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The Effect of History of Injection Drug Use and Alcoholism on HIV Disease Progression

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Abstract

The effectiveness of highly active antiretroviral therapy (HAART) in preventing disease progression can be negatively influenced by the high prevalence of substance use among patients. Here, we quantify the effect of history of injection drug use and alcoholism on virologic and immunologic response to HAART. Clinical and survey data, collected at the start of HAART and at the interview date, were based on the study Longitudinal Investigations into Supportive and Ancillary Health Services (LISA) in British Columbia, Canada. Substance use was a three-level categorical variable, combining information on history of alcohol dependence and of injection drug use, defined as: no history of alcohol and injection drug use, history of alcohol or injection drug use and history of both alcohol and injection drug use. Virologic response (pVL) was defined by ≥2 $\log_{10}$ copy/mL drop in viral load. Immunologic response was defined as an increase in CD4 cell count percent of ≥100%. We used cumulative logit modeling for ordinal responses to address our objective. Of the 537 HIV-infected patients, 112 (21%) were characterized as having history of both alcohol and injection drug use, 173 (32%) were non adherent (<95%), 196 (36%) had $CD4^+/pVL^+$ (Best) response, 180 (34%) a $CD4^+/pVL^-$ or a $CD4^-/pVL^+$ (Incomplete) response, and 161 (30%) a $CD4^-/pVL^-$ (Worst) response. For individuals with history of both alcohol and injection drug use, the estimated probability of of Best, Incomplete and Worse responses, respectively. Screening and detection of substance dependence will identify individuals at high-risk for non-adherence and ideally prevent their HIV disease from progressing to advanced stages where HIV disease can become difficult to manage.

Keywords

Alcohol; Injection drug use; Adherence; HAART; HIV; Disease progression

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INTRODUCTION

The primary goal of highly active antiretroviral therapy (HAART) is to achieve full and long-term suppression of viral replication, and thereby, to prevent the emergence of drug resistance and morbidity and mortality (Thompson et al., 2012). Unfortunately, the effectiveness of HAART in preventing disease progression can be negatively influenced by the high prevalence of alcohol and of illicit substance use among many HIV-infected patients (Montaner et al., 2010; Justice et al., 2006; Wu, Metzger, Lynch, & Douglas, 2011; Kerr et al., 2007; Trenz et al., 2012). Thus, a comprehensive assessment of the relationship between alcohol and illicit substance use on HAART outcomes is warranted.

METHODS

Data

Data from eligible participants were extracted from the British Columbia (BC) Centre for Excellence in HIV/AIDS' Drug Treatment Program (BCCfE) and from the study "Longitudinal Investigations into Supportive and Ancillary Health Services" (LISA) (Duncan et al., 2012). We included individuals from the LISA study who have initiated HAART for the first time from August, 1996 and until January, 2010. More details regarding the study data can be found in the Supplemental Material. In BC, the HIV epidemic is concentrated among injection drug users and men who have sex with men, and LISA participants reflect those infected with HIV via injection drug use. The final sample size was 1000, however, data from 83 participants excluded since they could not be linked to our clinical data.

Laboratory Monitoring

The BCCfE distributes antiretrovirals, at no cost, to all eligible individuals in BC; and it maintains HIV-specific monitoring clinical data on all individuals who have ever received HAART in BC. Thus, CD4 cell count and viral load data at the start of HAART and at the time of the interview were obtained for our study sample. Viral load was measured using different assays over time. Because the change in viral load assays, the lower and upper limits of quantification of these assays changed over time, and therefore, viral load measurements were re-coded to range from 500 to 100,000 copies/mL to minimize the measurement bias that would have been introduced if the data were left unchanged.

CAGE Questionnaire

CAGE is a commonly used screening tool to detect alcohol dependence (Chander, 2011; Mayfield, McLeod, & Hall, 1974; Ewing, 1984). It has been applied in the general medical population in primary care settings and among HIV-positive populations (Ewing, 1984; Samet, Phillips, Horton, Traphagen, & Fredberg, 2004). It contains four questions: Domain 1 (Cut): Have you ever felt you should cut down on your drinking? (yes/no); Domain 2 (Annoyed): Have people annoyed you by criticizing your drinking? (yes/no); Domain 3 (Guilt): Have you ever felt bad or guilty about your drinking? (yes/no); and Domain 4 (Eye Opener): Have you ever had a drink first thing in the morning (as an "eye opener") to steady your nerves or get rid of a hangover? (yes/no). In this study, we categorized individuals as having no indication of having a history of alcoholism (i.e. yes to at most 1 question), as having an indication of having a history of alcoholism (i.e. yes to 2 or 3 questions), and as having a confirmed history of alcoholism (i.e. yes to all 4 questions).

Outcome Variables, Main Exposure and Confounder Factors

Our main exposure, substance use, was a three-level categorical variable defined as: no history of alcohol and injection drug use, history of alcohol or injection drug use, and history of both alcohol and injection drug use. Disease progression was defined both virologically and immunologically, as:

$$\text{Viral load change} = \text{ViralLoad}_{\text{interview}} - \text{ViralLoad}_{\text{baseline}} = \begin{cases} \leq -2\log_{10}\text{copies/ml} & (\text{pVL}^{+}) \\ \leq -2\log_{10}\text{copies/ml} & (\text{pVL}-) \end{cases}$$

$$\text{CD4percent change} = 100 \times \left(\frac{\text{CD4}_{\text{interview}}}{\text{CD4}_{\text{baseline}}} - 1 \right) = \begin{cases} \geq 100\% & (\text{CD4}^{+}) \\ <100\% & (\text{CD4}-) \end{cases}$$

By combining each of the levels of viral and CD4 responses, our outcome was a three-level ordinal variable: $CD4^{+}/pVL^{+}$ (Best); $CD4^{+}/pVL^{-}$ or $CD4^{-}/pVL^{+}$ (Incomplete); and $CD4^{-}/pVL^{-}$ (Worst).

The potential confounders included baseline age, sex, CD4 cell count, adherence (measured 6 months prior to the LISA interview date), viral load ($\log_{10}$ transformed), baseline HAART regimen type and follow-up time (in years) from baseline to the interview. HAART regimen consisted of two nucleosides, or a nucleoside and a nucleotide reverse transcriptase inhibitor plus either: (1) a non-nucleoside reverse transcriptase inhibitor [NNRTI], or (2) a protease inhibitor boosted with ≤400mg/day ritonavir [boosted PI], or (3) a single protease inhibitor [unboosted PI]. Adherence was defined as the number of days of antiretroviral drugs dispensed divided by the number of days on antiretroviral therapy (expressed as percent). Adherence was categorized as ≥95% (adherent) versus <95% (non-adherent).

Statistical Analysis

In bivariable analyses, categorical variables were compared using the Fisher's exact test, and continuous variables were compared using the Wilcoxon rank sum test. We built a confounder model using cumulative logit modeling for ordinal response (Lima et al., 2012; Lee, 1992; Stokes, Davis, & Koch, 2000). We have adjusted all our multivariable analyses for measurement bias using inverse-probability-weights (Lima et al., 2012), since our main exposure and some of the potential confounders were self-reported. This particular adjustment has been shown to properly handle biases such as measurement bias. All reported p-values are two-sided, and all analyses were performed using SAS version 9.3 (SAS Institute Inc.).

RESULTS

Of the 537 eligible individuals, 141 were female (26%), 392 (73%) had a history of injection drug use, 230 (43%) started on a NNRTI-based regimen and 172 (32%) on a boosted PI regimen. Those with a history of both alcohol and injection drug use were more likely to be female, to have lower CD4 cell count at the time of interview, and a lower baseline viral load ($P<0.001$). These individuals also experienced a lower CD4 cell count increase from baseline, and a lower viral load change from baseline ($P<0.001$) (Table 1).

A total of 196 (36%) individuals had $CD4^{+}/pVL^{+}$ (Best) response, 180 (34%) a $CD4^{+}/pVL^{-}$ or a $CD4^{-}/pVL^{+}$ (Incomplete) response, and 161 (30%) a $CD4^{-}/pVL^{-}$ (Worst) response (Table 2). Individuals with response $CD4^{-}/pVL^{-}$ (Worst) were more likely to have a confirmed history of alcoholism, to have a history of both alcohol and injection drug use, to be female, to have a history of injection drug use, to have started HAART on an unboosted PI, and to be <95% adherent ($P<0.001$) (Table 2). Individuals with Worst response, in

comparison to Best or Incomplete responses, were more likely to be younger, to have a lower CD4 cell count at the time of the interview, a lower CD4 cell count increase from baseline, a lower baseline viral load and a lower viral load change from baseline ($P<0.0001$) (Table 2 and Figure 1). Based on the multivariable confounder model, the estimated probabilities of Best, Incomplete and Worse responses were, respectively, (0.51, 0.29, 0.20) for individuals with no history of alcohol and injection drug use, (0.34, 0.32, 0.33) for individuals with a history of alcohol or injection drug use, and (0.15, 0.25, 0.60) for individuals with a history of both alcohol and injection drug use (Table 3).

DISCUSSION

This study demonstrated that individuals with a history of both alcohol and injection drug use have a higher likelihood of experiencing the worst immunologic and virologic responses, mostly due to poor adherence. Our results are in agreement with other, albeit few, studies looking at the association of alcohol use and injection drug use with HAART adherence and outcomes (Henrich, Lauder, Desai, Sofair, 2008; Michel et al., 2010; Lucas, Gebo, Chaisson, & Moore, 2002). This finding further emphasizes the problem of non-adherence among this population, which may be the result of individuals engaging in high-risk activities, of poverty, of improper housing and nutrition (Palepu, Milloy, Kerr, Zhang, & Wood, 2011; Weiser et al., 2009; Milloy, Marshall, Montaner, & Wood, 2012; Anema et al., 2011).

This study has some limitations. Because of the LISA study's design, certain marginalized populations were over sampled and, therefore, our results are not representative of all HIV-infected individuals in BC. It is also important to mention that studies to date have used different methodologies to measure alcohol use (Chander, 2011). Here, we chose to use the CAGE questionnaire, which assesses problems arising from alcohol use and it does not provide a direct measure of the frequency of alcohol consumption (e.g., short-term binges). Furthermore, we used history of injection drug use instead of ongoing injection drug use, and therefore, this study did not capture changes in drug preference, and it also did not distinguish between opioid and stimulant use. Finally, as in all observational studies, even after adjusting for several demographic and clinical characteristics, unmeasured confounders and other types of biases (e.g. recall and volunteer biases) may have played a role in our results, and for this reason, our findings should be interpreted cautiously.

In conclusion, this study has provided more insight on the negative consequences of having a history of alcohol and injection drug use on treatment outcomes for HIV-positive individuals. It is important, therefore, that before and after starting antiretroviral treatment, physicians screen these individuals for any substance use and extensively discuss their addiction treatment options. Ultimately, the screening and detection of alcohol, injection drug use or polysubstance dependence will identify individuals at high-risk for non-adherence and ideally prevent their HIV disease from progressing to advanced stages where HIV disease can become difficult to manage.

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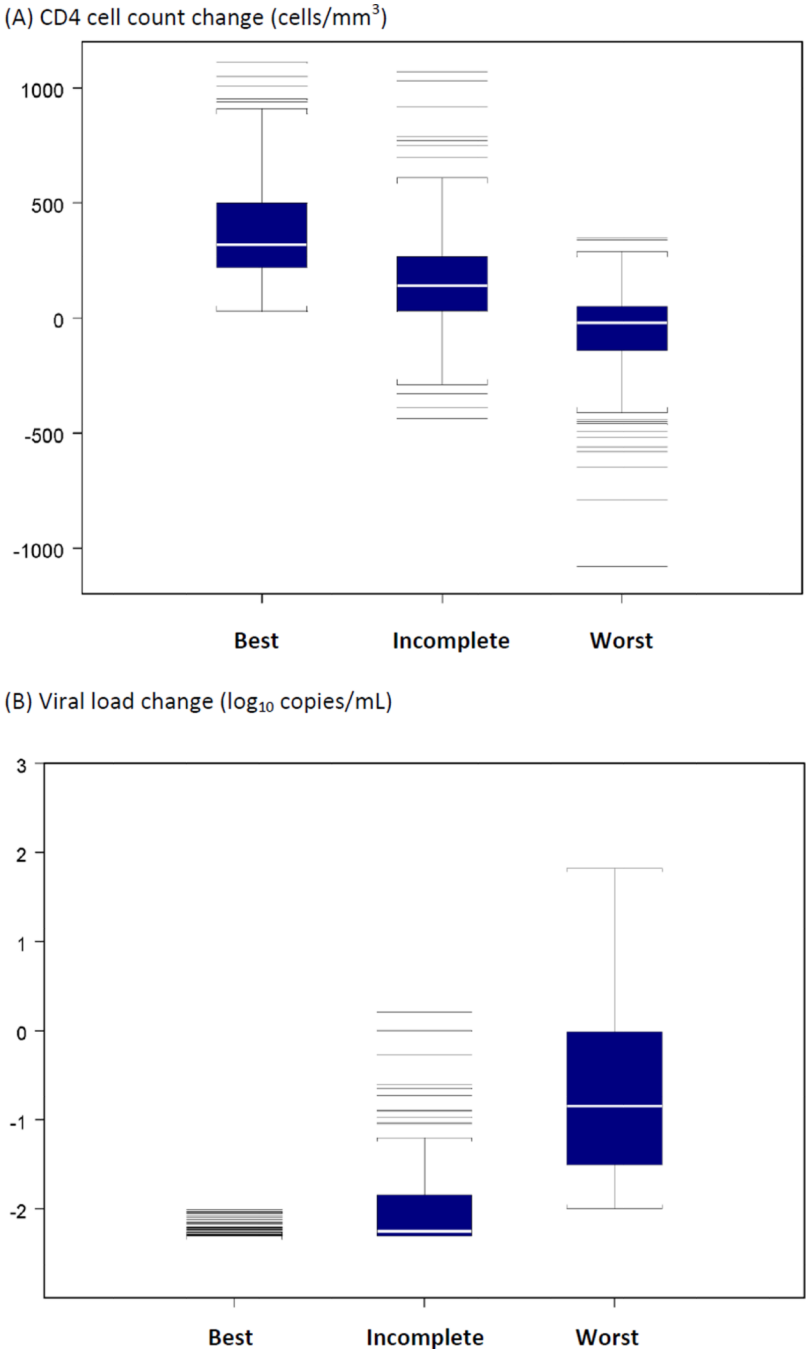

Figure 1.
CD4 cell count and viral load change from baseline to the time of the LISA interview by disease progression categories ($CD4^+/pVL^+$ (Best); $CD4^+/pVL^-$ or $CD4^-/pVL^+$ (Incomplete); and $CD4^-/pVL^-$ (Worst).

Table 1

Baseline and interview characteristics associated with the interaction of CAGE questionnaire results and history of injection drug use status for the participants in the LISA cohort.

Factors	Interaction of CAGE Questionnaire Results and History of Injection Drug Use			
	No history of alcohol and injection drug use N = 100	History of alcohol or injection drug use N = 325	History of both alcohol and injection drug use N = 112	p-value
Sex				
Male	88 (88%)	233 (72%)	75 (67%)	<0.0001
Female	12 (12%)	92 (28%)	37 (33%)	
Baseline HAART Regimen				
Unboosted PI	26 (26%)	85 (26%)	24 (21%)	0.6554
Boosted PI	36 (36%)	101 (31%)	35 (31%)	
NNRTI	38 (38%)	139 (43%)	53 (47%)	
Adherence to HAART (6 months before interview)				
≥95%	86 (86%)	220 (68%)	58 (52%)	<0.0001
<95%	14 (14%)	105 (32%)	54 (48%)	
Baseline Age (years)	43 (36 – 49)	40 (33 – 47)	41 (36 – 45)	0.1856
CD4 cell count (cells/mm^3)				
Baseline	225 (80 – 315)	190 (110 – 290)	190 (145 – 350)	0.3000
At the time of interview	500 (345 – 660)	350 (210 – 550)	280 (170 – 430)	<0.0001
• Percent change from baseline	128 (50 – 393)	93 (4 – 260)	30 (−14 – 135)	<0.0001
• Difference from baseline	260 (140 – 400)	159 (10 – 320)	65 (−35; – 220)	<0.0001
Plasma Viral Load (log_{10} copies/mL)				
Baseline	5 (4.8 – 5.0)	5 (4.6 – 5.0)	4.8 (4.3 – 5.0)	0.0001
• Difference from baseline	−2.3 (−2.3 – −2.0)	−2.2 (−2.3 – −1.5)	−1.7 (−2.3 – −0.6)	<0.0001
Follow-up from baseline to the interview (years)	5.2 (2.0 – 9.2)	5.3 (2.2 – 8.8)	3.9 (2.2 – 8.4)	0.4067

NNRTI: non-nucleoside reverse transcriptase inhibitor; Boosted PI: protease inhibitor boosted with ≤400mg/day ritonavir; Unboosted PI: single protease inhibitor.

Table 2

Baseline and interview characteristics associated with disease progression for the participants in the LISA cohort.

Factors	$CD4^+/pVL^+$ (Best) N = 196	$CD4^+/pVL^-$ or $CD4^-/pVL^+$ (Incomplete) N = 180	$CD4^-/pVL^-$ (Worst) N = 161	p-value
CAGE Questionnaire Results				
No indication of having a history of alcoholism	107 (55%)	95 (53%)	50 (31%)	<0.0001
Indication of having a history of alcoholism	63 (32%)	53 (29%)	47 (29%)	
Confirmed history of alcoholism	26 (13%)	32 (18%)	64 (40%)	
CAGE & History of injection drug use				
No history of alcohol and injection drug use	48 (24%)	38 (21%)	14 (9%)	<0.0001
History of alcohol or injection drug use	125 (64%)	114 (63%)	86 (53%)	
History of both alcohol and injection drug use	23 (12%)	28 (16%)	61 (38%)	
Sex				
Male	164 (84%)	132 (73%)	100 (62%)	<.0001
Female	32 (16%)	48 (27%)	61 (38%)	
History of injection drug use				
No	68 (35%)	56 (31%)	21 (13%)	<.0001
Yes	128 (65%)	124 (69%)	140 (87%)	
Baseline HAART regimen				
Unboosted PI	39 (20%)	49 (27%)	47 (29%)	0.0022
Boosted PI	83 (42%)	52 (29%)	37 (23%)	
NNRTI	74 (38%)	79 (44%)	77 (48%)	
Adherence to HAART (6 months before interview)				
≥95%	159 (81%)	142 (79%)	63 (39%)	<0.0001
<95%	37 (19%)	38 (21%)	98 (61%)	
Baseline age (years)	42 (36 – 48)	42 (34 – 48)	38 (32 – 43)	<0.0001
CD4 cell count (cells/mm^3)				
Baseline	120 (40 – 180)	240 (150 – 360)	260 (180 – 420)	<0.0001
At the time of interview	435 (315 – 670)	400 (260 – 575)	240 (140 – 350)	<0.0001
• Percent change from baseline	291 (150 – 650)	58 (10 – 138)	−12 (−43 – 26)	<0.0001
• Difference from baseline	320 (220 – 500)	140 (30 – 265)	−20 (−140 – 50)	<0.0001
Plasma Viral Load ($\log_{10}$ copies/mL)				
Baseline	5.0 (5.0 – 5.0)	5.0 (4.7 – 5.0)	4.4 (4.0 – 4.7)	<0.0001
• Difference from baseline	−2.3 (−2.3 – −2.3)	−2.2 (−2.3 – −1.8)	−0.8 (−1.5 – 0)	<0.0001
Follow-up from baseline to the interview (year)	4.3 (2.2 – 7.3)	5.1 (1.9 – 8.9)	6.5 (2.5 – 6.1)	0.0609

NNRTI: non-nucleoside reverse transcriptase inhibitor; Boosted PI: protease inhibitor boosted with ≤400mg/day ritonavir; Unboosted PI: single protease inhibitor; pVL: Viral load.

Table 3

Estimated probability based on the multivariable confounder models stratified by the interaction of CAGE questionnaire results and history of injection drug use status, using disease progression ($CD4^+/pVL^+$ (Best); $CD4^+/pVL^-$ or $CD4^-/pVL^+$ (Incomplete); and $CD4^-/pVL^-$ (Worst)) as the main outcome.

Main Variable	Estimated probability		
	CD4+/pVL+ (Best)	CD4+/pVL− or CD4−/pVL+ (Incomplete)	CD4−/pVL− (Worst)
CAGE & History of injection drug use			
No history of alcohol and injection drug use	0.5123	0.2892	0.1985
History of alcohol or injection drug use	0.3434	0.3244	0.3322
History of both alcohol and injection drug use	0.1472	0.2516	0.6012