

ORIGINAL RESEARCH ARTICLE

HIV Status Discordance: Associated Factors Among HIV Positive Pregnant Women in Lagos, Southwest Nigeria

Innocent AO Ujah^{*1}, Oliver C Ezechi¹ and Aigbe Gregory Ohihoin¹

Nigerian Institute of Medical Research, Yaba Lagos¹

***For Correspondence:** Email:innocentujah@gmail.com; +234-08086575544

Abstract

The HIV negative partner in a HIV serodiscordant relationship is at high risk of becoming HIV infected. The annual risk of HIV infection for a partner of a person with HIV is about 10%, with higher annual transmission rates of 20–25% per year reported in Rwanda and Zambia. Although there is considerable variation across countries, recent studies in southern and east Africa countries with mature epidemics reported that up to two-thirds of infected persons in stable relationship are discordant. HIV serodiscordance is thus a recognized priority for HIV prevention intervention. In Nigeria only few studies have studied the burden of serodiscordance, making planning difficult. In this study HIV serodiscordance rate and associated factors among pregnant women were assessed in a large PMTCT clinic in Lagos Nigeria over a 9 years period. Information on HIV status disclosure, partners HIV status (confirmed by HIV test results), sociodemographic characteristics and reproductive information were obtained from the women after enrollment and entered into the case file. In the study, relevant information was managed with SPSS for windows version 19.0. The variables independently associated with HIV status discordance were determined in both univariate and multivariate analysis. P values and Odd ratio with their confidence intervals were calculated. Out of the 4435 women enrolled during the study period, 3712 (83.7%) had disclosed their status to their partner. Partner's HIV status among the women with confirmed HIV status was negative in 2065 (66.8%) women, thus a discordant rate of 66.8%. HIV status disclosure rate was 83.7%; with significantly higher disclosure rate in concordant couple (83.3%) compared to 76.8% among women in serodiscordant relationship ($p=0.00$; OR: 1.5; 95% CI: 1.25-1.82). Discordant HIV status in a female positive relationship was found to be associated with history of at least two termination of pregnancy (OR: 3.05; 95% CI: 2.91-3.89) and five or more total life time sexual partnership (OR: 2.3; 95% CI: 1.27-3.21). The perception that men are the index cases is not supported by evidence from this study. We recommend the tracking of both men and women as index cases in order to reduce HIV transmission within stable relationship. Social marketing aimed at reducing concurrency should focus on both male and females, if we must reduce new HIV infection within stable relationships. (*Afr J Reprod Health* 2015; 19[2]: 108-116).

Keywords: HIV/AIDS, HIV status, Discordance, Pregnant, Nigeria

Résumé

Le partenaire séronégatif dans une relation sérodiscordantes du VIH est à haut risque de devenir infecté par le VIH. Le risque annuel d'infection par le VIH d'un partenaire d'une personne avec le VIH est d'environ 10%, avec des taux plus élevés de transmission annuels de 20-25% par an comme rapporté au Rwanda et en Zambie. Bien qu'il existe des variations considérables entre les pays, des études récentes dans les pays en Afrique australe et orientale avec des épidémies matures rapporté que jusqu'à deux tiers des personnes infectées en relation stable sont discordantes. La sérodifférence est donc une priorité reconnue pour l'intervention de prévention du VIH. Au Nigeria, peu d'études ont étudié la charge de sérodifférence, ce qui rend la planification difficile. Dans cette étude, le taux de sérodifférence du VIH et les facteurs associés chez les femmes enceintes ont été évalués dans une grande clinique de PTME à Lagos au Nigeria au cours d'une période de 9 ans. Les informations sur la divulgation du statut du VIH, le statut du VIH des partenaires (confirmé par les résultats des analyse pour détecter le VIH), les caractéristiques sociodémographiques et d'information en matière de reproduction ont été obtenues auprès des femmes après l'inscription et est entré dans les dossiers des femmes. Dans l'étude, l'information pertinente a été gérée avec SPSS pour Windows version 19.0. Les variables indépendamment associés à la discordance séropositivité du statut du VIH ont été déterminées à la fois dans l'analyse univariée et multivariée. Les valeurs de P et le ratio Odd avec leurs intervalles de confiance ont été calculés. Sur les 4435 femmes inscrites au cours de la période de l'étude, 3712 (83,7%) avaient révélé leur statut à leur partenaire, le statut du VIH des partenaires parmi les femmes dont le statut VIH est confirmée était négatif chez 2065 (66,8%) des femmes, donc un taux discordant de 66,8%. Le taux de la divulgation du statut du VIH était de 83,7%; avec un taux significativement plus élevé de divulgation chez les couples concordants (83,3%), par rapport à 76,8% chez les femmes en relation sérodiscordantes ($p = 0,00$; OR: 1,5; IC 95%: 1,25 à 1,82). Nous avons découvert que le statut du VIH dans une relation positive d'une femme a été associé à l'histoire d'au moins deux interruption de grossesse (OR: 3,05; IC 95%: 2,91 à 3,89) et cinq ou plus des partenaires sexuels de toute la vie (OR: 2,3; 95 % CI: 1.27 à 3.21). La perception que les hommes sont les cas index ne sont pas étayés par des preuves

de cette étude. Nous recommandons le suivi des hommes et des femmes comme des cas index pour réduire la transmission du VIH au sein de relation stable. Le marketing social visant à réduire la concurrence devrait se concentrer sur les deux mâles et les femelles, si nous devons réduire nouvelle infection par le VIH au sein des relations stables. (*Afr J Reprod Health* 2015; 19[2]: 108-116).

Mots-clés: VIH / sida, séropositivité, Discordance, enceinte, Nigeria

Introduction

Globally, Nigeria has the second highest number of new infections reported each year, and 4.0% of the population are living with Human Immunodeficiency Virus^{1,2}. Although the HIV prevalence in Nigeria is much lower than the double digit figures in Botswana, Lesotho, South Africa and Zambia, the size of Nigeria's 170 million population means that an estimated 3.23 million of its citizens are living with HIV^{1,2}. The HIV epidemic in Nigeria is complex, and rates of HIV and patterns of infection vary widely by zone; ranging from 1.8% in South East to 5.5% in South-South Nigeria³. While several states are experiencing epidemics in the general population, in other states the epidemics are concentrated and driven by high-risk behaviors^{2,3}. The HIV epidemic in Nigerian can best be described as a mixed epidemic, unlike generalized epidemic in Botswana, Lesotho, Uganda, Tanzania and Zambia^{1,4}. There are also urban and rural differences with prevalence figures in the urban areas (3%) lower than the 4% in rural areas. Without prejudice to the reported regional variations, the observed higher prevalence in females remained across all selected background characteristics².

Nigeria health system is hugely challenged by the HIV epidemic, with significant effect on mortality and average life expectancy of Nigerians^{1,5}. Though UNAIDS recently reported a reduction in the number of persons infected with HIV/AIDS globally, 48% of all new infection in sub Saharan Africa occurs in Nigeria, South Africa and Uganda⁴. Novel strategies are therefore needed to prevent new infection from occurring in these three countries⁵.

Sub-Saharan Africa has the highest prevalence and incidence of HIV infection globally, mostly due to heterosexual transmission^{4,6,7}. This could be the reason why intervention to reduce sexual

transmissions of HIV in our settings have focused mainly on transmission in new relationships^{8,9}. This strategy is insufficient as available evidence shows that about 50% of all HIV infections occur in discordant couples already in a stable relationship⁵. Several studies in sub-Saharan Africa have noted a high prevalence of HIV serodiscordance among heterosexual couples^{6,10-12}, ranging from 2% in Rwanda¹³ to 13% in Zimbabwe¹⁴ and Lesotho¹⁵ and 80% in Nigeria¹⁶. These reported high serodiscordance figures in Nigeria, though hospital based studies may give credence to the suggestion that Nigerian HIV epidemic and transmission dynamics are different from those of countries in southern and eastern Africa^{10,17}.

National population surveys and epidemiologic studies reports that the majority of African HIV infected individuals are married or are in a stable, long-term relationship, and approximately half of couples in which at least one partner is HIV-1-infected are HIV serodiscordant^{18,19}. Mathematical models suggest that a good proportion of new HIV infections occur among HIV serodiscordant couples in Africa, demonstrating that HIV serodiscordant couples are a significant population for HIV prevention intervention^{20,21}.

The HIV negative partner in a HIV serodiscordant relationship, is at high risk of becoming HIV infected²². While the common opinion is that the majority of HIV infection in serodiscordant couple occurred before the union, others posited that the infection may have occurred after the union^{20,21}. Unfortunately information on the percentage of serodiscordance resulting from infection before and after a stable union is unknown^{7,18,19}. The annual risk of HIV infection for a partner of a person with HIV is about 10%^{22,23}, with higher annual transmission rates of 20–25% per year reported in Rwanda and Zambia²⁴⁻²⁶. In most HIV high burden countries,

over 90% of new HIV infections are in couples living together^{1,4,6,7}. Although there is considerable variation across countries, recent studies in southern and east Africa countries with mature epidemics reported that up to two-thirds of infected persons in stable relationship are discordant^{14,15,27-30}.

Many HIV serodiscordant couples are not aware of their serodiscordant status, primarily because one or both partners have not been tested or have tested separately and did not disclose their HIV status to their partner^{6,31,32}. HIV serodiscordance is now recognized as a priority for HIV prevention interventions, as it can influence transmission of disease not only within adult but between mother and child and the development of antiretroviral drug resistance^{20,21}. However, for a particular intervention to be effective it requires a clear understanding of HIV transmission dynamics, burden of HIV serodiscordance and associated factors in the environment.

While several studies have established that women's greatest risk of contracting HIV lies within a marital relationship^{10,33-35}, only few studies have made attempts to establish a man's risk within marriage^{6,36}. In regions with generalised epidemics, high rates of serodiscordance among heterosexual couples in which the woman is HIV-positive suggest that a man's risk of marital HIV acquisition could also be substantial^{6,13,36}. In Nigeria, only few studies focused on the burden of serodiscordance with female positive^{10,16}, making prevention planning difficult.

In this study we assessed the rate of HIV serodiscordance and associated factors among HIV infected pregnant women attending the HIV clinic of a public funded institution. The HIV disclosure rate among the women was also investigated. Information obtained, will be useful for the planning of evidence-based intervention for HIV prevention.

Method

Pregnant HIV positive women who attended HIV treatment clinic at the Nigerian Institute of Medical Research (NIMR), Lagos from July 2004 to December 2013 were eligible for inclusion into

the study. Excluded from the study were women who declined consent and spouse HIV status could not be backed by laboratory test results.

Pregnant women were enrolled into the PMTCT clinic after confirmation of HIV positive status at the HIV counselling and testing centre. The women were thereafter counselled on the PMTCT Clinic routines, adherence to antiretroviral drugs, infant feeding practices, modes of delivery and status disclosure. Those who had not disclosed their status to their partners or significant person(s) were encouraged to disclose. In addition, the HIV status of the partners was enquired and HIV test results of the partners were requested to confirm the status. Partners' HIV status was accepted as known only if backed by a test result from government approved HIV testing facility. At booking women whose partners' HIV status was unknown were offered the opportunity to either invite their partner for testing or have him conduct the test at a preferred facility. Women who had not disclosed their status were also encouraged to do so.

Information on disclosure and partner's HIV status, sociodemographic, medical and reproductive history were routinely documented in the patient's case file. The information on the case files were transferred into the programme database by trained data entry clerks. For this study, relevant data were extracted from the programme database, exported and analyzed with SPSS for windows version 19.0. Frequency distributions were generated and univariate analysis using relevant statistics were performed to identify factors associated with HIV status disclosure and discordant status. Multivariate logistic regression was further used to identify independent risk factors for discordant HIV status while controlling for potential confounders. The variables were entered into the model in a step wise manner irrespective of their P value on univariate analysis but starting with variable with the weakest P value. In the analysis, the comparison group was those women with concordant HIV status. $P < 0.05$ was considered to be statistically significant. Odds Ratios (OR) and 95% Confidence Intervals (CI) for the OR were also calculated.

Approval for the study were obtained from the Institutional Review Board (IRB), Nigerian

Institute of Medical Research, Lagos Nigeria. Written informed consent was obtained from all women for the use of their data for study. However women who declined consent to participate in the study were provided care but excluded from research.

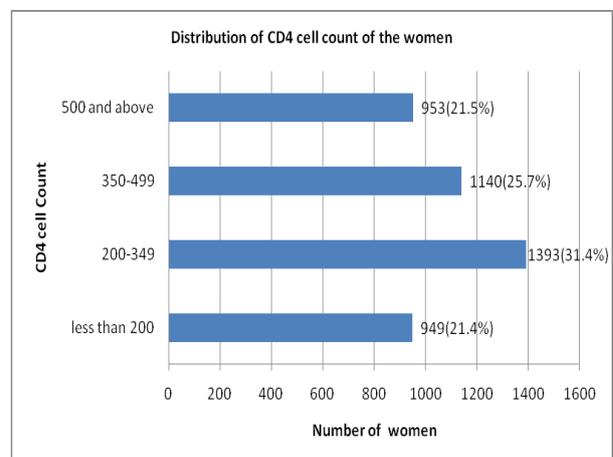
Table 1: Sociodemographic and Biologic Characteristics of the 4435 Pregnant Women Studied.

Characteristics	Number of participants (%)
Age	
Less than 20	191 (4.3)
20-24	680(14.2)
25-29	1027(23.2)
30-34	1543(34.8)
35-39	834(18.8)
>40	160(3.6)
Parity	
0	1379(31.1)
1 – 2	1805(40.7)
3 and above	1251(28.2)
Educational status	
Less than secondary	1078(24.3)
At least secondary	3357(75.7)
Marital status	
Married	3517(79.3)
Single	918(20.7)
Social class	
I and II	616(13.9)
III	1126(25.4)
IV & V	2693(60.7)
History of induced abortion	
0	1255(28.3)
1	1503(33.9)
2 or more	1676(37.8)
Life time sexual partners	
0 - 1	856 (19.3)
2 - 4	2479(55.9)
5 and above	1100(24.8)
Gestational age (weeks)	
Less than 13	918(20.7)
13 and above	3517(79.3)
HAART status	
Yes	616(13.9)
No	3819(86.1)
CD4 cell count	
Less than 350	2342(52.8)
350 and above	2093(47.2)
Viral load	
Less than 1000	1947(43.9)
1000 and above	2488(56.1)

Result

A total of 4435 HIV positive pregnant women were enrolled into PMTCT services during the study period. The sociodemographic characteristics of 4435 pregnant women are shown in Table 1. The majority of the women were less than 35 years of age (74.9%), married (79.3%) and completed at least a secondary education (75.7%). The mean gestational age at booking for PMTCT was 23.1 ± 4.1 weeks, with the majority booking after the first trimester of pregnancy (79.3%). Most of the women reported at least one previous termination of pregnancy (71.7%) and at least two previous sexual partners (80.7%). While 1947 (43.9%) had HIV viral load of less than 1000 copies, 616(13.9%) women were on highly active antiretroviral therapy (HAART) at the time of enrollment. The distribution of CD4 cell counts of the women are shown in Figure 1. The majority of the (2342; 52.8%) women had CD4 count value of less than 350.

Figure 1: Distribution of the Baseline CD4 Cell Count among the Women in the Study.



Of the 4435 women enrolled during the study period, 3712 (83.7%) had disclosed their status to their partner. Among the 3712 women that disclosed their status, the HIV status of the partner was known in 3092(83.3%). In the remaining 620(16.7%) the HIV status of the partner was not

confirmed by laboratory test and declared unknown. While majority (406; 65.5%) of the partners with unknown HIV status promised to undergo HIV test, later but never did, 198(31.9% declined out rightly to take a HIV test and in the remaining 18(2.6%) could not be reached by their female partner. The HIV status of the partners with known HIV status were negative in 2065 (66.8%) women and positive in the remaining 1027 (33.2%) women; giving a HIV discordant rate of 66.8%. The HIV status disclosure rate of 83.3% among women in seroconcordant relationship was significantly higher than disclosure rate of 76.8% and 77.3% respectively among women in serodiscordant relationship ($p=0.00$; OR: 1.5; 95% CI: 1.25-1.82). and those whose partner HIV status is unknown ($p=0.00$; OR:1.47; 95% CI:1.17-1.85). However, there was no statistical significant difference in disclosure rate between women in serodiscordant relationship and those whose partner HIV status is unknown (OR: 0.98; 95% CI: 0.76-1.25). Compared to the women who had disclosed their status, in which 16.7% knew their partners status, only 13.1% of those who had not disclosed their status knew their partners HIV status ($p=0.02$; OR:1.33;95% CI:1.04-1.68). HIV status disclosure rate was also significantly higher in women who knew their HIV status prior to the index pregnancy (92.3%; 872/945) compared to 89.8% (3134/3490) in those who did not know their HIV status before the index pregnancy($p=0.00$; OR:0.47;95% CI:0.47-0.72). Table 2 shows the association between sociobiological characteristic of the women and HIV status discordance. On univariate analysis, having at least a secondary education (OR: 1.52; 95% CI: 1.30-1.78) , five or more past sexual partners (OR:1.29; 95% CI:1.07-1.56) ,primiparity (cOR:2.02; 95% CI:1.66-2.45), two or more previous termination of pregnancy (cOR:3.36; 95% CI:2.75-4.10) and low socioeconomic class (cOR:1.70; 95% CI:1.43-2.02) were found to be significantly associated with discordant HIV status. HIV positive pregnant women with history of no past sexual partner before marriage (cOR: 0.73; 95% CI:0.61-0.89) and multipara (cOR: 0.50;95% CI:0.41-0.60) were less likely to be in a

HIV discordant relationship. After adjustment for potential confounding variables in multivariate logistic regression including but not limited to controlling for educational attainment, age, socioeconomic status, parity and past history of pregnancy termination and number of life time sexual partnership, discordant HIV status was found to be associated with only history of at least two termination of pregnancy (aOR: 3.05; 95% CI:2.91-3.89) and five or more total life time sexual partnership (aOR: 2.3; 95% CI:1.27-3.21)

Discussion

Over two-thirds of the pregnant HIV positive women studied were in a serodiscordant relationship. Those with history of at least two pregnancy terminations and five or more total life time sexual partnership were more likely to be in a serodiscordant relationship. The serodiscordant rate of 66.8% in this study though lower than the 80.0% reported previously in Lagos and Benin^{16,37} is higher than the rates of 2.0% to 58.8% reported in eastern and south African countries of Kenya, Uganda, Rwanda, Zimbabwe and Lesotho^{13-15,19,32}. It is however similar to 61.5% found in Port Harcourt Nigeria by Akani and his team³⁸. The generally higher serodiscordance rate in Nigerian studies compared to those from eastern and southern Africa studies may be due to the reported differences in the HIV epidemiologic and transmission dynamics, and could account for the higher new infection rate in Nigeria compared to the rates in Kenya, Rwanda and Zimbabwe^{4,17}. The serodiscordance rates in Nigeria also tend to be higher in studies conducted in South-South zone with highest average HIV prevalence^{2,3,16,38}. The differing rates across studies in Nigeria could also be a reflection of the reported mixed epidemic in Nigeria^{2,3}. Sagay and his team in their study conducted in three Nigerian cities with different HIV prevalence; found relationship between HIV prevalence and serodiscordant rate¹⁰. HIV serodiscordance rate of 78.8% in Benin city south-south Nigeria with highest average HIV prevalence was higher than rate of 48.8% in Jos North central and 7.7% in Kano, North west zone with lower average HIV prevalence^{2,10}.

Table 2: Maternal variables independently associated with discordant HIV status

Maternal Variables	Discordant status n= 2065	HIV Concordant status n=1027	HIV Crude OR(95% CI)	Adjusted OR(95% CI)
Age				
< 35	1384(67.0)	694(67.6)	1 (ref)	1(ref)
≥35	681(33.0)	333(32.4)	1.03(0.87-1.21)	1.09(0.05-2.43)
Parity				
0	839(40.6)	260(25.3)	2.02(1.66-2.45)	1.61(0.91-4.11)
1 – 2	585 (28.3)	366(35.6)	1(ref)	1(ref)
≥3	641(31.1)	401(39.1)	0.50(0.41-0.60)	0.71(0.21-1.09)
Educational status				
< secondary	668(32.3)	433 (42.2)	1(ref)	1(ref)
≥ secondary	1397(67.7)	594(57.8)	1.52(1.30-1.78)	1.12(0.89-3.46)
Marital status				
Married	1416(68.6)	644(62.7)	1.12(0.96-1.32)	1.03(0.95-3.98)
Unmarried	749(31.4)	383(37.3)	1(ref)	1(ref)
Social class				
I and II	337(16.3)	214(20.8)	1.01(0.81-1.25)	0.79(0.53-4.13)
III	620(30.0)	396(38.6)	1(ref)	1(ref)
IV & V	1108(53.7)	417(40.6)	1.70(1.43-2.02)	1.13(0.61-6.45)
History of induced abortion				
0	397 (19.2)	311(30.3)	0.87(0.74-1.06)	0.97(0.39-3.11)
1	781 (37.8)	535 (52.1)	1(ref)	1(ref)
2 or more	887(43.0)	181(17.6)	3.36(2.75-4.10)	3.05(2.91-3.89)
Life time sexual partners				
0-1	459(22.2)	309(30.1)	0.73(0.61-0.89)	0.81(0.53-1.21)
2-4	924(44.7)	457 (44.5)	1(ref)	1(ref)
5 and above	682(33.0)	261(25.4)	1.29(1.07-1.56)	2.3(1.27-3.21)
Gestational age (weeks)				
Less than 13	609(29.5)	299(29.1)	1.03(0.87-1.21)	1.41(0.54-2.10)
13 and above	1456(70.5)	728(70.9)	1(ref)	1(ref)

According to Sagay et al¹⁰ “the dynamics of HIV transmission in marital settings in Nigeria are different in the various regions of the country. Socio-cultural and religious settings play a significant role in HIV transmission among couples”. The present situation of “one jacket fits all strategy” is unlikely to succeed in reducing HIV transmission within stable heterosexual relationship and requires developing different prevention models for each zone and innovative approach.

The high serodiscordant rates of 66.8–80.0% in our study and studies by Akani et al.³⁸, Omilabu³⁷ and Olagbuji et al¹⁶, though worrisome may not be a true reflection of the actual situation at population level. These four studies were conducted among female positive couples. The findings should therefore be interpreted with caution. However, an important finding in our

study is that a large percentage of HIV transmission in Nigeria occurs within stable relationship. HIV prevention intervention in Nigeria should as matter of urgency include couple counselling and testing as priority. Specifically, partners of those found positive should be tracked and offered HIV counselling and testing. In addition, for those that refused tracking of their partners as a result of stigma and discrimination, antiretroviral drugs should be offered as treatment for prevention, as recommended for HIV serodiscordant couples³⁹. While the rate of 80.0% in Omilabu’s study³⁷ may be artifactual as the study involved only 10 participants, the rate found in Benin and Jos cannot be completely dismissed as the individual studies were sufficiently powered to make meaningful deductions¹⁰.

The HIV disclosure rate among this cohort was 83.7%, which is higher than the rate reported

in some other studies^{18,19,32,40}. The disclosure rate in women with HIV positive partners was found to be higher than the rate in those with HIV negative partner. This has been corroborated by some other studies^{18,32,40}. The possible explanation for the higher disclosure rate in concordant couple may be that the couples feel less guilty about their status and seek to develop shared coping mechanisms towards the management of the condition. This has been substantiated by some other workers⁴¹. The study also showed a higher HIV status disclosure rate among women who were aware of their HIV status prior to the index pregnancy. A possible logical explanation could be that with time, counseling and acceptance of the situation, the women may find it easier to disclose their status to their partners. Another possibility could be that positive women may feel obliged to protect their partners from contracting the infection.

The assessment of the predictors of serodiscordance in this study was to generate information that will be used for HIV prevention within stable relationship by identifying individuals that are likely to be at risk. This is especially important in situations where disclosure is difficult as a result of stigma and discrimination. A previous study by our team reported a threefold increase in intimate partner violence among women in discordant relationship⁴². After controlling for confounding variables, only history of five or more previous sexual partners and two or more previous pregnancy termination retained their independent association with serodiscordant relationship. Heterosexual sexual intercourse being a risk factor for HIV transmission could be expressed more in individuals with multiple sexual partners and unprotected sexual intercourse. In addition both multiple sexual partnership and unprotected sexual intercourse are known high risk behavior for unwanted pregnancy (that may result in termination of pregnancy), HIV acquisition and transmission^{5,8}. It may be a pointer that HIV infection in HIV positive women in a discordant relationship may have been acquired prior to the index relationship^{20,21}.

While this study may have provided the much needed information for HIV prevention planning in stable relationship, it has some limitations. This study is not only a facility based

study but was conducted among HIV positive women. This may limit the generalization of the findings of this study. In addition the findings may have been different if the study was conducted at population level or among HIV positive men. The findings should therefore be interpreted with caution. However, the high serodiscordance rate of 66.8% confirms that large percentage of HIV transmission in Nigeria occurs within stable relationship. This supports the current priority being placed on HIV prevention within stable relationship as a strategy to reducing new HIV infection. A population based study or at a minimum study that will address the subject from another perspective (male positive relationship) is likely to address this limitation.

Conclusion

The HIV discordant rate of 66.8% in this study though within the reported rates of 48.8% to 80% in Nigeria, is higher than rate of 2.0% to 58.8% in east and southern Africa regions. HIV disclosure rate was also high at 83.7%, especially among women in seroconcordant relationship. Women with past history of multiple sexual partnership and termination of pregnancy were more likely to be in a serodiscordant relationship. The perception that men are the index cases is not supported by evidence from this study. We recommend the tracking of both men and women as index cases in order to reduce HIV transmission within stable relationship. Social marketing aimed at reducing concurrency should focus on both male and females, if we must reduce new HIV infection within stable relationships.

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Author's Contribution

IAOU conceived, designed the study, supervised data collection and analysis. OCE contributed to the conception, supervised data, analysed the data and drafted the manuscript. GAO contributed

conception, reviews the original design, participated in data collection, reviewed and contributed to the manuscript drafts. All authors read and approved the final manuscript

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