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What's pregnancy got to do with it? Late presentation to HIV/AIDS services in Northeastern Brazil

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Competing interests

None of the authors have any conflicts of interest (including financial and other relationships) to declare.

Authors' contributions

This manuscript has not been submitted or accepted for publication elsewhere. All authors contributed to the concept of the paper and data analysis. ID, SM and SG were responsible for the writing of the final version of the manuscript. All authors have read and approved the paper, have met the criteria for authorship as established by the International Committee of Medical Journal Editors, believe that the paper represents honest work, and are able to verify the validity of the results reported.

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Abstract

Introduction—Despite the known benefits of early treatment initiation for individual morbidity and mortality, as well as for reducing the risk of transmission, late presentation (LP) to HIV/AIDS services remains a major concern in many countries. There is little information on LP from middle and low-income countries and studies that do evaluate LP commonly disaggregate data by sex. It is rare, however, for researchers to further disaggregate the data by pregnancy status so it remains unclear if pregnancy status modifies the effects associated with sex.

Methods—The study was conducted at the only State Reference Center for HIV/AIDS in Salvador, Brazil's third largest city. LP was defined as a patient accessing services with a CD4<350 cells/mm^3. Data were abstracted from the electronic medical records of 1421 patients presenting between 2007 and 2009. CD4 counts and viral load (VL) information was validated with data from the National CD4/VL Database. Descriptive and bivariate statistics were conducted to inform the multivariate analysis. Adjusted prevalence ratios (APR) were estimated using generalized linear models due to the high frequency of the outcome.

Results—Half of the sample (52.5%; n=621) was classified as LP. Compared to the prevalence among pregnant women (21.1%), the prevalence of LP was more than twice as high among non-pregnant women (56.0%) and among men (55.4%). The multivariate analysis demonstrated no statistical difference between men and non-pregnant women (APR 1.04; 95%CI 0.92–1.19), but the APR of LP for non-pregnant women was 53% less than men (APR 0.47; 95%CI 0.33–0.68).

Conclusion—These results highlight the importance of analyzing data disaggregated not only by sex but also by pregnancy status to accurately identify the risk factors associated with LP so that programs and policies can effectively and efficiently address LP in Brazil and beyond.

Keywords

HIV/AIDS; late presentation; CD4 count; pregnancy; Brazil

INTRODUCTION

Despite increasing availability of antiretroviral therapy (ART) in many countries, studies have documented that HIV-positive individuals continue to access HIV/AIDS services at an advanced stage of infection (Althoff et al., 2010; Metallidis et al., 2012; O'Shea, Ebrahim, Egli, Redmond, & McConkey, 2013; Oliva et al., 2010; Wohlgemut, Lawes, & Laing, 2012). This late presentation (LP) to HIV/AIDS services is a substantial concern given the known benefits of early treatment initiation for individual morbidity and mortality, as well as for reducing the risk of transmission. However, the majority of studies on LP have been conducted in high-income countries, where the proportion of LP ranges from 30 to 67% (Bamford, Ehrenkranz, Eberhart, Shpaner, & Brady, 2010; Cevallos Garcia, Verdejo Ortes, Martinez Rodriguez, & Izarra Perez, 2012; d'Arminio Monforte et al., 2011; de Olalla et al., 2011; Dennis, Napravnik, Sena, & Eron, 2011; Dickson, McAllister, Sharples, & Paul, 2012; Diez et al., 2012; Helleberg et al., 2012; Leutscher et al., 2011; Mocroft et al., 2013; Ursini et al., 2012; Vincent et al., 2012; Wohlgemut et al., 2012; Zoufaly et al., 2012). In Brazil, a middle-income country were ART has been free and universally available since 1996 (Teixeira, Vitoria, & Barcarolo, 2004), three national studies estimated that between

33% (Fernandes, Acurcio Fde, Campos, & Guimaraes, 2009; Souza-Jr, Szwarcwald, & Castilho, 2007) and 43.6% of people living with HIV utilized HIV/AIDS services with CD4 cell counts <200 cells/mm^3 or clinical symptoms of AIDS (Grangeiro, Escuder, Menezes, Alencar, & Ayres de Castilho, 2011). These studies suggest that even in Brazil, individuals living with HIV continue to utilize HIV/AIDS services at an advanced stage of HIV infection.

Increasingly, in Brazil and in other countries globally, the problem of LP is being recognized but issues impede the accurate analysisof LP in the peer-review literature. There is growing attention to the importance of controlling for sex as being male is commonly identified as a risk factor for LP. It is rare, however, for researchers to further control for pregnancy status as most studies examine LP among pregnant women in separate subgroup analyses (Fitzgerald et al., 2010; Izzo et al., 2011; Tariq, Elford, Cortina-Borja, & Tookey, 2012; Thayaparan, Balachandran, & Kawser, 2012). This potentially has major implications for the interpretation of results. Many women are tested during antenatal care and therefore are likely tested at an earlier stage of their disease progression. In comparison, non-pregnant women may be tested as a result of experiencing HIV/AIDS related symptoms and therefore are at a later stage of their disease progression and may be no different from men. It remains unclear if pregnancy status modifies the effects associated with sex, and despite controlling for sex, it is surprising that none of the studies in Brazil and only one of the studies outside of Brazil on LP controlled for pregnancy status (Krawczyk et al., 2006). Therefore the purpose of this study was to investigate the prevalence of LP in Brazil and determine if disaggregating the data based on sex and pregnancy status impacted our understanding of LP.

METHODS

The data (n=1,564) were collected in a cross-sectional study conducted at the only State Reference Center (SRC) for HIV/AIDS in Bahia, a state in the northeastern region of Brazil. The study population was comprised of all individuals ≥15 years of age living with HIV who were enrolled in HIV care for the first time at the SRC between 2007 and 2009. Data were abstracted from the electronic medical records of 1,564 patients. These records were then supplemented with additional information reviewed by trained research assistantsfrom “SINAN” (Information System on Disease Notification), a database of registered AIDS cases and HIV-infected pregnant women. 143 records with missing CD4 cell count data were excluded resulting in review of 1,421 patient records (90.9%). Information was reviewed by trained research assistants from hand written clinical records and from the national database “SISCEL” (Laboratory Test Control System of the Brazilian National CD4+/CD8+T Lymphocyte Count and Viral Load Network).

The outcome variable LP was based on the consensus statement released by the European Late Presenter Group that defined LP as individuals with a CD4 cell count<350 cells per/mm^3 and/or symptoms of AIDS-defining illnesses (Antinori et al., 2011; Antinori, Johnson, Moreno, Yazdanpanah, & Rockstroh, 2010). For our analysis, the outcome was restricted to individuals with available CD4 cell count.

We conducted a comprehensive review of the literature to identify variables of interest that should be included in the data analysis. Key descriptive statistics were generated for all study variables available in the electronic medical records. For the multivariate analysis, we included variables highlighted in the literature review and fromthe bivariate analysis if they had a p-value smaller than 0.20. Adjusted prevalence ratios (APR) were estimated using generalized linear models due to the high frequency of the outcome (McNutt, Wu, Xue, & Hafner, 2003) using STATA 10. This study was approved by the Ethics and Research Committee of the State Health Department of Bahia and written informed consent was given by all participants.

RESULTS

Of the 1,421 patients included in the study from 2007–2009, 54% were males (769) and among females (652), 21.3% were pregnant (139). While the prevalence of LP among men was 55.4% and 48.9% among all women, further analysis showed differences based on pregnancy status: The prevalence of LP (CD4<350 cells/mm^3) was slightly higher among non-pregnant women (56.0%) as compared to men (55.4%), but was twice that compared to prevalence among pregnant women (22.1%). The proportion of non-pregnant women (32.5%) and men (37.5%) presented for HIV/AIDS care at an advanced stage of the infection (CD4<200 cells/mm^3) was much higher compared to the proportion of pregnant women (7.1%). Complete descriptive statistics are provided in Table 1 and bivariate statistics are provided in Table 2. In terms of the distribution of CD4 counts, pregnant women had higher median CD4 counts (543 cells per mm^3) than non-pregnant women (357 cells per mm^3) and substantially higher than men (298 cells per mm^3) (Figure 1). The differences in the median values were statistically significant (p-value=0.0001) and highlights that pregnancy statussubstantially confounds the effect of sex.

The multivariate analysis demonstrated no statistical difference between men and non-pregnant women (APR 1.04; 95%CI 0.92–1.19), but the APR of LP for non-pregnant women was 53% less than men (APR 0.47; 95%CI 0.33–0.68). Compared to individuals age 15–24, the APR of LP increased with each age category: from 1.46 (95%CI 1.13–1.87), to 1.59 (95%CI 1.24–2.04), to 1.77 (95%CI 1.37–2.29). Alcohol use seemed associated with lower prevalence of LP but only bordered statistical significance(Table 3).

DISCUSSION

In some respects, the findings of our study may appear simple, however the implications are significant. For example, there was no difference in the proportion of LP based on sex, but further disaggregating the data by pregnancy status showed that pregnant women, compared to non-pregnant women and men, were less likely to record a first CD4 count below 350 cells per mm^3. Currently there is a strong assumption in the peer-reviewed literature that males delay in accessing care as several studies stated that men have a higher risk of LP than women (Choe et al., 2011; Cornell M, 2012; Dennis et al., 2011; Mocroft et al., 2013; Moreira et al., 2011). However, none of these studies accounted for pregnancy status in their analysis, nor did they compare non-pregnant women with men. Evidence from our study suggests that controlling for pregnancy status may minimize, if not eliminate, the difference

among men and non-pregnant women. Thus, as the problem of LP is increasingly recognized among men, these results suggest that greater attention should also be given to LP among non-pregnant women.

Additional research should disentangle the role of pregnancy status in defining health-seeking behaviors. Doing so would enable programs and policies to more effectively ensure that all individuals who test positive are then successfully linked to sustained HIV/AIDS care, whether male, female, pregnant, or not. If the current status quo persists then individuals who are not traditionally considered at increased risk for HIV, such as non-pregnant women, may continue to be overlooked which has severe implications for individual health, as well as the risk of transmission to sexual partners.

LP was also associated with age among men and non-pregnant women. This is consistent with the findings from other studies (Adler, Mounier-Jack, & Coker, 2009; Helleberg et al., 2012; Metallidis et al., 2012; Tey et al., 2012; Vincent et al., 2012; Vives et al., 2012). Studies suggest that the progression of infection may be more rapid in older individuals (Kirk & Goetz, 2009; Manfredi, 2002, 2004). It is also possible that providers do not perceive their older age patients to be at risk for HIV infection, nor do older age individuals themselves feel at risk, and therefore are less likely to be tested for HIV. Even among individuals who may be aware their risk for HIV, other physical barriers (such as access to testing sites) or social barriers (such as HIV-related stigma) (Mussini, 2012)may prevent them from utilizingavailable services.

Limitations of our study should be acknowledged. The cross-sectional study design limited our ability to assess temporal association and to adjust for time. Incompleteness of documentation in the patient's electronic database and charts for education, income and occupation limited our ability to assess these variables. Finally, the outcome defines patients as late presenters based on their CD4 count so it is unclear if individuals were late in their diagnosis of HIV or late in their subsequent linkage to care (Kozak, Zinski, Leeper, Willig, & Mugavero, 2013; Maccarthy, Bangsberg, Fink, Reich, & Gruskin, 2013). Importantly, thisstudy highlights the need to controlfor pregnancy status, and although this seems relatively straightforward, it is not consistently done in studies on LP.

CONCLUSIONS

This study underscores the need for the risk factors of LP to be accurately identified. Specifically, it is critical that the role of pregnancy status be addressed in analyses to ensure results can be translated into programmatic and policy action for all populations who need them. Only in so doing can we begin to reduce and eventually eliminate LP to testing, treatment and care in Brazil and beyond.

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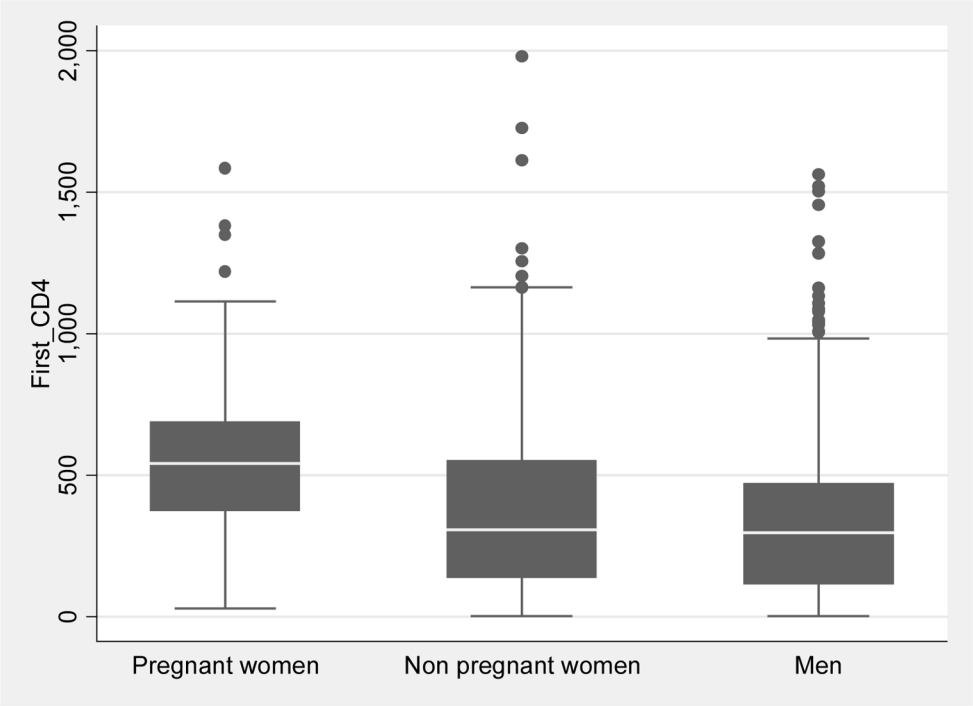

Figure 1.
Distribution and median CD4 count for pregnant women (543 cells per mm^3), non-pregnant women (307 cells per mm^3) and men (298 cells per mm^3)

Table 1

Descriptive statistics of pregnant women, non-pregnant women and men (n=1421) receiving HIV/AIDS care at the State Reference Center in Salvador, Brazil between 2007 and 2009

Variable	Pregnant women	Non-pregnant women	Men	p-value
	N (%)	N (%)	N (%)	
CD4 cell at enrolment				0.0001
CD4 >=350 cells per mm^3	88 (77.9)	191 (44.0)	284 (44.6)	
CD4<350 cell per mm^3	25 (22.1)	243 (56.0)	353 (55.4)	
Presented with an advanced stage of thedisease				0.0001
CD4 >=200 cells per mm^3	105 (92.9)	293 (67.5)	398 (62.5)	
CD4 <200 cells per mm^3	8 (7.1)	141 (32.5)	239 (37.5)	
Age				0.0001
15–24	50 (35.9)	76 (14.1)	95 (12.4)	
25–34	69 (49.6)	190 (37.0)	322 (41.9)	
35–44	20 (14.4)	164 (31.2)	216 (28.1)	
45 or older	-	83(16.2)	136 (17.7)	
Education[*]				0.008
Greater than 8 years	9 (33.3)	40 (35.1)	101 (51.8)	
Up to 8 years	18 (67.7)	74 (64.9)	94 (48.2)	
Skin color				0.001
White	9 (6.6)	47 (9.3)	116 (15.4)	
Black or brown	128 (93.4)	459 (90.7)	638 (84.6)	
Sexual orientation				0.0001
Heterosexual	135 (98.5)	489 (97.4)	397 (52.0)	
Homosexual or bisexual	2 (1.5)	13 (2.6)	367 (48.0)	
Civil status				0.001
With a partner	37 (27.0)	111 (21.8)	120 (15.8)	
Without a partner	100 (73.0)	398 (78.2)	638 (84.2)	
Type of sexual partner				0.0001
Main partner[**]	122 (91.0)	330 (76.7)	375 (53.6)	
Non-main partner	12 (9.0)	100 (23.3)	325 (46.4)	
Condom use				0.0001
Always or sometimes	79 (58.8)	296 (59.2)	572 (75.1)	
Never	60 (47.2)	204 (40.8)	190 (24.9)	
Drug use				0.0001
Never	128 (93.4)	466 (91.6)	636 (83.5)	
Frequently and/or sometimes	9 (6.6)	43 (8.4)	126 (16.5	
Alcohol use				0.0001
Never	88 (66.2)	310 (64.7)	323 (46.9)	
Frequently and/or sometimes	45 (33.8)	169 (35.3)	366 (53.1)	
Location				0.003

Variable	Pregnant women	Non-pregnant women	Men	p-value
	N (%)	N (%)	N (%)	
Metropolitan region of Salvador	92 (66.2)	347 (67.6)	581 (75.6)	
Outside metropolitan region of Salvador	47 (33.8)	166 (32.4)	188 (24.5)	

* Data on education only available for 24% of the participants;

** To be with someone for more than a month

Table 2

Bivariate statistics including the number, proportion, prevalence ratio (PR) and 95% confidence interval (CI) of late presentation among patients receiving HIV/AIDS care at the State Reference Center in Salvador, Brazil between 2007 and 2009

	Late Presentation				
Variable	***N***	***%***	**PR**	**95% CI**	**p-value**
Sex					0.001
Men	353	55.4	1.00		
Non-pregnant women	434	56.0	1.01	0.91–1.13	
Pregnant women	113	22.1	0.40	0.28–0.57	
Age					0.001
15–24	167	33.5	1.00		
25–34	480	50.0	1.49	1.18–1.88	
35–44	343	57.1	1.70	1.35–2.15	
45 or older*	194	66.5	1.98	1.57–2.51	
Skin color					0.84
White	150	53.3	1.00		
Black	1012	52.5	0.98	0.84–1.16	
*Education***					0.32
Up to 8 years	162	60.5	1.00		
Greater than 8 years	137	54.7	1.11	0.91–1.35	
Civil status					0.510
With a partner	223	50.8	1.00		
Without a partner	945	53.1	1.05	0.91–1.21	
Sexual orientation					0.13
Heterosexual	850	50.9	1.00		
Homosexual or bisexual	320	55.9	1.10	0.98–1.24	
Condom use					0.290
Never	381	54.6	1.00		
Always or sometimes	786	51.3	0.83	0.84–1.05	
Drug use					0.090
Never	1037	53.3	1.00		

Variable	Late Presentation				
	N	*%*	PR	95% CI	p-value
Frequently and/or sometimes	134	45.5	0.85	0.70–1.04	
Alcohol use					0.070
Never	614	54.6	1.00		
Frequently and/or sometimes	478	49.0	0.90	0.80–1.01	
Location					0.860
Metropolitan region of Salvador	851	52.3	1.00		
Outside metropolitan region of Salvador	333	52.9	0.99	0.88–1.11	

* Pregnant women not included in this category as there was no pregnant women older than 44 years of age;

** Data on education only available for 24% of the participants;

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Table 3

Prevalence ratios and 95% confidence intervals of the association between late presentation among patients receiving HIV/AIDS care at the State Reference Center in Salvador, Brazil between 2007 and 2009

	Late Presentation		
Variable	*** APR**	****95%CI**	**p-value**
Sex (men as reference)	1.00		
Non-pregnant women	1.04	0.92–1.19	0.510
Pregnant women	0.47	0.33–0.68	0.001
Age (15–24 as reference)	1.00		
25–34	1.46	1.13–1.87	0.003
35–44	1.59	1.24–2.04	0.001
45 or older	1.77	1.37–2.29	0.001
Sexual orientation			
Heterosexual	1.00		
Homosexual or bisexual	1.07	0.93–1.23	0.340
Drug use			
Never	1.00		
Frequently and/or sometimes	0.93	0.75–1.15	0.500
Alcohol use			
Never	1.00		
Frequently and/or sometimes	0.88	0.79–0.99	0.040

* APR: adjusted prevalence ratios from GLM (generalized linear models) regression;

** Pregnant women not included in this category as there was no pregnant woman older than 44 years of age;