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Abstract: (216 words)

Retention in early HIV care has been associated with decreased mortality and improved viral suppression, however the consequences of poor retention in early care in Brazil remain unknown. We assessed the effect of poor retention on mortality in a Brazilian HIV-infected clinical cohort. The analysis included ART-naïve, HIV-infected adults linked to care at the Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz between 2000 and 2010, who did not become pregnant nor participate in a clinical trial during the first two years in care (early care). Poor retention in early care was defined as less than 3 out of 4 six-month intervals with a CD4 or HIV-1 RNA laboratory result during early care. Cox proportional hazards models were used to identify factors associated with mortality, and Kaplan-Meier plots were used to describe the survival probability for participants with poor retention versus good retention. Among 1054 participants with a median (interquartile range) follow-up time of 4.2 years (2.6, 6.3), 20% had poor retention in early care and 8% died. Poor early retention [adjusted hazard ratio (aHR) 3.09; 95% CI 1.65-5.79], AIDS defining illness (aHR 1.95; 95% CI 1.20-3.18), lower education (aHR 2.33; 95% CI 1.45-3.75) were associated with increased mortality risk. Our findings highlight the importance of adopting strategies to improve retention in early HIV care.

Introduction

Brazil's policy of universal access to antiretroviral therapy (ART) has been credited with improving survival among HIV-infected persons and avoiding generalization of the AIDS epidemic . Access to HIV testing and ART have been fundamental to the success of the Brazilian HIV/AIDS program; however, there are disparities in clinical outcomes. In particular, using intravenous drugs , being of self-reported black race and having lower education have been associated with increased mortality and faster progression to AIDS.

In high-income settings, retention during the first 1-2 years of HIV care has been shown to improve survival , but there is limited information on the effects of retention on mortality from low- and middle-income countries in Latin America . We previously reported that early ART initiation, older age and higher educational level were associated with good retention in early care ; however, the effect of retention in early care on mortality among HIV-infected persons in our setting remains unknown. We aimed to assess whether poor retention in early HIV care is associated with increased mortality in an urban, Brazilian, clinical HIV cohort.

Methods

The Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz (INI) is a national reference center for HIV/AIDS care, research and training. Since 1998, INI has maintained a clinical cohort of HIV-infected adults in care . All cohort procedures were approved by the INI Institutional Review Board. This analysis used de-identified health information, and was exempt by the Institutional Review Board of the University of California, Los Angeles.

For the present analysis, ART-naïve, HIV-infected persons ≥18 years old initiating care at INI between January 1, 2000 and June 30, 2010 were eligible for inclusion. Participants must have been

linked to care (defined as the first outpatient $CD4^+$ T lymphocyte count [CD4] or HIV-1 RNA measurement or ART initiation date) within 6 months after their first clinic visit and have survived 2 years post-linkage (early care) to be included in the analysis. Individuals who became pregnant during early care (N=35) or ever participated in a clinical trial (N=492) were excluded because of unique laboratory monitoring requirements (please see Silva et al., 2015 for further details).

Follow-up began at the end of early care (i.e., 2 years after linkage to care). End of follow-up was defined as the date of death, and, for those not known to have died, as 1 year after the date of last clinical contact (last CD4, HIV-1 RNA or clinic visit) with a maximum censor date of December 31, 2013. Loss to follow-up (LTFU) was defined for participants with a censor date before December 31, 2012. Mortality data was exhaustively verified up to December 31, 2013 using participants' medical charts, outreach to participants' personal contacts and by linkage with the State of Rio de Janeiro Mortality database using a previously validated algorithm .

The Brazilian Ministry of Health recommendations of laboratory monitoring every 6 months guided our definitions for linkage and retention. Poor retention in early care was defined as the presence of an outpatient CD4 or HIV-1 RNA measurement in less than 3 out of 4 six-month intervals during early care, as described previously . Socio-demographic and clinical factors were extracted from the clinical cohort database. Year of linkage was used as a dichotomous variable because a prior study of this cohort demonstrated two periods from 2000–2002 and from 2003–2011 when the prevalence of good retention was significantly different, increasing from 54–61 to 77–89 %, respectively.

Kaplan-Meier plots were used to describe the survival probability for participants with poor versus good retention in early care. Factors associated with mortality were identified using Cox proportional hazards regression models. Factors with an unadjusted p-value ≤0.25 were included in

4

the initial adjusted model, and kept in the final model when factor adjusted p-value was ≤0.05 or when factor removal changed the effect size of another factor in >10% . Additionally, factors known to be associated with mortality through prior studies were kept in the final model (i.e. ART initiation). Moreover, sex and age were included in the adjusted models and maintained a priori. The proportional hazards assumption was tested using Schoenfeld residuals. Schoenfeld residuals were significant for our exposure of interest (i.e. poor retention in early care), suggesting time-varying effects on mortality which were resolved with the inclusion of an interaction term between year of linkage (as defined above) and poor retention in early care. Analyses were performed using R Statistical Software.

Results

The study population consisted of 1054 participants with a median (interquartile range [IQR]) follow-up time of 4.2 years (2.6, 6.3), LTFU rate of 1.6 per 100 person-years (PY) and mortality rate of 1.8 per 100 PY. Participants with good retention in early care (80%) had a median follow-up time of 4.3 years (2.8, 6.1), LTFU rate of 0.9 per 100 PY and mortality rate of 1.4 per 100 PY. Participants with poor retention in early care (20%) had a median follow-up time of 3.8 (1.4, 7.8), LTFU rate of 4.7 per 100 PY and mortality rate of 3.2 per 100 PY.

In total, 89 (8%) participants died after completing early care. Compared to those who survived, participants who died were older and had higher frequencies of poor retention in early care (37% vs 19%, p <0.001), AIDS defining illness (63% vs 40%, p <0.001) and ≤8 years of education (72% vs 46%, p<0.001) (Table 1). Participants with poor retention in early care had significantly worse survival than those with good early retention (log-rank p<0.0001; Figure 1).

In the final adjusted model, poor retention in early care had the highest association with mortality (adjusted hazard ratio [aHR] 3.09; 95% confidence interval [95% CI] 1.65, 5.79). Having an AIDS defining illness (aHR 1.95; 95% CI 1.20, 3.18), ≤8 years of education (aHR 2.33; 95% CI 1.45, 3.75) were also associated with increased mortality risk.

Discussion

In this study, poor retention in early HIV care was strongly associated with mortality, highlighting the potential value of monitoring and improving retention in early care. Our results emphasize the need for interventions to improve clinical outcomes among HIV-infected persons with AIDS defining illnesses and lower education in Brazil.

Increased mortality risk among HIV-infected persons with poor retention in early HIV care may be explained by missed opportunities for effective management of their HIV infection. Our measure of retention was based on laboratory results, which served as proxies for clinic visits as patients require a prescription from their HIV care provider in order to have tests performed. Thus, poor retention implied inadequate HIV monitoring though not necessarily worse management of HIV disease. However, worse retention in HIV care has been associated with worse adherence to ART , and it is plausible that patients with poor retention also had worse management of HIV disease. In addition, unmeasured factors, such as unmet housing needs, may have played a role in retention as well as mortality risk . Available data for this analysis did not include unmet needs, which should be addressed in future studies.

We previously reported that poor retention in early care was associated with younger age and 8 years of education . In the present analysis, lower education was associated with increased mortality risk. Importantly, lower education has also been associated with virologic failure in this

cohort , which likely contributes to our findings. Lower education may be an indicator of lower socio-economic status , which has also been associated with increased mortality risk . We also observed an approximately two-fold increased mortality risk among persons with AIDS defining illnesses, consistent with prior results from our cohort that showed that AIDS defining illnesses increased risk of AIDS-related and non-AIDS related deaths [REF]. Presence of AIDS defining illness at baseline implies late entry, and prior studies have shown that late entry to care in Brazil stems from many factors and prevails even in well-developed urban settings with access to HIV testing and care   REF]. Our findings thus corroborate and highlight the importance of early entry into care and early ART initiation in improving survival.

Our analysis is not without limitations. First, although poor retention has been previously associated with poor ART adherence , we were unable to adjust for ART adherence. However, as ART adherence and its immunologic impact are on the causal pathway to AIDS-related mortality, similar survival analyses have not adjusted for these factors . We were also unable to adjust for substance abuse, which has been shown to correlate with both retention in HIV care and mortality , and should be addressed in future research. We did not include causes of death because our data was incomplete for 2012 and 2013. Further studies are necessary to investigate the possible link between good and poor retention in early HIV care with mortality from specific causes. Finally, considering this a non-probabilistic sample, our results may not be generalizable to other HIV-infected cohorts or populations.

Conclusion
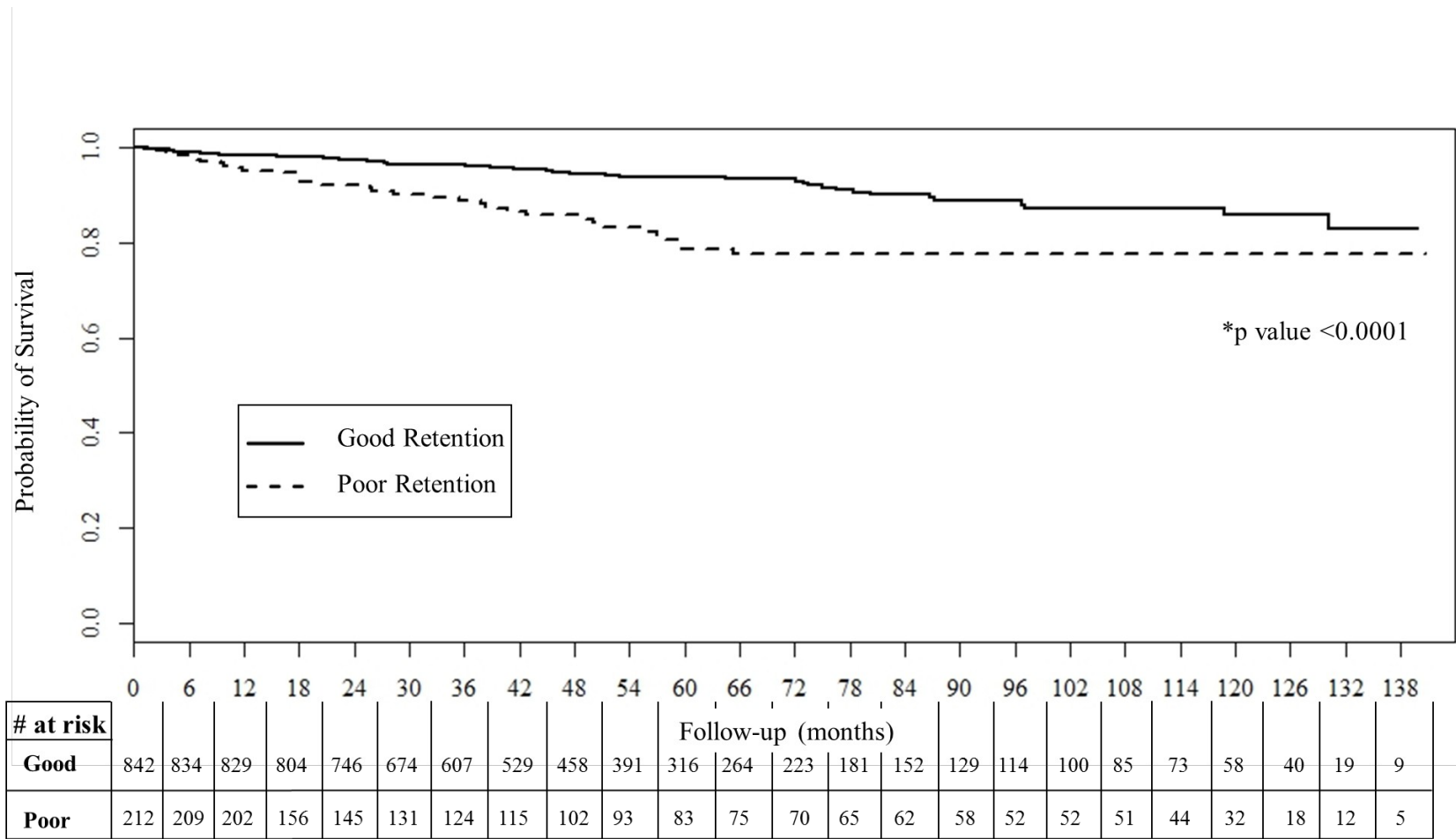
This analysis demonstrated associations between poor retention in early care, lower education and history of an AIDS diagnosis with increased risk of mortality in an urban Brazilian cohort of

HIV-infected persons with universal access to ART. Monitoring retention in early care and adopting strategies to improve retention in early HIV care may to lead to improved health outcomes.

References:

Figure 1: Kaplan-Meier survival curve of good versus poor retention in early HIV care at INI, 2002-2013

*p value <0.0001

Good Retention

Poor Retention

Probability of Survival

Follow-up (months)

# at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120	126	132	138
Good	842	834	829	804	746	674	607	529	458	391	316	264	223	181	152	129	114	100	85	73	58	40	19	9
Poor	212	209	202	156	145	131	124	115	102	93	83	75	70	65	62	58	52	52	51	44	32	18	12	5

*log-rank test

	Study population (n=1054)	Alive (n=965)	Dead (n=89)	p value[‡]	Unadjusted Hazard Ratio	p value	Adjusted Hazard Ratio[◊]	p value
Sex (male)[a]	758 (72)	692 (72)	66 (74)	0.71	1.20 [0.75, 1.93]	0.45	1.43 [0.87, 2.33]	0.15
Race (non-white)[b]	478 (45)	432 (45)	46 (52)	0.25	1.16 [0.95, 1.43]	0.14		
Median Age (IQR)[c]	35 (28, 42)	35 (28, 42)	36 (30, 45)	0.15	1.47 [0.97, 2.23]	0.07	1.21 [0.99, 1.50]	0.06
Education (≤8 years)[d]	511 (48)	447 (46)	64 (72)	**< 0.001**	**2.65 [1.73, 4.36]**	**<0.0001**	**2.33 [1.45, 3.75]**	**0.0005**
Transmission Route[e]				0.95				
Heterosexual	585 (56)	535 (55)	50 (56)		Ref	Ref		
MSM	412 (39)	379 (39)	33 (37)		1.02 [0.66, 1.59]	0.92		
Other	14 (1)	51 (5)	6 (7)		1.40 [0.60, 3.26]	0.44		
ART initation[f] (>3 months post-linkage)	555 (53)	515 (53)	40 (45)	0.16	0.80 [0.52, 1.22]	0.3	1.17 [0.73, 1.89]	0.52
Nadir CD4 Count (<200 cells/mm^3)[g]	437 (41)	394 (41)	43 (48)	0.21	1.19 [0.78, 1.81]	0.41		
AIDS Defining Disease[h]	445 (42)	389 (40)	56 (63)	**<0.001**	**2.21 [1.43, 3.40]**	**0.0003**	**1.95 [1.20 3.18]**	**0.007**
Depression[i]	180 (17)	166 (17)	14 (16)	0.84	0.87 [0.49, 1.54]	0.63		
Metabolic Disease[j]	549 (52)	495 (51)	54 (61)	0.11	1.37[0.90, 2.10]	0.14		
Year of linkage ≤ 2003	220 (21)	180 (19)	40 (45)	**< 0.001**	**1.73 [1.10, 2.73]**	**0.02**	1.72 [0.97, 3.05]	0.06
Poor retention in early care	212 (20)	179 (19)	33 (37)	**< 0.001**	**2.42 [1.57, 3.73]**	**<0.0001**	**3.09 [1.65, 5.79]**	**0.0004**

‡ Chi-squared test for categorical factors and Kruskal-Wallis test for continuous asymmetric factors

◊ Results also adjusted by an interaction term between year of linkage ≤2003 and poor retention in early care (adjusted hazard ratio = 0.46 [0.19, 1.11]; p value = 0.11)

a Biological sex at birth

b Categorized as white or non-white

c Age = date of care initiation – date of birth, adjusted and unadjusted HR per 10 year increase

d Categorized as >8 years and ≤8 years

e Hierarchically categorized into intravenous drug use (IDU, regardless of sexual exposure), men who have sex with men (MSM), heterosexual (including bisexual women), other, and unknown. Women with unknown HIV transmission route (n=45) were categorized as heterosexual. Vertical transmission (n=2), work accident (n=3), and transfusion (n=6), intravenous drug use (n=14) and unknown (n=34) were included in the "other" transmission group.

f Determined by first recorded ART initiation date

g Nadir CD4 < 200 cells/mm^3 before the start of follow-up (i.e end of early care period) + 6 months. 5 participants with missing values categorized as CD4 ≥ 200 cells/mm^3.

h Diagnosis of an AIDS defining disease, per the Centers for Disease Control and Prevention 1993 criteria, before the start of follow-up (i.e. end of early care period) + 6 months.

i Clinical diagnosis before the start of follow-up (i.e. end of early care period) + 6 months.

j Diagnosis before the start of follow-up (i.e. end of early care period) + 6 months with ≥1 of the following: diabetes (fasting blood glucose ≥126mg/dL, random blood glucose ≥200 mg/dL or hemoglobin A1c >6.5%), dyslipidemia (LDL >159 mg/dL or HDL <40 mg/dL), hypercholesterolemia (total cholesterol >239mg/dL), hypertriglyceridemia (triglycerides >199mg/dL) or hypertension (diastolic blood pressure >100mmHg)

Table 1: Descriptive statistics and Cox proportional hazards models for predicting mortality among HIV-infected persons receiving care at INI, 2002-2013