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Full Length Research Paper

Clinical Experience with Pre-exposure Prophylaxis in Sero-discordant Male Partners of HIV-positive Women Seeking Natural Conception

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The reproductive health needs of sero-discordant couples are issues of concerns, especially in view of high cost of various assisted conception methods in the low-resource economies. Often times, many of these couples resort to un-informed and unsafe practices of unprotected heterosexual intercourse, leading to human immune deficiency virus (HIV) acquisition. The magnitude of the health burden of these populations in Nigeria and other developing economies are currently not fully determined. Pre-exposure prophylaxis (PrEP) in conjunction with other HIV prevention strategies provides the only veritable and possibly safe mean of achieving their reproductive desire. This is a cohort study of 42 HIV-1 sero-discordant male partners of known HIV-1 positive women who were desirous of conception. All the male participants recruited were aware of their female partners' status, had their HIV status determined by fourth generation enzyme linked immunosorbent assay kit and were HIV negative, but declined the offer of assisted conception. The HIV positive women were all on highly active antiretroviral therapy (HAART). Thirty sero-discordant partners were sequentially and equally randomised into the two treatment groups [TDF and daily tenofovi/emtricitabine (TDF-FTC)], while 12 participants who declined PrEp made up the control group. In resource constraint settings, where assisted conception methods are either unacceptable, declined or un-affordable to male sero-discordant couples in heterosexual relationships, pre-exposure prophylaxis, preferably oral daily tenofovir-emtricitabine combination may be considered in addition to other HIV prevention strategies and timed sexual exposure, towards achieving safe reproductive health needs.

Key words: Human immune deficiency virus (HIV), pre-exposure prophylaxis, sero-discordant heterosexual partners, reproductive desire.

INTRODUCTION

The World Health Organisation (WHO) reports indicated that about 68% of all people living with human immune deficiency virus (HIV) in the world resided in sub-Saharan Africa (WHO, 2011), of which 60% are women (WHO, 2008). Also, in sub-Saharan Africa, 47% of HIV-infected women are reportedly in stable sero-discordant relationships (Eyawo et al., 2010). According to a national probability study, in the United States, 52% of HIV-infected women reported being in a sero- discordant relationship and approximately half of HIV sero-discordant

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heterosexual couples desire children (Chen et al., 2001).

Pre-exposure prophylaxis (PrEP) is the use of antiretrovirals in HIV-uninfected people to block the acquisition of HIV infection (Peng et al., 2012). World Health Organisation (WHO) in its July 2012 publication has reported five large studies that had come to varying conclusions on the effectiveness and safety of PrEP in either sero-discordant same sex or heterosexual couples. However, the summation of systematic review of evidence by WHO concluded that in countries where HIV transmission occurs among sero-discordant couples, where discordant couples can be identified and where additional HIV prevention choices for them are needed, daily oral PrEP (specifically tenofovir or the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention for the uninfected partner. These needs in Africa and other low resource economies with greatest burden of HIV are recognised, but are currently not fully determined (Iliyasu et al., 2009; Oladapo et al., 2005; Hughes et al., 2012). For these populations of patients in developing economies, with greatly hampered economic strength, absence of health care support and high cost of assisted conception methods, the option left is natural conception through heterosexual relationship. This however is fraught with high risk of HIV acquisition.

Beyeza-Kashesya et al. (2010) reported from Uganda that 59% (135/228) of the participants desired to have children. The belief that their partner wanted children was a major determinant of the desire to have children, irrespective of the HIV sero-status. Among couples in which the woman was HIV-positive, young age and relatives' expectations for children were significantly associated with increased fertility desire. Oladapo et al. (2005) in South-Western Nigeria reported that despite the fact that 79.6% (117/147) of the respondents already had 1 or more children, 68.4% (65/95) of women aged 18 to 45 and 53.8% (28/52) of men aged 18 to 55 still desire children (Eyawo et al., 2010). Pre-exposure prophylaxis (PrEP) in conjunction with other HIV prevention strategies provides the only veritable and possibly safe mean of achieving their reproductive desire.

PrEP still remain an emerging intervention strategies in HIV prevention programs with attempts to provide guidelines and recommendations on its application amongst both heterosexual and same sex sero-discordant partners (WHO, 2012). At the moment, drugs reported with some benefits are oral tenofovir (TDF), combination of oral tenofovir (TDF)/emtricitabine (FTC) or tenofovir vaginal gel (WHO, 2012; Baeten et al., 2012; Okwundu et al., 2012). This study reports our experience with PrEp amongst some sero-discordant heterosexual couples in our practice.

MATERIALS AND METHODS

This is a cohort study of 42 HIV-1 sero-discordant male partners of known HIV-1 positive women and desirous of conception. The study was conducted between March, 2008 and July, 2010, at Ladoke Akintola University of Technology Teaching Hospital Osogbo, Nigeria. All the male participants recruited were aware of their female partners' status, had their HIV status determined by fourth generation enzyme linked immunosorbent assay (GENSCREEN® Ultra HIV Ag/Ab, Bio-Rad Laboratories, Hercules, CA) kit and were HIV negative, but declined the offer of assisted conception, due to lack of fund. The HIV positive women were all on highly active antiretroviral therapy (HAART) of zidovudine 300 mg b.d, lamivudine 150 mg b.d and nevirapine 200 mg b.d combination, with median duration of HAART use of 5 months. The baseline CD4 counts were above 350 cells/µl.

Thirty sero-discordant male partners voluntarily accepted antiretroviral therapy for use as pre-exposure prophylaxis were recruited into the "treatment arms"; however 12 partners who declined both the assisted conception methods and the offer of pre-exposure prophylaxis were recruited and allocated into the "no treatment" arm. The thirty participants had their baseline serum creatinine and creatinine clearance determined (> 60 ml/min by Cochroft-Gault formula) at enrolment into the study and thereafter commenced on oral PrEP. Enrolments into the two treatment groups were by random allocation through balloting, using pre-labelled allotment papers, concealed in opaque envelopes, into daily tenofovir disoproxil fumarate 300 mg (TDF) or combination of daily oral tenofovir disoproxil fumarate 300 mg (TDF)/emtricitabine 200 mg (FTC). All participants provided written informed consent and received a comprehensive package of HIV-1 prevention services: HIV-1 testing with counselling before and after testing, individual and couples risk-reduction counselling, screening and treatment for sexually transmitted infections (STIs) including hepatitis B infection and free condoms with training and counselling. Also, none of the sero-discordant male partner was uncircumcised. HIV screening with the Ag/Ab kit were repeated in the sero-discordant male partners at interval of every 3 months, as well as serum creatinine levels. Unprotected sexual exposures were limited to the periods of female partners' ovulation which was determined from presumptive ovulation period based on calculation (timed sexual exposure); otherwise, condom use was advised at other times.

The hospital ethical committee reviewed and approved the protocol for the study. All participants were followed up monthly for a period of 12 months. Adherence was monitored with monthly pill counts and re-enforced with counselling. Outcome measures were incidences of HIV acquisition and conception rates in the groups. Data were analysed for simple frequencies, percentages, mean (standard deviation) and median (range) as appropriate, using statistical package for social sciences version 16 (SPSS Inc, Chicago, IL, USA).

RESULTS

In this study, the ages of the HIV 1 positive women were between 24 to 35 years, with the parity median of 1 (range = 0 to 2). The CD4 counts at the point of enrolment ranged between 363 to 570 cells/µl. Among the sero-discordant male partners, the mean ages in the groups were 38.2 ± 4.1 years (TDF), 36.6 ± 3.2 years (TDF-FTC) and 39.1 ± 4.4 years (control), respectively. Majority of the male partners in the treatment groups (9/15 each) were of the secondary school level of education, in comparison to 7/12 in the control group with primary school level of education. In the treatment groups, 12/15 (TDF) and 13/15 (TDF-FTC) were engaged

Table 1. Characteristics of serodiscordant male partners.

Characteristics	TDF group (n=15)	TDF-FTC group (n=15)	Control (n=12)
Age, mean (SD)	38.2 (4.1)	36.6 (3.2)	39.1 (4.4)
Educational status			
None	-	-	2
Primary	4	6	7
Secondary	9	9	3
Tertiary	2	-	-
Occupation			
Unemployed	-	-	-
Unskilled	2	2	5
Skilled	12	13	7
Professional	1	-	-
Religion			
Traditional	1	-	2
Christianity	7	9	5
Islam	7	6	5

in skilled occupation, while this group was 7/12 in the control group. Participants in the 3 groups were majorly Christians and Muslims (Table 1). Table 2 showed at enrolment the mean CD4 counts of the respective group was 424 cells/µl (TDF), 403 cells/µl (TDF-FTC) and 395 cells/µl (controls) ($F = 0.209$; $p = 0.812$). The highest proportion of sexually transmitted (mainly *Trichomonas vaginalis*) infection (50%) was recorded in the control group at enrolment and also during the study (33%).

The incidences of successful conception in each group by the 12th month of the study duration were 60.0, 40.0 and 16.7% in the TDF, TDF-FTC and the control groups, respectively. The highest rate of loss-to-follow-up of 8/12 (66.7%) was recorded in the control group. Overall, the incidence of HIV sero-conversion adjusted for loss-to-follow-up in the study was 9/33 (27.3%) The highest group incidence per 100 women year was recorded in the control group at 38.1 and least in the TDF-FTC group at 6.6. The relative reductions in the rates of HIV acquisition were 61 and 79% in the TDF only and TDF-FTC groups, respectively (Table 3). Side effects reported in the treatment groups were mainly nausea/vomiting in 5/15 (33.3%) of the TDF group and 7/15 (46.7%) of the patients in TDF-FTC group, fatigue in 3/15 (20%) and 7/15 (46.7%) of the TDF and TDF-FTC groups, respectively. On a preference scale, 11/15 (73.3%) and 6/15 (40%) in the TDF and TDF-FTC groups, respectively expressed satisfaction with their drug regimen.

DISCUSSION

The reproductive health needs of sero-discordant couples have in recent times become issues of concerns, especially in view of high cost of various assisted conception methods in the low-resource economies. Often times, many of these couples resort to un-informed and unsafe practices of unprotected heterosexual intercourse, leading to HIV acquisition. The magnitude of the health burden of these populations in Nigeria and other developing economies are currently unknown. In this cohort (observational) study, we report on 42 sero-discordant male partners in heterosexual relationship with HIV-1 positive female partners who are desirous of conception, but declined all offers of assisted conception methods. Majority of the sero-discordant male partners in the 3 groups were Christians and were in skilled occupations. However, there was a preponderance (7/12) of primary/elementary education levels among the control group. This might have influenced the decision making abilities in this group, who despite health education and counselling, declined both the offers of assisted conception methods and PrEP. Peng et al. (2012) had reported that education level influenced willingness to accept PrEp with 32.8% of Chinese female sex workers with elementary levels of education unwilling to use PrEP.

The immunological statuses of the HIV-1 positive female partners were comparable across the groups and all were highly motivated and regular on HAART. However, the incidences of STIs at both enrolment and during the study were proportionately highest in the control group's female partners. Hayes et al. (2010) reviewing evidences from observational and biologic data had concluded that evidence strongly supports the

Table 2. CD4 count status at enrollment and incidence of sexually transmitted infections in the HIV positive women.

Factor	TDF (n=15)	TDF-FTC (n=15)	Control (n=12)
CD4 count at Enrollment (Cells/µl)			
Mean (SD)	424 (135)	403 (121)	395 (105)
STI (at enrolment), n (%)	1 (6.7)	3 (20.0)	6 (50.0)
STI (during study), n (%)	-	1 (6.7)	4 (33.3)

STI = Sexually transmitted infection.

Table 3. Incidence of conception, loss to follow-up in the study groups and HIV infection in male partners.

Factor	TDF n =15	TDF-FTC n = 15	Control n = 12
Conception			
Conception at 6 months	3	2	-
Conception at 7 - 12 months	6	4	2
No of conception by 12 month, n (%)	9 (60)	6 (40)	2 (16.7)
Loss to follow-up			
Loss to follow-up at 6/12	-	-	3
Loss to follow-up at 12/12	-	1	5
Total Number of Loss to Follow-up, n (%)	-	1(6.7)	8 (66.7)
No of Participants who completed the study, n (%)	15 (100)	14(93.3)	4 (33.3)
Incidence of HIV seroconversion in partners, n (rate/100 women year)	2 (13.3)	1(6.6)	4 (38.1)

concept that STI treatment prevents HIV infection (Hayes et al., 2010), though doubts have been raised about the link between STI and HIV risk. This is possibly because intervention studies were not conclusive and designs/implementations of interventions were not clearly outlined (Ward and Ronn, 2010). In this study, identified STIs were promptly treated in both partners to minimize the risk of HIV acquisition.

The findings in our study suggested that once-daily oral TDF and TDF–FTC were associated with risk reductions of 61 and 79%, respectively against HIV-1 infection acquisition in sero-discordant male partners, when combined with other HIV-1 prevention services and timed sexual exposure. These findings are similar to those reported by Baeten et al. (2012) though the risk reduction in our study with oral TDF was 51%, which is lower than the 67% reported by Baeten et al. (2012). Also, Thigpen et al. (2012) had reported an overall 63% risk reduction in heterosexual men and women in Botswana. However, another study reported that with higher levels of adherence, as suggested by TDF levels in plasma, the effectiveness of oral TDF was 86% and that of the TDF/FTC combination was 90% (Donnell et al., 2012). The incidence of STI, when considered in the context of the HIV acquisition rates observed in this study, might suggest involvement of some participants in this study in extra-marital affairs. However, giving the sensitivity of this issue, especially in the context of this study, it was difficult to verify this suspicion.

However, while effectiveness of PrEP seems clearer amongst sero-discordant male partners in this and other studies, reports are conflicting amongst women. The trial of daily oral TDF/FTC in African women at higher risk of HIV in Kenya, South Africa and the United Republic of Tanzania was terminated early when equal numbers of infections were seen in the PrEP and placebo arms at interim analysis. The likely cause of apparent futility of this study had been attributed to poor adherence with resultant low drug concentrations in study participants (Van Damme et al., 2012). However, Vernazza et al. (2011) conducted an observational study in Switzerland among serodiscordant couples seeking conception where the male partner was HIV-infected with a suppressed viral load on ART and the female was HIV-uninfected. Of the 46 couples who chose periconceptional PrEP, 75% of couples successfully conceived by 12 months with no cases of incident HIV.

The desire for natural conception in these couples and refusal or inability to fund assisted conception techniques necessitated this study. The overall conception rate over the 12 months study period was 40.5% (17/42). The incidence of group conception was highest (60%) in the

TDF group and least (16.7%) in the control group. However, with very high loss to follow-up (66.7%) in the control conception in this group might be under-reported. In this study, our great concerns were problems of adherence, loss to follow-up and possible drug resistance. To mitigate the first two concerns, monthly follow-up meetings were scheduled for each couple to address all emerging issues, and re-emphasize risk-reduction counselling, as well as evaluate and support PrEp adherence (pills count inclusive). Evaluation for drug resistance is presently not available in our institution

HIV acquisition incidences were 13.3, 6.6 and 38.1 per 100 women year, respectively in the TDF, TDF-FTC and control groups. This translated to HIV acquisition risk reduction, compared with the control group of 61 and 79% for both the TDF and TDF-FTC groups in this study, respectively. Side effects recorded in the treatment groups were mainly nausea/vomiting in 33.3% of the TDF group and 46.7% of the patients in TDF-FTC group and fatigue in 20 and 46.7% of the TDF and TDF-FTC groups, respectively. On preference scale, 11/15 (73.3%) and 6/15 (40%) in the TDF and TDF-FTC groups, respectively, expressed satisfaction with their drug regimen while TDF has been reported to cause small but insignificant reduction in the glomerular filtration rates in a population of HIV-1 positive patients (Cooper et al., 2010). This observation could not be ascertained in our study, as none of the patients had evidence of elevated serum creatinine throughout the study. However, the small size and the limited duration of our study preclude a definite statement in this regard.

The recorded side effects and patients' likely preference/tolerability of drug burden might be some factors to consider in drug adherence issues and should be addressed at every session of counselling to elicit the maximum understanding and cooperation of the patients. In our study, the highest incidence was recorded in the first 6 weeks of commencing the PrEp and abated thereafter.

While this our study is observational in nature, the limitations inherent are the small population of participants, high incidence of loss-to-follow-up and infrastructural constraints resulting in inability to determine viral load in the HIV positive female partners, inability to assess for drugs serum levels in the male sero-discordant partners to monitor adherence and viral sensitivity test to determine possible drug resistance. These shortcomings notwithstanding, the obligations on the part of Researchers and Clinicians are to convince national agencies on HIV control programs for policy change in favour of universal accessibility to PrEP to those at risk of HIV acquisition in their quest to fulfil their reproductive desires and identify ways to promote reliable and assessable adherence.

CONCLUSION

In resource constraint settings, where assisted conception methods are either unacceptable, declined or unaffordable to male sero-discordant couples in heterosexual relationships, pre-exposure prophylaxis, preferably oral daily tenofovir-emtricitabine combination may be considered in addition to other HIV prevention strategies and timed sexual exposure towards achieving safe reproductive health needs.

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