alive Foundation Clinic in Jos attends to over 5000 PLWH per month, while Rural Hospital, Idong, a primary healthcare setting, attends to less than 50 PLWH.[23,24]

Inclusion criteria were: known HIV-antibody positive patients attending clinic, any age, willing to participate in the survey. For children less than 18 years old, parents were asked for consent and if willing, provided responses to the survey. Hospitalised patients, patients who were acutely unwell and any unconfirmed patient in the clinic were excluded. We utilised a structured questionnaire adapted from Langlois-Klassen et al. who previously evaluated herbal medication use among PLWH.[9] The questionnaire was modified for our purpose and was applied to evaluate use of herbal medications across age, gender, education, employment status, date of diagnosis, date of starting herbal medications, type of herbal medication, source of recommendation for herbal use, source of procurement of herbal, reasons for use and perceived effectiveness of the herbals. Someone was considered a herbal user if he/she utilises concoctions (from known or unknown plant products) from herbal vendors or plant product recommended by family, friend or anybody. The primary outcome was prevalence of herbal medication use among PLWH. Secondary outcomes were use of herbals in relation to initiation of antiretroviral drugs, differences by gender, by age, by educational attainment, employment status and perception of benefit from herbal use. Herbal sample collection from vendors was random, and collection at different regions of the country was ensured for fair representation of different regions of the country.

Statistical analysis. Data were analysed using IBM SPSS statistics version 22.0 (IBM Corp., 2013). Participants who answered positively when asked, 'Do you use herbal medicine?' were considered as herbal medicine users. Data on herbal use and baseline social and demographic factors were pooled across all four centres to produce aggregate, descriptive overall frequencies at 5% level of significance (Table 1). We then compared social and demographic factors in PLWH who used or did not use herbal medicines. First, univariate analysis was performed using binary logistic regression with herbal use as the dependent variable. Next, all univariate associations with $P \leq 0.1$ were included in the final multivariable model. Groups were compared for relationships and confounders on the dependent variable (use of herbal medication) were resolved using multiple regression models (Table 2).

Ethical approval. Ethics approval for the survey was obtained from Dalhatu Araf Specialist Hospital, Lafia, Faith Alive Foundation Hospital and PMTCT Centre, Jos (protocol assigned number: FAFHREC/08/34/5) and parental consent for including children was sought from parents before interviewing the parents for their children's information. Only verbal consent and permission from hospital management was obtained from patient in primary healthcare Idong and Gombe Specialist Hospital.

Results

A total of 742 (approximately 12% of patients receiving treatments in these facilities) consecutively attending PLWH aged between 2 and 91 years were surveyed across the four centres. Of these, 715 (96.4%) were adults aged 18 and above, 457 (61.6%) were female, 281 (37.9%) were males, and details of gender were missing in 4 (0.9%). Further details of demographic characteristics are provided in Table 1. Of the 742 PLWH surveyed, 594 (80.1%) were receiving ARVs.

Herbal use was reported in a total of 310 individuals (41.8%). Of these, 119 (38.4%) took herbals prior to starting ARV while 191 (61.6%) started taking herbals after starting ARV (Table 2). Educational attainment was significantly associated with herbal medication use; individuals with secondary and tertiary education were more likely (70%) than those with little or no education (26.1%) to use herbals ($P < 0.001$) and with employment status (70.7% of the employed vs. 28.4% of unemployed patients admitted using herbals, $P < 0.001$). Time from diagnosis of HIV ($P = 0.73$) and whether individuals were receiving ARVs

Table 1. Prevalence of social and demographic factors in PLWH who use or do not use herbal medicines.

Variable	Use herbal medications (n = 310) n (%)	Do not use herbal medications (n = 432) n (%)
Age (years)		
• Median (range)	33 (2–91)	32 (13–74)
Gender		
• Male	119 (38.4)	162 (37.9)
• Female	191 (61.6)	266 (62.1)
• Missing data		4 (0.9)
Level of education		
• Little or no education	81 (26.1)	139 (32.1)
• Secondary and tertiary education	217 (70.0)	285 (66.0)
• Missing data	12 (3.9)	8 (1.9)
Employment status		
• Employed	219 (70.7)	281 (65.1)
• Unemployed	88 (28.4)	140 (32.4)
• Missing data	3 (0.9)	11 (2.5)
Months since HIV diagnosis		
• <6 months	146 (47.1)	136 (31.5)
• >6 months	152 (49.0)	284 (65.7)
• Missing data	12 (3.9)	12 (2.8)
Commenced ARVs		
• Yes	259 (83.6)	335 (77.5)
• No	45 (14.5)	78 (18.1)
• Missing data	6 (1.9)	19 (4.4)

HIV: human immunodeficiency virus; ARV: antiretroviral.

(P = 0.53) were not significantly associated with herbal medication use. PLWH who use herbals did so for a variety of reasons: to cure HIV (46.8%), or following the advice of family (67.4%) or friends (31.6%). Altogether, 40.3% said they felt herbals were ineffective for HIV while 4.5% believed themselves cured (Table 2). Ingestion of herbal medications while on ARVs was more likely in the elderly (OR 2.31; 95% CI 1.34, 3.99) and the employed (OR 1.23; CI 0.89, 1.70) compared to the unemployed (Table 3).

As an extension to this study, 138 herbal samples were sourced from herbal vendors in diverse locations across Nigeria to assay for the presence of ARVs. Of the 138 samples collected and analysed, three (2%) contained detectable ARVs. One sample from Jos contained tenofovir and emtricitabine (estimated as 0.02 ng/mg powder and ≤0.01 ng/mg powder, respectively), while two samples from Ibadan contained tenofovir (estimated as <0.01 and 0.13 ng/mg powder) and emtricitabine (estimated as <0.01 ng/mg powder), with one of these also containing lamivudine (estimated as 0.02 ng/mg powder). Other ARV classes were not detected.

Dosing recommendations provided by the herbal vendors are often not precise. We found a typical dose recommendation was '3 fingers' or scoops of medicinal powder in the palm of the hand, conservatively estimated as 1–2 teaspoons (1 teaspoon estimated as 5 g). Based on these recommendations, a single dose of 2 teaspoons (approximately 10 g) of contaminated herbal powder could potentially deliver up to 1.3 μg of tenofovir, 0.1 μg of emtricitabine and 0.2 μg of lamivudine. Although amount of drug detected is small, repeated exposure, or exposure to higher doses with different batches or preparations, could promote drug resistance.

In Nigeria, tenofovir and emtricitabine are available in fixed-dose combination as TRUVADA®. We wanted to examine if the discrepancy in the amount of tenofovir and emtricitabine observed could have been explained by differential degradation when crushed or dissolved, or recovery during the extraction process. Recovery from dissolved TRUVADA® tablets in water at room temperature carried out after 12 weeks and 9 months, respectively, was 63.2% and 1.47% for emtricitabine, compared with 0.8% and 1.47% for tenofovir. There were also considerable differences in drug solubility, recovery (extraction efficiency) and matrix effects (ion suppression) between different herbal preparations, which more likely explained the differences in measured quantity between both drugs.

Discussion

We observed widespread use of herbal medicines in Nigeria (Table 1) regardless of age, gender, educational

or employment status. Our data are consistent with previous studies conducted in this region.[9,25] A total of 594 (80%) of PLWH were receiving ARV and herbal medicine use was highly prevalent in patients receiving HIV treatment (259/594 [43.6%] of those receiving ARV use herbal or traditional medicines). Among the herbal users, 38.4% were using these remedies prior to initiation of ARVs, while 61.2% started using it after HIV diagnosis (Tables 1 and 2).

Table 2. Source of recommendations, reasons for use, when herbal was started and perceived effectiveness among PLWH who use herbal medication (n = 310).

Variable	Use herbal medications (n = 310) n (%)
When did you start using herbal medications?	
• Pre-HIV diagnosis	119 (38.4)
• Post-HIV diagnosis	191 (61.6)
Who recommended the herbal medications	
• Family	209 (67.4)
• Friends	98 (31.6)
• Missing data	3 (1.0)
Source of herbal medicines	
• City vendors	108 (34.8)
• Village herbalist	145 (46.8)
• Others	15 (4.8)
• Missing data	42 (13.6)
Reasons for herbal medication use	
• To Relieve Symptoms	108 (34.8)
• To achieve cure of disease	145 (46.8)
• Others	15 (4.8)
• Missing data	42 (13.6)
Perceived effectiveness of herbal medication	
• No help	125 (40.3)
• Moderate relieve of symptoms	89 (28.7)
• Completely relieved symptoms	43 (13.9)
• Cures disease (HIV) completely	14 (4.5)
• Missing data	39 (12.6)

HIV: human immunodeficiency virus.

Of concern, 45 (14.5%) of herbal users were yet to initiate ARVs which could be detrimental to their treatment in the future if exposed to low levels of ARV in herbal remedies (Table 1). Previous reports of low-level ARV exposure to neonate during PMTCT suggest that continuous low-level exposure to ARVs could drive resistance.[25,26] Our finding of contamination of herbals with ARVs is a concern, though concentration was very small and may not be sufficient to drive resistance, finding contamination in herbals is detrimental to treatment and HIV programme success. Around half of the subjects perceived use of herbal medicines to either moderately or completely relieve symptoms such as headaches, fever and generalised body weakness.

We found 2% of herbal medicines contained small, but detectable quantities of ARVs, yielding an estimated dose of 0.1–1.3 μg ingested per dosing occasion. The clinical relevance of this is unclear. However, continuous low-level exposure to drug can lead to resistance, provided sufficient drug is present to drive selection pressure for resistant mutants. Furthermore, potential drug–drug interaction of herbals and ARVs as well as safety[8,17] was difficult to ascertain since constituents of the herbal medicines were unknown.[27] Although the concentrations detected were very low, actual concentrations may have been higher given the different efficiencies of extraction and degradation over time that were observed.

The finding that traditional or herbal remedies may contain pharmaceutic agents is not new. Previously, herbal medicines have been found to contain antipyretics, anti-inflammatory agents or steroids, diuretics, antidiabetics, sedatives, antihistamines and vasodilators through accidental or deliberate contamination.[28] Accidental contamination may result from carryover of drug during local manufacture of medicines; however, this is less likely here as HIV drugs are not locally co-manufactured with herbals to our knowledge. It is difficult to ascertain whether contamination was

Table 3. Association of surveyed variables and herbal medication use among PLWH.

	Univariate analysis			Multivariate analysis		
Variable	β	Odds ratio (OR) (95% confidence interval)	P	β	Odds ratio (OR) (95% confidence interval)	P
Age	0.688	1.990 (1.183, 3.347)	0.009	0.839	2.314 (1.343,3.987)	0.003
Gender	–0.039	0.797 (0.712, 1.298)	0.797			
Level of education	0.248	1.282 (0.930, 1.766)	0.130	0.190	1.209 (0.868, 1.686)	0.262
Employment status	0.192	1.228 (0.887, 1.696)	0.228			
Months since HIV diagnosis	–0.688	0.502 (0.370, 0.681)	<0.001	–0.724	0.485 (0.355, 0.663)	<0.001
Commenced ARVs	0.154	1.167 (0.080, 1.696)	0.418			

HIV: human immunodeficiency virus; ARV: antiretroviral.

deliberate or accidental in this case. HIV drugs are dispensed free of charge through the National Treatment Programme; their use and belief that they are beneficial for the treatment of HIV disease may provide both the opportunity and the motive for any deliberate contamination. Herbalists and their medicines can play an important role in supplementing and supporting HIV treatment in treatment settings[18,29] where weak health systems and complex cultural beliefs around symptom management[30] promote widespread herbal use. Enforcing the regulation of herbal medicine practices[3] and re-evaluating policies guiding herbal practitioners in Nigeria is urgently required to avoid harmful practices that put the general public at risk.

Limitations

We were not able to ascertain how herbal use influenced engagement with HIV services, or adherence to ARVs although these are important questions to address in future research. Moreover, we were only able to assess PLWH already engaged with treatment services. There is currently no clear understanding of positive or negative effects of traditional medicines as adjunctive treatment in PLWH. However, the lack of regulation and standardisation in these preparations argues strongly for further work to confirm our findings in other countries where herbal medicine use is prevalent and to understand whether ARV contamination of herbal medicines has a negative impact on ARV programmes through the generation of drug resistance. Surveys were only conducted in small population from northern Nigeria, which may vary from other regions of the country. Therefore, a larger study that aims at ensuring fair representation of all the regions of Nigeria is required.

Conclusion

Herbal medicine use was widespread and mostly utilised concomitantly with ARVs. Although a fairly large proportion utilised herbals prior to ARV initiation, co-administration of herbal medicines with ARVs is concerning, since the constituents and safety profiles of the herbal medicines are unknown. Toxicity and herbal–ARV interactions are uncharacterised which favours urgent evaluation of policies by authorities to regulate their practices. Erroneous perception of herbals to relieve HIV symptoms or cure disease is a problem and herbals need to be further evaluated for their medicinal benefits. Finally, further evaluation of our findings by researchers to establish the best approach to monitor and enforce safe practices of herbalist for public safety of herbal products as well as collaborative research of medicinal herbs is required.

Acknowledgements

We are grateful to the State Specialist Hospital, Gombe, Faith Alive Foundation Hospital and PMTCT Centre, Dalhatu Araf Specialist Hospital, Lafia, Nasarawa State, and Rural Hospital, Idong, Kaduna State, for allowing us to conduct surveys in their HIV clinics.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Nigerian Government via the National Universities Commission (NUC) and Tertiary Education Trust Fund (TETFund) as part of funding for PhD programme to a beneficiary of 2011 Presidents Honours Award scholarship from Federal Ministry of Health Nigeria. The authors acknowledge infrastructural support from the Liverpool Biomedical Research Centre funded by Liverpool Health Partners. The Liverpool Drug Interactions website has received funding from Gilead Sciences, ViiV Healthcare, Janssen and Merck.

ORCID iD

J Gini http://orcid.org/0000-0001-5701-2115

References

1. Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. *J Intern Med* 2002; 252: 107–113.
2. Awodele O, Amagon KI, Wannang NN, et al. Traditional medicine policy and regulation in Nigeria: an index of herbal medicine safety. *Curr Drug Saf* 2014; 9: 16–22.
3. Osuide GE. Regulation of herbal medicines in Nigeria: the role of the National Agency for Food and Drug Administration and Control (NAFDAC). *Adv Phytomed* 2002; 1: 249–258.
4. Awodele O, Olayemi O, Adeyemo AT, et al. Use of complementary medicine amongst patients on antiretroviral drugs in an HIV treatment centre in Lagos, Nigeria. *Curr Drug Saf* 2012; 7: 120–125.
5. Oku AO, Owoaje ET, Oku OO, et al. Prevalence and determinants of adherence to highly active antiretroviral therapy amongst people living with HIV/AIDS in a rural setting in South-South Nigeria. *Afr J Reprod Health* 2014; 18: 133–144.
6. Heestermans T, Browne JL, Aitken SC, et al. Determinants of adherence to antiretroviral therapy among HIV-positive adults in sub-Saharan Africa: a systematic review. *BMJ Glob Health* 2016; 1: e000125.
7. Granich R, Gupta S, Hall I, et al. Status and methodology of publicly available national HIV care continua and

90-90-90 targets: a systematic review. *PLoS Med* 2017; 14: e1002253.
8. Seeff LB, Bonkovsky HL, Navarro VJ, et al. Herbal products and the liver: a review of adverse effects and mechanisms. *Gastroenterology* 2015; 148: 517–532.e3.
9. Langlois-Klassen D, Kipp W, Jhangri GS, et al. Use of traditional herbal medicine by AIDS patients in Kabarole District, western Uganda. *Am J Trop Med Hyg* 2007; 77: 757–763.
10. Tamuno I. Traditional medicine for HIV infected patients in antiretroviral therapy in a tertiary hospital in Kano, Northwest Nigeria. *Asian Pac J Trop Med* 2011; 4: 152–155.
11. Oladele EA, Badejo OA, Obanubi C, et al. Bridging the HIV treatment gap in Nigeria: examining community antiretroviral treatment models. *J Int AIDS Soc* 2018; 21: e25108.
12. UNAIDS, www.unaids.org/en/regionscountries/countries/nigeria (accessed 15 October 2018).
13. Fakeye TO, Adisa R and Musa IE. Attitude and use of herbal medicines among pregnant women in Nigeria. *BMC Complement Altern Med* 2009; 9: 53.
14. Chukwuemeka A, Adeyemi O, Dolapo A, et al. Evaluation of the frequency of use of herbal drugs with concomitant administration of highly active antiretroviral therapy and its effect on medication adherence in two health care facilities in south western Nigeria. *J AIDS HIV Res* 2017; 9: 8–16.
15. Peters DH, Garg A, Bloom G, et al. Poverty and access to health care in developing countries. *Ann N Y Acad Sci* 2008; 1136: 161–171.
16. Oku AO, Owoaje ET, Ige OK, et al. Prevalence and determinants of adherence to HAART amongst PLHIV in a tertiary health facility in south-south Nigeria. *BMC Infect Dis* 2013; 13: 401.
17. Henderson L, Yue Q, Bergquist C, et al. St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *Br J Clin Pharmacol* 2002; 54: 349–356.
18. Thomford NE, Dzobo K, Chopera D, et al. Pharmacogenomics implications of using herbal medicinal plants on African populations in health transition. *Pharmaceuticals* 2015; 8: 637–663.
19. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol* 2014; 4: 177.
20. Barnes J. Quality, efficacy and safety of complementary medicines: fashions, facts and the future. Part I. Regulation and quality. *Br J Clin Pharmacol* 2003; 55: 226–233.
21. Awodele O, Agbaje E, Ogunkeye F, et al. Towards integrating traditional medicine (TM) into National Health Care Scheme (NHCS): assessment of TM practitioners' disposition in Lagos, Nigeria. *J Herbal Med* 2011; 1: 90–94.
22. Else L, Watson V, Tjia J, et al. Validation of a rapid and sensitive high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) assay for the simultaneous determination of existing and new antiretroviral compounds. *J Chromatogr B* 2010; 878: 1455–1465.
23. Naca.gov.ng (accessed 31 March 2017). [AQ4]
24. www.faithalivenigeria.org/about/hospital.htm (accessed 31 March 2017).
25. Kuhn L, Hunt G, Technau K-G, et al. Drug resistance among newly-diagnosed HIV-infected children in the era of more efficacious antiretroviral prophylaxis. *AIDS (London, England)*. 2014; 28: 1673.
26. Zeh C, Weidle PJ, Nafisa L, et al. HIV-1 drug resistance emergence among breastfeeding infants born to HIV-infected mothers during a single-arm trial of triple-antiretroviral prophylaxis for prevention of mother-to-child transmission: a secondary analysis. *PLoS Med* 2011; 8: e1000430.
27. Kamsu-Foguem B and Foguem C. Adverse drug reactions in some African herbal medicine: literature review and stakeholders' interview. *Integr Med Res* 2014; 3: 126–132.
28. Zhang J, Wider B, Shang H, et al. Quality of herbal medicines: challenges and solutions. *Complement Ther Med* 2012; 20:100–106.
29. Tabassum N and Ahmad F. Role of natural herbs in the treatment of hypertension. *Pharmacogn Rev* 2011; 5: 30.
30. Airhihenbuwa CO, Ford CL and Iwelunmor JI. Why culture matters in health interventions lessons from HIV/AIDS stigma and NCDs. *Health Educ Behav* 2013. [AQ5]