Declining Suicide Mortality among Persons living with HIV/AIDS who Initiated Highly Active Antiretroviral Therapy in British Columbia, Canada

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INTRODUCTION:

Chronic illnesses in general, and HIV in particular, have long been associated with an increased risk of suicide [1,2]. The sense of hopelessness that can accompany the life-long implications of being HIV positive can contribute to compromised quality of life and significant mental distress [3] [4-8]. With the prevalence of mental health disorders, namely depression, reported at greater rates among people living with HIV/AIDS (PLHIV) compared to the general population, it is not surprising that suicide rates within this population have been historically elevated [2,9,3].

However, the advent of Highly Active Antiretroviral Therapy (HAART) transformed HIV from a terminal illness to a manageable chronic condition [3]. Effectively reducing the risk of developing potentially lethal AIDS-defining illnesses and opportunistic infections, HAART produced the potential for enhanced quality and longevity of life for persons living with HIV/AIDS (PLHIV) [3,10] [5,11,9,12-14]. In light of these widespread benefits, it was anticipated that elevated rates of suicide among PLHIV could be favorably affected [9,15,16].

Two recent studies have reported declines in suicide risk among PLHIV between the pre-HAART era (before 1996) and the HAART era (1996 onwards); however, the studies concluded that suicide risk[5] and suicide rates[16] remain substantially elevated among PLHIV at approximately 9 times and 2-3 times that of the general population, respectively [5,16]. This implies that despite effective HIV treatment an elevated propensity towards suicide persists, perhaps indicating that there are factors, other than issues

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directly related to HIV infection[7,16], that predispose PLHIV to
suicidality [16,17,18].

Identifying these factors is essential to deriving
meaningful targets for interventions that can effectively
mitigate suicide risk in this population[1]. We therefore conducted
the present analysis to characterize longitudinal suicide rates
and ascertain factors associated with suicide among PLHIV
accessing free HAART in the province of British Columbia, Canada.

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METHODS:

Study Sample: HIV/AIDS Drug Treatment Program:

HAART is provided free-of-charge to PLHIV in BC through the provincially funded Drug Treatment Program (DTP) at the BC Centre for Excellence in HIV/AIDS (BC – CfE). Individuals enrolled in the DTP who participated in the HOMER cohort – PLHIV who are over the age of 19, who initiated HAART from August 1996 to June 2012 — were eligible for inclusion in this study [19]. Socio-demographic and clinical data including HAART history as well as immunological and virological markers, were obtained through a linkage with the Drug Treatment Program. Cause and date of death were obtained through monthly linkages with the BC Vital Statistics event registry up to June 2012, and all deaths that occurred in this sample up to this time were included.

Variable Selection:

Our primary outcome variable was suicide as listed as the underlying cause of death on the vital statistics death record. The definition of suicide utilized in this study was adapted from the Manitoba Centre for Health Policy and includes several poisoning codes, such as "accidental poisoning", that account for ICD-10 codes suspected of capturing a significant proportion of suicides[20]. The following ICD – 10 codes from BC Vital Statistics were utilized in this definition: accidental poisoning: E850–E854, E858, E862, E868; X40–X42, X46, X47; poisoning with undetermined intent: Y10-Y12, Y16, Y17; self-inflicted poisoning: E950–E952, X60–X69; self-inflicted injury by hanging, strangulation and suffocation: E953, X70; self-inflicted injury

by drowning: E954, X71; self-inflicted injury by firearms and explosives: E955, X72-X75; self-inflicted injury by smoke, fire, flames, steam, hot vapors and hot objects: E958.1, E958.2; X76, X77; self-inflicted injury by cutting and piecing instruments: E956; codes X78, X79; self-inflicted injury by jumping from high places: E957, code X80; self-inflicted injury by jumping or lying before a moving object: code E958.0, code X81; self-inflicted injury by crashing of motor vehicle: code E958.5, X82; self-inflicted injury by other and unspecified means: E958.3, E958.4, E958.6-E958.9; X83, X84.

The socio-demographic variables evaluated included: gender, Aboriginal identity (extracted from several sources including: surveys, physicians' reports, death information, etc.), median income (the median income recorded in census data for each patient's postal code was taken as the patient's median income), whether individuals were from urban versus rural neighborhoods (determined by postal code information held at the DTP), age at death and year of death. Clinical variables evaluated included: ever having been diagnosed with an AIDS-defining illness (ADI), ever having had a positive hepatitis C (HCV) diagnosis, HAART treatment adherence in the last year prior to death – calculated by number of days on therapy (based on number of days of coverage provided by a given prescription) divided by the number of days the patient is alive in the last year, last/most recent HAART regimen, Efavirenz as part of the last/most recent regimen, number of years on HAART, most recent and nadir CD4, and latest viral load. History of injection drug use was the only socio-

behavioral variable assessed.

Data Analysis & Statistical Methods:

Two main analyses were conducted in this study. We conducted the first analysis examining the predictors of suicide among all HOMER participants who committed suicide or remained alive over the study period, while the second analysis was limited to all deaths (suicides and non-suicides). Statistical comparisons were conducted using Pearson χ^2 test or Fisher's Exact Test for dichotomous variables and the Wilcoxon Rank-Sum test for continuous variables.

A Cox Proportional Hazards model and logistic regression model were performed. The Cox analysis was used to identify the independent predictors of suicide among HOMER participants who remained alive or committed suicide during the study period. A logistic regression was used to identify independent predictors of suicide among suicides and non-suicides. Variables for inclusion in both Cox and logistic regression models were selected using exploratory model selection process based on Akaike Information Criterion (AIC) and Type III p-values.

Overall and annual rates of suicide mortality were estimated for HOMER and the general population from 1997 to 2011. These calculations were restricted to 1997 – 2011 to ensure full-year comparisons between HOMER participants and the BC general population. Person-years of risk in HOMER were based on participants' time under observation in the cohort, while for the BC population they were based on annual population estimates[21,22]. The number of deaths from suicide in the general population, by

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year, were obtained from BC Vital Statistics reports.[15] Crude

rates were expressed as deaths per 100,000 person years.

RESULTS:

Our analysis was based on 5,229 PLHIV in the HOMER cohort who

initiated HAART from August 1996 to June 2012 in BC. A total of

82 deaths from suicide were observed. Figure 1 highlights the

decline in suicide rates over our study period from 961 deaths

per 100,000 person-years in 1998 to 2.81 deaths per 100,000

person years 2010 (the last year any suicides were recorded in

this cohort), with a relatively constant suicide rate in the BC

general population.

The bivariate analysis in Table 1 describes the sample characteristics of all HOMER participants who committed suicide (n=82) compared to those who remained alive (n=4,236), while excluding those who died of causes other than suicide (n = 911). As noted in Table 1, 78% of all suicides were male, the median age was 42 years and the median number of years on HAART was three. Aboriginal ancestry, younger age, lower annual income and injection drug use were found to be associated with suicide. Clinical predictors of suicide included: ever having received a positive HCV diagnosis, never having an AIDS defining illness, poor treatment adherence in the last/most recent calendar year, and lower CD4 and higher viral load in the last/most recent calendar year.

A second bivariate analysis (Table 2) was performed to compare suicide deaths (n=82) to non-suicide deaths (n=911). Here, younger age and death in an earlier calendar year were found to be associated with suicide. In addition, higher nadir CD4, baseline CD4 and most recent CD4 prior to death were associated with suicide. Never having had an AIDS defining illness and ever having had a positive HCV diagnosis were also significantly predictive of suicide.

Table 3, highlights the results of the Cox proportional hazards model. In this analysis, those who died of non-suicide deaths were censored. Never having had an AIDS defining illness (Adjusted Hazard Ratio [AHR] = 4.45; CI [1.62 – 12.25]) or having a history of injection drug use (AHR = 3.95; CI [1.99 – 7.86]) was independently associated with an increased rate of suicide.

This model also found a 51% reduction in the suicide rate per calendar year increase into the HAART era.

Table 4 highlights results from the logistic regression model comparing suicide to non-suicide deaths in HOMER. The model indicated that never having an AIDS defining illness was associated with nearly a seven-fold increase in the probability of suicide (Adjusted Odds Ratio [AOR] = 6.63 95% CI [2.34 – 18.83]), while having a history of injection drug use was associated with a two-fold increase in the likelihood of suicide (AOR = 1.92 95% CI [0.87 – 4.28]). Death at an older age (AOR = 0.96 95% CI [0.94 –0.99]), or in a later calendar year (AOR = 0.85 95% CI [0.79 –0.91]) were both associated with decreased odds of suicide. A higher last CD4 count was associated with an increased likelihood of suicide (AOR = 1.21 95% CI [1.06 –1.38]).

In light of recent findings showing associations between suicide and specific ARVs, a distribution highlighting the proportion of HOMER participants whose treatment regimens include specific classes of ARVs is provided in Table 5.

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INTERPRETATION:

Our results indicate that suicide rates among HIV infected individuals who have accessed highly active antiretroviral therapy have declined substantially since 1996. Suicide mortality decreased significantly with each calendar year during the HAART era, and was greater among those who never experienced advanced HIV disease in the form of an AIDS defining illness (ADI). Consistent with previous research, injection drug use was independently associated with higher rates of suicide mortality [17,23].

Suicide rates declined from a peak of 961 deaths per 100,000 person-years in 1998 – a rate 91 times the rate in the general population, to 28 deaths per 100,000 person years at a rate three times that of the general population in 2010 (the last year any suicides were recorded in this cohort) (Figure 1). Several factors may have contributed to this decline. First, as the HAART era progressed, treatment regimens became simpler, more effective, less toxic and better tolerated;[18,24] thereby, potentially reducing treatment burden and impact on patients' quality of life. Secondly, initially characterized as a terminal illness – and therefore inherently associated with an elevated risk of suicide[18,25] – HAART transformed HIV into a chronic-manageable condition, [9,24] and as a result may have generated a renewed sense of HAART related hope and optimism. Lastly, public perception may have evolved over time, leading to greater social acceptance and less alienation of PLHIV; therefore, helping to mitigate suicide risk within this population.

Recent research has reported an association between Efavirenz containing regimens and an increased risk of suicidality[26]. We only detected an association between Efavirenz and suicide in univariate results comparing those who died of suicide to those who remained alive (Table 1 & 4). Moreover, we did not find NNRTI containing HAART regimens (Table 1 & 2) in general, or Efavirenz in particular, to be independently predictive of suicide (Table 4). It is likely that our relatively small number of suicides (n=82), and small proportion of individuals prescribed Efavirenz in their most recent regimen (n=7) limited our statistical power and ability to quantify a true association. Moreover, the majority of suicides in HOMER occurred in the earlier HAART era (between 1996 – 2004), a time when Nevaripine was the primary NNRTI prescribed.

Conflicting results have been reported with respect to the relationship between disease stage and suicide [5,16,17,25,27,28]. Several studies report that advanced HIV disease is associated with a greater likelihood of suicide [6,18,29], while others report that disease progression/symptomatic disease is not associated with an increased risk of suicide [17,18 30–32]. Consistent with Marzuk et al.'s finding that 70% of all autopsied suicides among HIV positive individuals showed no signs of AIDS-related pathology [17] our results also showed those who have never experienced an ADI are more likely to commit suicide; thus, implying that relatively "healthier" PLHIV are at greater risk of suicide. This is reinforced by findings in Table 2 that show the median last CD4 among those who committed suicide was above the definitive value

of 200cells/mm^{3} that characterizes disease progression to the stage of AIDS [33]. Within this group, it appears that those who committed suicide were physiologically healthier than those who died of all other causes. It is possible that individuals living with chronic illness may take their lives[25] out of the fear of becoming terminally ill, or becoming a burden to loved ones and losing dignity throughout this process [9]. Lastly, although those who died of suicide may have appeared to be healthier (i.e. higher CD4, no ADI), it is possible that psychologically speaking, they may not have been. Within this cohort, 77% of suicides were non-adherent to treatment in the year preceding their death. Compromised mental health is a widely-recognized mediator of treatment non-adherence among PLHIV [34-36]; and thus, this trend towards non-adherence could be indicative of underlying, and possibly undiagnosed, mental health illness.

Many PLHIV in British Columbia experience a host of psychosocial, behavioral and/or socio-economic challenges including poverty, homelessness, trauma, addictions and injection drug use. These psychosocial and socio-economic stressors that place individuals at an increased risk for HIV infection, are synonymous with those that place individuals at increased risk of suicide [11,1 7,18,23,4,7,28]. More specifically, previous studies have established injection drug use and substance use behaviors as strong correlates of elevated suicide risk/suicidality [1,4,16-18,23,28,37]. Within HOMER, 38% of participants have a history of injection drug use, a behavior known to often occur in the presence of concomitant mental health illness, [38,39]. It may be that

compromised mental health becomes neglected in the face of injection drug use, HIV infection and more visibly apparent health concerns; thus, contributing to exacerbation of suicide risk/suicidality[16,18,40]

Readers should be cautious when interpreting our results. First, our data pertains to a very specific population of PLHIV, who have initiated HAART in British Columbia, Canada – a universal healthcare setting with free access to treatment and HIV related care. Second, the lack of accepted methodology within this field of research – suicidality in HIV-positive populations, limits the comparability and generalizability of results across studies [9,11, 1,41,42]. Third, suicides may be under-estimated as those that occur in the form of drug overdoses or as a result of self-administered withdrawal of care, often cannot be distinguished as such; thus, the number of suicides may actually be higher than reported. Fourth, our sample size and gender distribution is limited and finally we had no access to clinical information regarding previous psychiatric history, particularly depression, or any mental health related treatments.

CONCLUSION:

Suicide rates among HIV infected individuals accessing antiretroviral therapy have declined substantially since 1996; however, in the most recent comparison, suicide rates in our cohort remained elevated at nearly three times the rate of the general population. Although the declines observed are promising, longer follow up will be required to ascertain whether these

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trends are persistent. Finally, our results reinforce the need

for further integration of care, and proactive mental health

screening and treatment among individuals infected with HIV

infected individuals to identify suicidal risk.

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Figure 1: Comparison of suicide rates in the HOMER cohort to the BC general population from 1997 – 2011
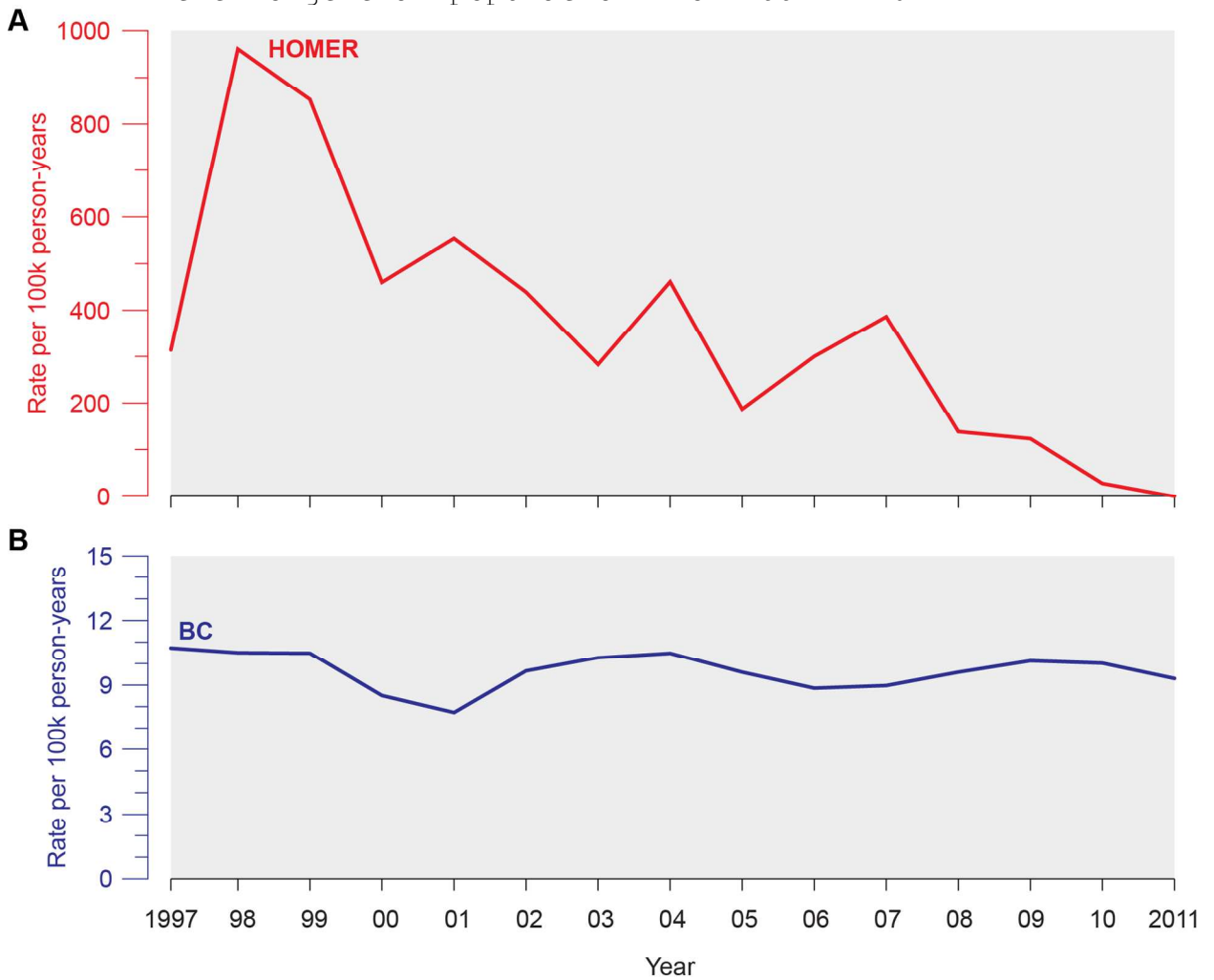
*To ensure full-year comparisons this figure was restricted to the years 1997 – 2011. BC general population data was retrieved from BC Statistics and BC Vital Statistics Agency[21,22].

Table 1

Comparison of characteristics of patients initiating HAART who died by suicide or remained alive

Variable		Suicide	Alive	*p*
		N=82	*N=4236*	
		n %		
Gender				
	Female	18(22)	773(18)	0.3876
	Male	64(78)	3463(82)	
Ethnicity				
	Aboriginal	16(20)	473(11)	0.0133
	Non-Aboriginal	24(29)	1805(43)	
	Unknown	42(51)	1958(46)	
Geographic region				
	Rural	2(2)	162(4)	0.8254
	Urban	64(78)	3327(79)	
	Unknown	16(20)	747(18)	
Injection drug use history				
	Yes	47(57)	1535(36)	<.0001
	No	10(12)	1973(47)	
	Unknown	25(30)	728(17)	
ADI diagnosis				
	Yes	4(5)	758(18)	0.0011
	No	78(95)	3478(82)	
Hepatitis C				
	Yes	63(77)	1582(37)	<.0001
	No	13(16)	2355(56)	
	Unknown	6(7)	299(7)	
Most recent HAART regimen				
	Single PI	47(57)	2131(50)	0.0022
	Single NNRTI	30(37)	1717(41)	
	Any IIN		299(7)	
	OTHER	5(6)	89(2)	
Efavirenz included in last/most recent regimen				
	Yes	7(9)	1086(26)	0.0002
	No	75(91)	3150(74)	
Adherence				

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Table 1

Comparison of characteristics of patients initiating HAART who died by suicide or remained alive

Variable	Suicide	Alive	p
	N=82	N=4236	
	n %		
>= 95%	19(23)	2685(63)	<.0001
< 95%	63(77)	1551(37)	
Age at the end of follow up[1]			<.0001
Median	42	47	
25th- 75th percentile	38-49	41-54	
Year of death			<.0001
Median	2003		
25th- 75th percentile	2000-2006		
Median Income(CAD)[2]			0.0115
Median	21015	23406	
25th- 75th percentile	14750-27799	18258.5-29901	
Baseline CD4+ cell count (cell/mm^3)			0.0010
Median	290	220	
25th- 75th percentile	170-400	325-670	
Most recent CD4+ cell count (cell/mm^3) before the end of follow up[1]			<.0001
Median	355	490	
25th- 75th percentile	200-500	325-670	
Nadir CD4+ cell count (cell/mm^3)			0.2155
Median	170	160	
25th- 75th percentile	70-290	60-250	
Most recent viral load (log10 copies/ml) before the end of follow up[1]			<.0001
Median	5	2.69	
25th- 75th percentile	2.69-5	2.69-2.69	
Number of years on HAART			<.0001
Median	3	6	
25th- 75th percentile	2-6	3-10	

1. End of follow up can be the death date, last contact date, last contact date prior to moving out of BC or to participating in ARV blinded trials.
2. Median Income was calculated with 945 missing values (17 Suicides and 928 alive).

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Table 2

Comparison of characteristics of patients initiating HAART who committed suicide or died non-suicide deaths

Variable		Suicides	Non-suicide deaths	*p-value*
		N=82	*N=911*	
		n %		
Gender				
	Female	18(22)	194(21)	0.8884
	Male	64(78)	717(79)	
Ethnicity				
	Aboriginal	16(20)	195(21)	0.9419
	Non-Aboriginal	24(29)	267(29)	
	Unknown	42(51)	449(49)	
Geographic region				
	Rural	2(2)	42(5)	0.7486
	Urban	64(78)	699(77)	
	Unknown	16(20)	170(19)	
Injection drug use history				
	Yes	47(57)	449(49)	0.1148
	No	10(12)	196(22)	
	Unknown	25(30)	266(29)	
ADI diagnoses				
	Yes	4(5)	296(32)	<.0001
	No	78(95)	615(68)	
Hepatitis C				
	Yes	63(77)	548(60)	0.0126
	No	13(16)	250(27)	
	Unknown	6(7)	113(12)	
Last/most recent HAART regimen				
	Single PI	47(57)	537(59)	0.4025
	Single NNRTI	30(37)	281(31)	
	Any IIN	0(0)	25(3)	
	OTHER	5(6)	68(7)	
Efavirenz included in last/latest regimen				
	Yes	7(9)	142(16)	0.1053
	No	75(91)	769(84)	
Adherence				
	>= 95%	19(23)	197(22)	0.7799

Table 2

Comparison of characteristics of patients initiating HAART who committed suicide or died non-suicide deaths

Variable	Suicides	Non-suicide deaths	p-value
	N=82	**N=911**	
	n %		
< 95%	63(77)	714(78)	
Age at death			0.0005
Median	42	46	
25th- 75th percentile	38-49	39-54	
Year of death			<.0001
Median	2003	2006	
25th- 75th percentile	2000-2006	2002-2009	
Median Income (CAD)[2]			0.6707
Median	21015	19346.5	
25th- 75th percentile	14750-27799	14518-26073	
Baseline CD4+ cell count (cell/mm^3)			<.0001
Median	290	150	
25th- 75th percentile	170-400	50-270	
Last/most recent CD4+ cell count (cell/mm^3) before the end of follow up[1]			<.0001
Median	355	140	
25th- 75th percentile	200-500	30-310	
Nadir CD4+ cell count (cell/mm^3)			<.0001
Median	170	50	
25th- 75th percentile	70-290	10-140	
Last/most recent viral load (log10 copies/ml) before the end of follow up[1]			0.4607
Median	5	5	
25th- 75th percentile	2.69-5	2.69-5	
Number of years on HAART			0.5176
Median	3	3	
25th- 75th percentile	2-6	1-6	

1. End of follow up can be the death date, last contact date, last contact date prior to moving out of BC or to participating in ARV blinded trials.
2. Median Income was calculated without 1156 missing values --17 Suicide, 211 Non-suicide and 928 all other patients.

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Table 3

Factors associated with suicide among patients initiating HAART in the HOMER cohort who committed suicide or remained alive at the end of the study N = 4318

Variable	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
ADI diagnosis		0.002		0.004
Yes	1.00 (-)		1.00 (-)	
No	4.90(1.79, 13.39)		4.45(1.62, 12.25)	
History of injection drug use		<0.001		<0.001
No	1.00 (-)		1.00 (-)	
Yes	5.86(2.96, 11.60)		3.95(1.99, 7.86)	
Unknown	9.13(4.38, 19.03)		2.59(1.21, 5.56)	
Adherence in the last year before death		<0.001	Not selected	
< 95%	1.00 (-)			
>= 95%	0.16(0.10, 0.27)			
Age at the end of follow up[1]	0.93(0.90, 0.95)	<0.001	Not selected	
Year of the end of follow up[1]	0.49(0.44, 0.53)	<0.001	0.49(0.45, 0.54)	<0.001
Latest CD4+ cell count (cell/mm^3) before the end of follow up[1]	0.77(0.70, 0.85)	<0.001	Not selected	
Latest viral load (log10 copies/ml) before the end of follow up[1]	3.14(2.54, 3.87)	<0.001	Not selected	
Efavirenz included as part of last regimen			Not selected	
No	1.00 (-)			
Yes	3.01 (1.37, 6.54)	0.005		

[1.] End of follow up can be the death date, last contact date, last contact date prior to moving out of BC or to participating in ARV blinded trials.

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Table 4

Factors associated with suicide among patients initiating HAART who committed suicide or died other than suicide N = 993

Variable	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
ADI diagnosis		<0.001		<0.001
Yes	1.00 (-)		1.00 (-)	
No	9.39(3.40, 25.88)		6.63(2.34, 18.83)	
History of injection drug use		0.1340		0.0230
No	1.00 (-)		1.00 (-)	
Yes	2.02(1.02, 4.14)		1.92(0.87, 4.28)	
Unknown	1.84(0.86, 3.92)		0.89(0.37, 2.14)	
Age at the end of follow up[1]	0.96(0.93, 0.98)	<0.001	0.96(0.94, 0.99)	0.0060
Year of the end death[1]	0.87(0.82, 0.92)	<0.001	0.85(0.79, 0.91)	<0.001
Nadir CD4 ever (per 100 cells/mm3)	1.71(1.47, 1.99)	<0.001	1.23(0.97, 1.56)	0.0930
Latest CD4 before death ever (per 100 cells/mm3)	1.24(1.15, 1.34)	<0.001	1.21(1.06, 1.38)	0.0040

[1.] End of follow up can be the death date, last contact date, last contact date prior to moving out of BC or to participating in ARV blinded trials.

Table 5: Distribution of regimens that include specific classes of ARVS among those who remained alive or died from suicide (Panel A) and those who died from all other causes and suicide (Panel b)

Panel A

Regimen Contains	Alive	Suicide
	N=4236	*N=82*
	n %	
1 NUC	76(2)	5(6)
2 NUC	4006(95)	70(85)
3 NUC	89(2)	3(4)
4 or more NUC	7(0.17)	0(0)
1 PI	6(0.14)	1(1.22)
2 PI	43(1.02)	0(0)
3 PI	1(0.02)	0(0)
1 NNR (NEV)	6(0.14)	1(1.22)
1 NNR (DMP)	1(0.02)	2(2.44)
1 IIN (MKS)	1(0.02)	0(0)
T20	-	-
Total	4236(98.1)	82(1.9)

Panel B

Regimen Contains	Non Suicide	Alive
	N=911	*N=82*
	n %	
1 NUC	58(6.37)	5(6.1)
2 NUC	765(83.97)	70(85.37)
3 NUC	46(5.05)	3(3.66)
4 or more NUC	5(0.55)	0(0)
1 PI	12(1.32)	1(1.22)
2 PI	18(1.98)	0(0)
3 PI	-	-
1 NNR (NEV)	3(0.33)	1(1.22)
1 NNR (DMP)	2(0.22)	2(2.44)
1 IIN (MKS)	-	-
T20	2(0.22)	0(0)
Total	911(91.74)	82(8.26)

PI: Protease Inhibitors, NNRTI: N̲on-nucleoside reverse transcriptase inhibitor.

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3 **NRTI: Nucleoside reverse transcriptase inhibitor. IIN: Integrase inhibitor. MVC: maraviroc.**
4 **T20: Enfuvirtide**
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