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HIV Seroconversion in Serodiscordant Couples: An Experience from Malaysia

Wan Nor Aina Ar-Mardiyah Wan Jeffery[1], *Nazmi Liana Azmi[2]
[1]Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia-16150
[2]Department of Pharmacy, Raja Perempuan Zainab II Hospital, Ministry of Health Malaysia, Kota Bharu, Kelantan, Malaysia-15586
*Correspondence: nazmiliana@moh.gov.my

***Abstract*— Introduction:** *Many evidences support the use of antiretroviral therapy (ART) and condom in reducing the transmission of HIV through heterosexual contact especially in serodiscordant couples. Thus, this study aimed to determine the prevalence and factors associated with HIV seroconversion in serodiscordant couples in Kelantan, Malaysia.* **Methods:** *This was a case-control study involving 161 HIV serodiscordant couples on follow-up in Raja Perempuan Zainab II Hospital. Sociodemographic and clinical characteristics as well as sexual background were obtained from medical records. Data were analyzed using SPSS version 22.0.* **Results:** *The prevalence of HIV seroconversion in serodiscordant couples in Kelantan was 28.6% (95% CI: 22.2-36.0%) with a total of 46 spouses were infected. The mean (SD) age of index partners was 28.0 (6.3) years old with male predominance (62.1%, n=100). Only 8 (5.0%) spouses received pre-exposure prophylaxis and all of them remained HIV-negative. It was found that 84.5% (n=136) were adherent to ART while 50.3% (n=81) couples were compliant to condom use. The majority of index partners had baseline CD4 count <200 cells/μL (56.8%, n=84) and latest HIV viral load <50 copies/ml (82.9%, n=97). In the multivariable analysis, gender (AOR 0.313; 95% CI 0.117-0.835; p=0.020), ART adherence (AOR 0.121; 95% CI 0.030-0.486; p=0.003) and condom compliance (AOR 0.007; 95% CI 0.001-0.060; p<0.001) were determined as factors associated with HIV seroconversion.* **Conclusion:** *Kelantan had a high prevalence of HIV seroconversion in serodiscordant couples. Seronegative female spouses had increased risk of HIV infection especially when the index partners were nonadherent to ART and condom use. Couples-based educational intervention is crucial in minimizing the spread of HIV transmission.*

***Keywords*—** *HIV, seroconversion, serodiscordant couples, condom, antiretroviral therapy*

I. INTRODUCTION

The transmission of HIV through heterosexual sex has been one of the primary drivers of HIV epidemic worldwide [1], [2]. The main mode of HIV transmission through heterosexual contact has surpassed that due to either injection drug use or homosexual sex especially in China [2]. Therefore, serodiscordant couples or mixed status couples are at greater risk of acquiring HIV [3], [4]. This term refers to couples in a relationship whereby one partner is HIV-positive and the other is not [4].

The use of antiretroviral therapy (ART) has been known to curb the transmission of HIV from an index patient (HIV-positive patient) to a sexual partner by lowering the concentration of HIV in the genital tract [5]. The findings reported from HPTN 052 randomized controlled trial showed that ART used in combination with condoms and education on safe sexual course managed to reduce heterosexual transmission in serodiscordant couples by 96·4% [6]. Nevertheless, this does not totally eliminate the risk of infection as there are many predictors involved in HIV seroconversion [7].

Other significant risk factors include the gender of HIV-positive partner whereby male-to-female HIV transmission occurs with higher frequency than female-to-male transmission [1]. Women are at higher risk of HIV infection from within their regular partnership, presumably due to their higher biological susceptibility [3], [8]. There were also evidences which mentioned the importance of viral load in HIV transmission [4], [6]. The systematic review by Attia et al. (2009) found that no transmission events occurred in patients who were treated with ART or who manifested viral loads <400 copies/ml in studies of heterosexual serodiscordant relationship [9].

Up until now, there is no research pertaining to predictors that contribute to HIV seroconversion in serodiscordant couples in Southeast Asia population. Kelantan, a state in Malaysia is different from other parts of the world especially when it comes to its sociodemographic background. Identifying those factors could indeed help in predicting the seroconversion possibility among serodiscordant couples and implementing HIV prevention strategies to tackle the epidemic in general. In view of this, a study aimed at determining the prevalence of HIV seroconversion within serodiscordant couples in the state of Kelantan, Malaysia as well as its associated factors was conducted.

II. METHODS

A. Design and Study Population

This was a retrospective record review whereby assessment of medical records was done for index partners (HIV-positive partners) and their spouses for a period of 1 year starting from May 2017 until May 2018.

All HIV serodiscordant couples registered and on follow-up from January 2000 till December 2016 under Infectious Disease Clinic, Raja Perempuan Zainab II Hospital (HRPZ II) were recruited in the study. Exclusion criteria were the death of index partners for any reason as there would be no more exposure to their spouses as well as index partners with concomitant psychiatric illness for they were less likely to be started on ART. Seroconverters were defined as spouses who were HIV-seronegative at the beginning of the marriage but

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later were found to be HIV-seropositive with the same index partners.

B. Data Collection

Medical records of index partners and their spouses were reviewed for sociodemographic and sexual background. Included in the assessment were clinical characteristics such as medical and medication history, adherence to ART and condom use as well as the laboratory data. As for pre-pregnancy counselling, it was reviewed from the counselling notes. Serial CD4 counts, HIV viral load and ELISA tests were also examined and documented in the data collection form. The date of HIV seroconversion was estimated as the midpoint between the last negative and the first positive test date.

Utilizing the values of $\alpha = 0.05$, absolute precision = 0.05 and population proportion = 0.115 [10], the sample size was calculated using single proportion formula [11] which yielded a minimum of 157 couples.

C. Statistical Analysis

Statistical analysis was performed using SPSS version 22.0. All data were gathered and analyzed using descriptive statistics; mean (SD) and n (%).

For bivariable analysis, simple logistic regression was used to determine the potential factors for HIV seroconversion. Variables with p-value <0.25 were chosen to be included in the final model.

Multiple logistic regression was then applied using forward stepwise method to determine the factors associated with HIV seroconversion in serodiscordant couples. The final model was checked for interaction and multicollinearity as well as its goodness of fit. Factors with *p*-values <0.05 were considered as statistically significant.

D. Ethical Approval

This research was registered with the National Medical Research Registry (NMRR-17-513-34237) while ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (USM) and the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. Permission to conduct the study at the site was obtained from the Director of HRPZ II. All subjects were remained as anonymous to ensure their confidentiality.

III. Results

A. Prevalence of HIV Seroconversion

A total of 378 medical records were reviewed. However, only 322 subjects which entailed for 161 serodiscordant couples were recruited based on the study criteria. The prevalence of HIV seroconversion in serodiscordant couples in Kelantan was 28.6% (95% CI: 22.2-36.0%). Of those 46 spouses who were infected, 32 of them were female.

B. Sociodemographic and Clinical Characteristics

All couples were heterosexual with 62.11% (n=100) of them were male index partners with female serodiscordant spouses. The overall mean (SD) age of index partners was 28.0 (6.3) years old and they were mainly of Malay ethnicity (92.5%, n=149). As for their spouses, they were also mostly Malays with the overall mean (SD) age was 37.2 (8.2) years old. The mean (SD) duration of marriage in this study was 10.2 (7.6) years.

Only 8 (5.0%) spouses received pre-exposure prophylaxis (PrEP) and all of them remained HIV-negative at the end of the study. It was found that 84.5% (n=136) were adherent to ART while 50.3% (n=81) couples were compliant to condom. The majority of index partners had baseline CD4 count <200 cells/μL (56.8%, n=84) and latest HIV viral load <50 copies/ml (82.9%, n=97).

The characteristics of the index partners, their spouses as well as variables concerning the couples were summarized and compared between those who seroconverted and those who did not (Table 1).

TABLE 1. Characteristics of the index partners, spouses and couples by seroconversion status

Characteristics	HIV seroconversion of the spouses	
	Yes (n=46) n (%)	No (n=115) n(%)
Variables concerning the index partners		
Age (years old)	28.3 (6.9)*	27.9 (6.0)*
Gender		
Male	32 (19.9)	68 (42.2)
Female	14 (8.7)	47 (29.2)
Race		
Malay	42 (26.1)	107 (66.5)
Non-Malay	4 (2.5)	8 (5.0)
Education level		
None / primary	13 (8.1)	19 (11.8)
Secondary / tertiary	33 (20.5)	96 (59.6)
Occupation		
Regular	19 (11.8)	51 (31.7)
Odd	27 (16.8)	64 (39.8)
Income (RM)		
Low	18 (11.2)	32 (19.9)
High	28 (17.4)	83 (51.6)
Duration of illness (years)	9.4 (4.1)	7.0 (4.4)
Duration of ART treatment (years)	5.9 (3.1)*	5.0 (3.2)*
Adherent to ART		
No	17 (10.6)	8 (5.0)
Yes	29 (18.0)	107 (66.5)
ART regimen		
1st line	40 (24.8)	106 (65.8)
2nd / 3rd line	6 (3.7)	9 (5.6)
History of substance abuse		
No	20 (12.4)	75 (46.6)
Yes	26 (16.1)	40 (24.8)
History of sexual promiscuity		
No	17 (10.6)	55 (34.2)
Yes	29 (18.0)	60 (37.3)
Baseline CD4 count (cells/μL)		
<200	23 (15.5)	61 (41.2)
≥200	14 (9.5)	50 (33.8)
Latest CD4 count (cells/μL)		
<200	7 (4.8)	11 (7.5)
≥200	35 (24.0)	93 (63.7)
Latest viral load (copies/ml)		
<50	28 (23.9)	69 (59.0)
≥50	7 (6.0)	13 (11.1)
Variables concerning the spouses		
Age (years old)	37.3 (7.8)*	37.2 (8.4)*
Gender		
Male	14 (8.7)	47 (29.2)
Female	32 (19.9)	68 (42.2)
Race		

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Malay	42 (26.1)	7 (4.3)
Non-Malay	4 (2.5)	49 (30.4)
Education level		
None / primary	17 (10.6)	15 (9.3)
Secondary / tertiary	29 (18.0)	100 (62.1)
Occupation		
Regular	13 (8.1)	43 (26.7)
Odd	33 (20.5)	72 (44.7)
Income (RM)		
Low	31 (19.3)	54 (33.5)
High	15 (9.3)	61 (37.9)
Variables concerning the couples		
Compliant to condom use		
No	45 (28.0)	35 (21.7)
Yes	1 (0.6)	80 (49.7)
Pre-pregnancy counseling		
No	9 (5.6)	12 (7.5)
Yes	37 (23.0)	103 (64.0)

***** Mean (SD)

C. Factors Associated with HIV Seroconversion in Serodiscordant Couples

In the bivariable analysis, potential factors taken from variables concerning the index partners and the couples were initially screened with simple logistic regression. Ten (10) variables with p-values <0.25 were selected to be included in the final model (Table 2).

After forward stepwise multiple logistic regression, only 3 factors were considered significant which were gender of index partner, ART adherence and condom compliance ($p<0.05$). It was found that should the index partner was a female, HIV seroconversion was 68.7% less likely to happen to her male spouse (OR=0.313; 95% CI: 0.117-0.835; p=0.020). Also, spouses of index partners who were adherent to ART and compliant to condom use were 87.9% and 99.3% less likely to seroconverted (OR=0.121; 95% CI: 0.030-0.486; p=0.003 and OR=0.007; 95% CI: 0.001-0.060; p<0.001, respectively) (Table 3).

IV. Discussion

In our setting, we found that the majority of HIV serodiscordant relationships were seropositive men which was in contrast with the population in Southwestern Ethiopia [12] and East Africa[13]. However, our result bore the same resemblance as the one conducted in Uganda, whereby 65.5% study population were HIV-positive male partners [14].

We observed that the prevalence of HIV seroconversion in serodiscordant couples in Kelantan was almost similar to HIV prevalence reported in Malaysian population of men having sex with men (MSM) in 2017 which was 21.6% [15]. Therefore, this finding suggested that HIV transmission through sexual contact could be the dominant mode in Malaysia [16].

However, the prevalence rate was obviously higher than that in China. The systematic review and meta-analysis by Wang et al. (2012) documented that the overall estimate for HIV prevalence through heterosexual transmission in serodiscordant couples was 11.5% in China. Henan was noted as having the lowest prevalence rate of 3.9%, followed by Yunnan 17.0% and other provinces showed a collective prevalence rate of 21.5% [10]. A more recent work by Zheng et al. (2018) also noted that out of 5,544 serodiscordant couples in Guangxi, Southern China, 567 were seroconverted after 12 months making the prevalence rate as 10.2% [17]. This could be due to the fact that we investigated the prevalence rate in a population of 16 years which was longer than other researches.

We found that women were more vulnerable to HIV infection than men which was concurrent with a good deal of published literature [1], [12], [18]. More than 80% new HIV infections in women were from heterosexual transmission. In sub-Saharan Africa, HIV infection was higher in women and they acquired the illness earlier [8]. Among the reason for HIV susceptibility among women was deemed biological; larger surface area of the vagina and the ability of the virus to pass easily through the cells of the vaginal lining [1], [19]. This statement was further supported by Biraro et al. (2013) and Colombe et al. (2019) who reported that female sex was independently associated with HIV seroconversion [1], [20]. Gender of the serodiscordant spouse was the only significant variable in the cohort in Tanzania (HR= 8.86; 95% CI: 1.16-67.70, $p = 0.036$) [1] while HIV incidence was 2 times higher in female spouses of serodiscordant couples in rural Uganda (HR=2.02, 95% CI: 1.06-3.83;p=0.03) [20].

Our findings also pointed out that index partners who were nonadherent to ART could contribute to the likelihood of their spouses to acquire HIV. Most of the evidences confirmed the use of ART and its early initiation could reduce the risk of HIV transmission between spouses [2], [4], [6], [21]. However, in the long run, the ultimate key to its success is adherence [22]. According to the guidelines for the management of adult HIV infection with ART, adherence is compulsory for maximal response to ART for ART works by suppressing the viral load and increasing CD4 counts [23]. The systematic review by Anglemyer et al. (2013) concluded that the use of ART in serodiscordant couples were associated with decreased HIV transmission by relative risk of 0.36 [24].

Finally, our results depicted that the rate of HIV transmission between spouses were high when the index partners were not compliant to the use of condom. This statement was proven undisputable by numerous publications [1], [4]. A systematic review and meta-analysis by Giannou et al. (2016) mentioned that HIV transmission among serodiscordant couples was reduced to 70% with consistent use of condom [25]. In Henan, China, Wang et al. (2010) reported that serodiscordant couples who used condoms irregularly had 8.42 times higher risk of contracting HIV (RR=8.42; 95% CI, 4.83-14.67) [26]. Meanwhile, a study in South India revealed that index partners who failed to use condoms had 2.32 times the odds to transmit HIV to their seronegative spouses (OR=2.32; 95% CI: 1.85-2.65) [27]. This was further supported by Tang et al. (2016) who revealed that serodiscordant couples who consistently used condoms had a significantly lower rate of HIV seroconversion (OR = 0.04, 95% CI: 0.01-0.16, p<0.01) [21].

Serodiscordant couples need to be identified, approached and educated to protect themselves against HIV. Educational intervention is important in reducing risk of seroconversion in this population. The counselling should include supported disclosure, education on factors affecting the seroconversion

and special planned pregnancy. When couples understand their HIV status and transmission risks, follow-up needs to be carried out to prevent seroconversion and curb the spread of HIV.

Our study has several limitations. It was conducted at a single tertiary centre for HIV patients and hence, the findings could not be generalized to all serodiscordant couples in Malaysia. We were not able to obtain or measure some of the variables due to the nature of retrospective study such as baseline viral load, disclosure of HIV status and intention to conceive a child.

V. CONCLUSION

Kelantan had a high prevalence of HIV seroconversion in serodiscordant couples. Seronegative female spouses had increased risk of HIV infection especially when the index partners were nonadherent to ART and condom use. Couples-based educational intervention is crucial in minimizing the spread of HIV transmission.

CONFLICT OF INTEREST

The authors have none to declare.

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TABLE 2. Factors associated with HIV seroconversion in serodiscordant couples from simple logistic regression

Variables	Crude OR (95% CI)	Wald Statistics (df)	*p*-value
Age (years old)			
	1.009 (0.956, 1.066)	0.108 (1)	0.745
Gender			
Male	1.00		
Female	0.633 (0.305, 1.313)	1.508 (1)	0.219*
Race			
Malay	1.00		
Non-Malay	1.274 (0.364, 4.456)	0.143 (1)	0.705
Education level			
None / primary	1.00		
Secondary / tertiary	0.502 (0.224, 1.128)	2.783 (1)	0.095*
Occupation			
Regular	1.00		
Odd	1.132 (0.566, 2.264)	0.124 (1)	0.725
Income (RM)			
Low	1.00		
High	0.600 (0.292, 1.231)	1.943 (1)	0.163*
Duration of illness (years)	1.133 (1.046, 1.228)	9.348 (1)	0.002*
Duration of ART treatment (years)	1.099 (0.987, 1.223)	2.981 (1)	0.084*
Adherent to ART			
No	1.00		
Yes	0.128 (0.050, 0.325)	18.628 (1)	<0.001*
ART regimen			
1st line	1.00		
2nd / 3rd line	1.767 (0.591, 5.282)	1.037 (1)	0.308
History of substance abuse			
No	1.00		
Yes	2.437 (1.213, 4.898)	6.261 (1)	0.012*
History of sexual promiscuity			
No	1.00		
Yes	1.564 (0.775, 3.154)	1.560 (1)	0.212*
Baseline CD4 count (cells/μL)			
<200	1.00		
≥200	0.743 (0.346, 1.592)	0.585 (1)	0.444
Latest CD4 count (cells/μL)			
<200	1.00		
≥200	0.591 (0.212, 1.647)	1.010 (1)	0.315
Latest viral load (copies/ml)			
<50	1.00		
≥50	1.327 (0.479, 3.674)	0.296 (1)	0.586
Compliant to condom use			
No	1.00		
Yes	0.010 (0.001, 0.073)	20.19 (1)	<0.001*
Pre-pregnancy counseling			
No	1.00		
Yes	0.479 (0.187, 1.229)	2.344 (1)	0.126*

*Variables included in the final model (p<0.25)

TABLE 3. Factors associated with HIV seroconversion in serodiscordant couples from multiple logistic regression

Variables	Adjusted OR (95% CI)	Wald Statistics (df)	*p*-value
Gender			
Male	1.00		
Female	0.313 (0.117, 0.835)	5.388 (1)	0.020
Adherent to ART			
No	1.00		
Yes	0.121 (0.030, 0.486)	8.856 (1)	0.003
Compliant to condom use			
No	1.00		
Yes	0.007 (0.001, 0.060)	20.846 (1)	<0.001

The model reasonably fits well (84.5% cases are predicted correctly, area under the curve of ROC=0.912). Model assumptions are met. There are no interaction and multicollinearity problems.

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