Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
0(0) 1–9

DOI: 10.1177/0956462417714094
journals.sagepub.com/home/std

SAGE

Evaluating the care cascade after antiretroviral therapy initiation in Latin America

Marcelo J Wolff[1], Claudia P Cortes[1], Fernando A Mejìa[2], Denis Padgett[3], Pablo Belaunzarán-Zamudio[4,5], Beatriz Grinsztejn[6], Mark J Giganti[7], Catherine C McGowan[7] and Peter F Rebeiro[7]; on behalf of the Caribbean, Central and South America network for HIV epidemiology (CCASAnet)

Abstract

Accelerating antiretroviral therapy (ART) administration, improving retention, and achieving viral suppression in low- and middle-income countries must be prioritized. We evaluated trends and disparities in these milestones in a large Latin American cohort. Adults starting ART (ART_{start}) from 2003 to 2014 at Caribbean, Central, and South America network for HIV epidemiology sites were assessed for care cascade outcomes: CD4 cell count >200 cells/mm^3 at ART_{start}; retention (≥ 1 visit at one year after ART_{start}); viral suppression (≥ 1 HIV-1 RNA <200 copies/ml at one year after ART_{start}). Modified Poisson regression provided adjusted prevalence ratios by age, gender, and HIV transmission risk, accounting for site and year of ART_{start}. Proportions achieving ART_{start} and suppression improved over time ($p < 0.05$). Older age was associated with better retention and viral suppression, but not ART_{start} at CD4 cell count >200 cells/mm^3. Females and men who have sex with men (MSM) were more likely to have CD4 cell count >200 cells/mm^3 at ART_{start}. Injection drug users (IDUs) were less likely to be retained while MSM were more likely to achieve viral suppression (all $p < 0.05$). Despite improvements in these outcomes over the course of a decade in this cohort, significant disparities existed, disadvantaging younger patients, men, and IDUs. These gaps indicate continued progress in providing early diagnosis and ART_{start} remain critical.

Keywords

HIV, AIDS, Epidemiology, ART, HIV, homosexual, South America

Date received: 28 February 2017; accepted: 5 May 2017

Background

The HIV epidemic continues to affect large and diverse populations in low- and middle-income countries, including approximately two million individuals in Latin America.[1] Within many of those countries, key populations such as men and women aged <24 years and men who have sex with men (MSM) are disproportionately affected.[2]

Recent revisions to treatment guidelines in the region have emphasized improving outcomes through milestones in the care cascade: initiation of combination antiretroviral therapy (ART) closer to the time of HIV diagnosis and at higher CD4 cell counts (early ART_{start}), retention in HIV care, and ultimately, HIV viral suppression.[3] This is consistent with a treatment-as-prevention paradigm

[1]Fundacion Arriaran, University of Chile, School of Medicine, Santiago, Chile
[2]Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru
[3]Instituto Hondureño de Seguridad Social and Hospital Escuela Universitario, Tegucigalpa, Honduras
[4]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[5]División de Investigación de Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico
[6]Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
[7]Vanderbilt University School of Medicine, Nashville, TN, USA

Corresponding author:
Peter F Rebeiro, Department of Medicine, Division of Infectious Diseases, Vanderbilt University School of Medicine, 1161 21st Ave. S., A-2200 MCN, Nashville, TN 37232, USA.
Email: p.rebeiro@vanderbilt.edu

emphasizing ART as a pathway to improved individual-level HIV outcomes and reduced population-level HIV transmission.[4] Indeed, as of 2012, the number of individuals treated with ART approached 725,000 in the region, constituting fully 75% of those who were treatment eligible under the 2010 World Health Organization (WHO) guidelines. Of those receiving first-line therapy, 78% received WHO-sanctioned initial regimens.[5] Despite these encouraging advances in expanding treatment, a large longitudinal analysis in high-, middle-, and low-income settings, including more than 350,000 individuals globally, demonstrated persistently lower median CD4 cell counts at ART_{start} in low- and middle-income settings, which included Latin American countries. In particular, the proportion initiating ART at CD4 cell count <200 cells/mm^3, representing delayed initiation, was persistently higher in these settings (59–71%, depending on gender and upper- versus lower-middle-income status), compared to high-income settings (31–35%) in 2010.[6] The high proportions with late initiation and disparities with other regions indicate an impediment to treatment-as-prevention goals for the region and merit continued monitoring of treatment uptake alongside the extension of analyses to subsequent stages of the care continuum.

Given the substantial burden of disease in the region; the need to monitor progress and temporal trends in ART initiation; the lack of other cohorts with the breadth, depth, and geographic reach of our collaboration; and the need to assess changes in the epidemiology of HIV clinical care to quantify progress and remaining gaps in clinical and public health responses, we assessed trends in these metrics over a decade in a Latin American cohort to identify key populations meriting increased attention.

Methods

Study population

Adults ($\geq$18 years) starting ART (regimen of $\geq$3 antiretroviral agents) from 2003 through 2014 at Caribbean, Central and South America network for HIV epidemiology (CCASAnet) sites were included. CCASAnet includes nine sites in seven countries, and it is one of seven member regions of the NIH-funded International Epidemiologic Databases to Evaluate AIDS.[7] CCASAnet sites contributing were Hospital Fernandez and Centro Médico Huésped, Buenos Aires, Argentina; Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil; Fundación Arriarán, Santiago, Chile; Le Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes, Port-au-Prince, Haiti (GHESKIO-Haiti); Instituto Hondureño de Seguridad Social and Hospital Escuela Universitario, Tegucigalpa, Honduras; Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, México; and Instituto de Medicina Tropical Alexander von Humboldt, Lima, Perú. Clinical and epidemiological data were collected at each site, deidentified, and sent to the CCASAnet Data Coordinating Center at Vanderbilt University (VDCC; Nashville, Tennessee, USA), for data harmonization. Data quality checks and on-site audits were performed by VDCC to ensure data accuracy. Institutional review board approval was obtained from each site and from Vanderbilt University Medical Center.

Study definitions and outcomes

The care cascade was assessed using three binary outcomes: CD4 cell count >200 cells/mm^3 at time of ART initiation (ART_{start}), retention in care ($\geq$1 HIV primary care visit at one year after ART_{start}), and viral suppression ($\geq$1 plasma HIV-1 RNA <200 copies/mL at one year after ART_{start}). ART_{start} with CD4 cell count >200 cells/mm^3 was chosen to indicate the initiation of therapy before advanced disease, further indicating successful diagnosis and linkage to care at an earlier disease stage.[3] Retention and viral suppression outcomes were assessed at one year as early indicators of successful engagement in care and achievement of initial milestones in the HIV care cascade following linkage to care.[8,9] Though individuals who died or failed to demonstrate any care engagement at all in the initial year after ART_{start} were excluded from the retention denominator in the primary analysis, they were included in the sensitivity analysis to assess the robustness of our inferences to different inclusion criteria.

Demographic and clinical factors including age at ART_{start} (in years), biological sex (male or female), probable HIV transmission risk factor (MSM, injection drug use [IDU], heterosexual contact [Hetero], or Other), and calendar year of ART_{start} were included as covariates by which the probability of attaining the study outcomes may vary. Calendar year of ART_{start} was used to assess trends in achievement of outcomes over the course of the study period. Clinic site was included as a potential confounder of these relationships.

For ART_{start} with CD4 cell count >200 cells/mm^3, outcomes were measured <6 months before and $\leq$7 days following ART_{start}. ART_{start} was an incident event, therefore each outcome anchored to this event was an incident outcome; individuals contributed a maximum of one observation for each outcome. Retention and viral suppression outcomes were assessed using the closest visit or lab measurement $\leq$90 days before/after the one-year ART_{start} anniversary.

Individuals contributed outcomes up to 15 months following initiation of ART. Participants from GHESKIO-Haiti were excluded from viral suppression outcomes analyses due to unavailable HIV-1 RNA testing there during the study period.

Statistical analysis

Bivariate comparisons of characteristics by outcomes were conducted using Chi square and Wilcoxon rank sum tests of differences in proportions and medians for categorical and continuous variables, respectively. Modified Poisson regression was used to estimate adjusted prevalence ratios (aPR) with 95% confidence intervals (95%CI) for each outcome by age, gender, and HIV transmission risk, accounting for clinic site and calendar year of ART_{start}; age and year of ART_{start} were modeled using restricted cubic splines with four knots.[10,11] Predicted values for each outcome were predictive margins: modeled predictive values of each outcome for each patient, averaged over all patients in the study. Those with missing outcome measures or death <1 year after ART_{start} were excluded. All analyses were conducted in Stata v.12.1 (StataCorp, College Station, TX).

Results

Among 17,653 individuals initiating ART in the CCASAnet cohort during the study period, 15,163 (85.9%) were eligible for the CD4 at ART_{start} outcome and 17,114 (97.0%) for retention outcome analyses. Among 10,426 individuals not receiving care at GHESKIO-Haiti and initiating ART during the study period, 6159 (59.1%) were eligible for the viral suppression analysis (Figure 1).

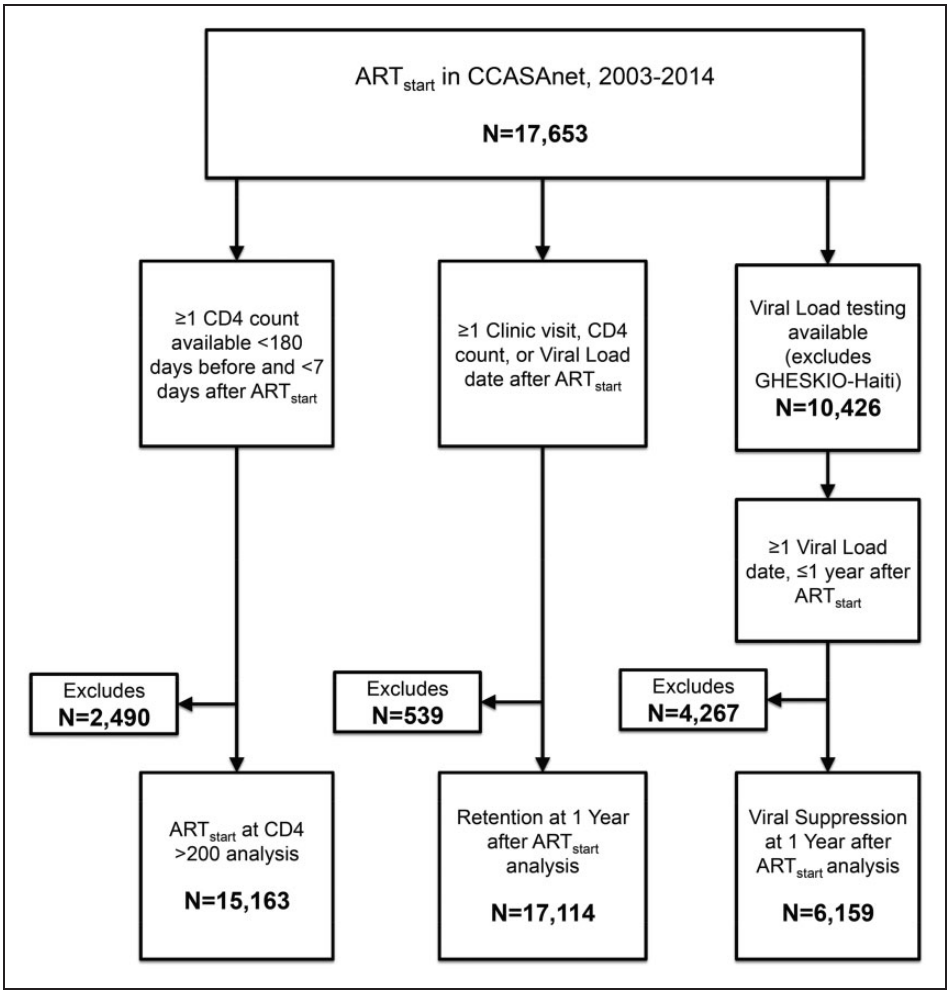

Figure 1. Flow diagram for inclusion in ART_{start} with CD4 cell count >200 cells/mm^3, retention at one year after ART_{start}, and viral suppression at one year after ART_{start} analyses, CCASAnet, 2003–2014. ART: antiretroviral therapy; CCASAnet: Caribbean, Central and South America network for HIV epidemiology.

Among those eligible for CD4 at ART_{start} analysis, 6398 (42.2%) had a CD4 cell count >200 cells/mm^3 at ART_{start}. Median age was 36.7 years (interquartile range [IQR]: 30.2, 44.4), 6060 (40.0%) were female, 3353 (22.1%) had MSM risk, 118 (0.8%) had IDU risk, and 4049 (26.7%) had Hetero risk.

Among those eligible for retention analysis, 12,384 (72.4%) were retained. Median age was 36.6 years (IQR: 30.2, 44.2), 6754 (39.5%) were female, 3929 (23.0%) had MSM risk, 154 (0.9%) had IDU risk, and 4629 (27.1%) had Hetero risk. There were 539 individuals who died <1 year after ART_{start} or were lost to follow-up and were therefore ineligible for retention analyses.

Among those eligible for viral suppression analysis, 4728 (76.8%) were virally suppressed. Median age was 35.8 years (IQR: 29.7, 43.7), 1638 (26.6%) were female, 2480 (40.3%) had MSM risk, 75 (1.2%) had IDU risk, and 2873 (46.7%) had Hetero risk.

The significant differences in most demographic and clinical characteristics (age, sex, and HIV transmission risk category), as well as percent observed in each calendar period, by each outcome (except by sex, for retention) are described in Table 1.

Adjusted proportions achieving ART_{start} with CD4 cell count >200 cells/mm^3 and viral suppression improved over time ($p < 0.05$ trend, each) (Figure 2). In adjusted analyses, older age (>35 years) at ART_{start} was uniformly associated with better retention and viral suppression (aPR = 1.05, 95%CI: 1.01–1.10; aPR = 1.08, 95%CI: 1.03–1.15, for 65 versus 35 for retention and suppression, respectively), but not with ART_{start} at CD4 cell count >200 cells/mm^3 (aPR = 1.05, 95% CI: 0.96–1.15 for 65 versus 35). Females (aPR = 1.22, 95%CI: 1.17–1.28 versus males) and patients with MSM as HIV risk (aPR = 1.24, 95%CI: 1.17–1.31 versus Hetero risk) were more likely to have CD4 cell count >200 cells/mm^3 at ART_{start}. Those with IDU risk were less likely to be retained (aPR = 0.82, 95%CI: 0.71–0.95) while MSM were more likely to achieve viral suppression (aPR = 1.05, 95% CI: 1.01–1.09) compared to those with Hetero risk (Table 2). Upon inclusion of the 539 individuals excluded from the primary analysis in a sensitivity analysis, inferences did not change, with the sole exception of slight decreases in the relative rates of retention in care in more recent years compared to 2008: a decrease of roughly 8% in 2011 and 14% in 2013 (data not shown).

There were also significant intersite differences in each outcome, with the probability of ART_{start} at CD4 cell count >200 cells/mm^3 ranging from 0.31 to 0.59, the probability of retention ranging from 0.65 to 0.83, and the probability of viral suppression ranging from 0.63 to 0.95 across clinical sites (Supplementary Figures 1 to 3, respectively).

Though there was substantial missingness of CD4 at baseline during early years of the study (26.8% of ART initiators in 2003), adjusted probabilities of missing CD4 cell count steadily declined over time and was below 10% for nine out of 11 years in the study period (Figure 3).

Discussion

In this Latin American cohort, achievement of HIV care cascade milestones generally improved over time. However, even with equivalent access to care (denoted by initiation of ART) and adjusting for site differences and secular trends, there were notable demographic and HIV transmission risk factor disparities in these care cascade outcomes.

As noted in prior work, the problems of late ART initiation persist in Latin American settings, even in the face of improved availability and uptake of ART and increasing median CD4 at ART initiation in the region.[5,6] In Mexico, and in prior cross-sectional analyses in our entire cohort, a high prevalence of late ART initiators (76%), primarily due to late testing (diagnosis with a lower CD4 cell count), has also been described.[12,13] This gap, despite progress, has been noted to result in adverse outcomes in both Mexico and Peru, with older individuals, those with IDU risk, and those belonging to sexual minorities at increased risk of advanced disease due to late presentation to care and ART initiation.[14,15] In these same analyses, there was also great variation in the overall prevalence of late ART initiation between Latin American locations, and by population of interest, ranging from 49 to 91%.[12–15] This observation was reflected in the differing adjusted probabilities of ART_{start}, retention, and viral suppression outcomes across our cohort's clinical sites in this analysis.

Over the study period, there was a significant trend toward increased probabilities of initiating ART relatively 'early' (with CD4 cell count >200 cells/mm^3) compared to earlier years. Still, the adjusted probability of early initiation only barely exceeded 0.5 in 2014. Despite this progress toward a goal of either earlier diagnosis and initiation of therapy, or at a minimum, earlier initiation among those successfully linked to care before more advanced HIV disease progression, there obviously remains much room for improvement both in testing and linkage to care. Interestingly, the age trend observed with ART_{start} at higher CD4 counts was counter to that observed for retention and suppression outcomes: younger age groups were more likely to start at higher CD4 counts than their middle-aged counterparts. While this cannot be confirmed without examining prelinkage data, this again suggests those with more advanced disease are less likely to be

Table 1. Distribution of demographic and clinical factors by indicators related to the HIV Cascade of Care after ART_{start} in CCASAnet, 2003–2014 (excludes those with missing outcomes).

	ART_{start} at CD4 cell count >200 cells/mm^3 Yes		No			Retained at one year after ART_{start} Yes		No			VL < 200 at one year after ART_{start} Yes		No		
	N	(%)	N	(%)	P[a]	N	(%)	N	(%)	P[b]	N	(%)	N	(%)	P[c]
Age (yrs.)[d]	36.1	(29.5, 44.0)	36.7	(30.6, 44.3)	<0.001	36.7	(30.5, 44.4)	33.3	(27.2, 40.7)	<0.001	36.0	(30.2, 44.1)	34.8	(28.9, 41.5)	<0.001
Sex					<0.001					0.76					<0.001
Male	3693	(40.6)	5410	(59.4)		7488	(72.3)	2872	(27.7)		3573	(79.0)	948	(21.0)	
Female	2705	(44.6)	3355	(55.4)		4896	(72.5)	1858	(27.5)		1155	(70.5)	483	(29.5)	
HIV risk					<0.001					<0.001					<0.001
MSM	1621	(48.3)	1732	(51.7)		2840	(72.3)	1089	(27.7)		2032	(81.9)	448	(18.1)	
IDU	48	(40.7)	70	(59.3)		84	(54.6)	70	(45.5)		60	(80.0)	15	(20.0)	
Hetero	1615	(39.9)	2434	(60.1)		3287	(71.0)	1342	(29.0)		2041	(71.0)	832	(29.0)	
Other	3114	(40.7)	4529	(59.3)		6173	(73.5)	2229	(26.5)		595	(81.4)	136	(18.6)	
Year of ART start					<0.001					<0.001					<0.001
2003	433	(36.8)	744	(63.2)		1141	(71.6)	452	(28.4)		298	(75.4)	97	(24.6)	
2004	354	(28.3)	897	(71.7)		1235	(76.7)	376	(23.3)		372	(69.0)	167	(31.0)	
2005	261	(26.9)	710	(73.1)		828	(70.7)	343	(29.3)		340	(65.4)	180	(34.6)	
2006	364	(32.5)	755	(67.5)		951	(74.4)	328	(25.7)		328	(56.5)	253	(43.6)	
2007	450	(28.4)	1136	(71.6)		1325	(75.0)	441	(25.0)		365	(56.8)	278	(43.2)	
2008	755	(40.8)	1094	(59.2)		1598	(78.5)	437	(21.5)		601	(81.4)	137	(18.6)	
2009	1081	(51.4)	1022	(48.6)		1699	(72.9)	632	(27.1)		566	(85.5)	96	(14.5)	
2010	1166	(53.1)	1031	(46.9)		1755	(74.1)	614	(25.9)		685	(88.3)	91	(11.7)	
2011	821	(52.9)	730	(47.1)		1235	(73.6)	444	(26.4)		707	(90.1)	78	(9.9)	
2012	400	(52.0)	369	(48.0)		530	(67.7)	253	(32.2)		421	(89.4)	50	(10.6)	
2013	296	(53.2)	260	(46.8)		87	(18.0)	396	(82.0)		45	(91.8)	4	(8.2)	
2014	17	(50)	17	(50)		0	(0)	14	(100)		0	(0)	0	(0)	
Total	6398	(42.2)	8765	(57.8)		12,384	(72.4)	4730	(27.6)		4728	(76.8)	1431	(23.2)	

Numbers displayed as 'N(%)' except for continuous variables, which are 'Median (interquartile range)'

Percentages may not sum to 100 due to rounding

Haiti excluded from viral suppression outcome due to unavailable HIV-1 RNA testing at the site during the study period.

Only odd values of 'Year of ART start' are presented, merely to save space in the table while providing adequate information to assess temporal trends.

ART: antiretroviral therapy; CCASAnet: Caribbean, Central and South America network for HIV epidemiology; Hetero: heterosexual contact; IDU: injection drug use; MSM: men who have sex with men; VL: viral load.

[a]p-value from Chi square test for difference in proportions for categorical variables and Wilcoxon rank sum test for difference in medians for continuous variables, comparing those in whom ART was initiated at CD4+ cell count >200 cells/mm^3 (frequencies shown) versus not (frequencies not shown).

[b]p-value from Chi square test for difference in proportions for categorical variables and Wilcoxon rank sum test for difference in medians for continuous variables, comparing those who were retained in care (≥1 visit at one year ± 90 days after ART initiation) (frequencies shown) versus not (frequencies not shown)

[c]p-value from Chi square test for difference in proportions for categorical variables and Wilcoxon rank sum test for difference in medians for continuous variables, comparing those who had a viral load <200 copies/ml at one year ±90 days after ART initiation (frequencies shown) versus not (frequencies not shown).

[d]Age at ARTstart.

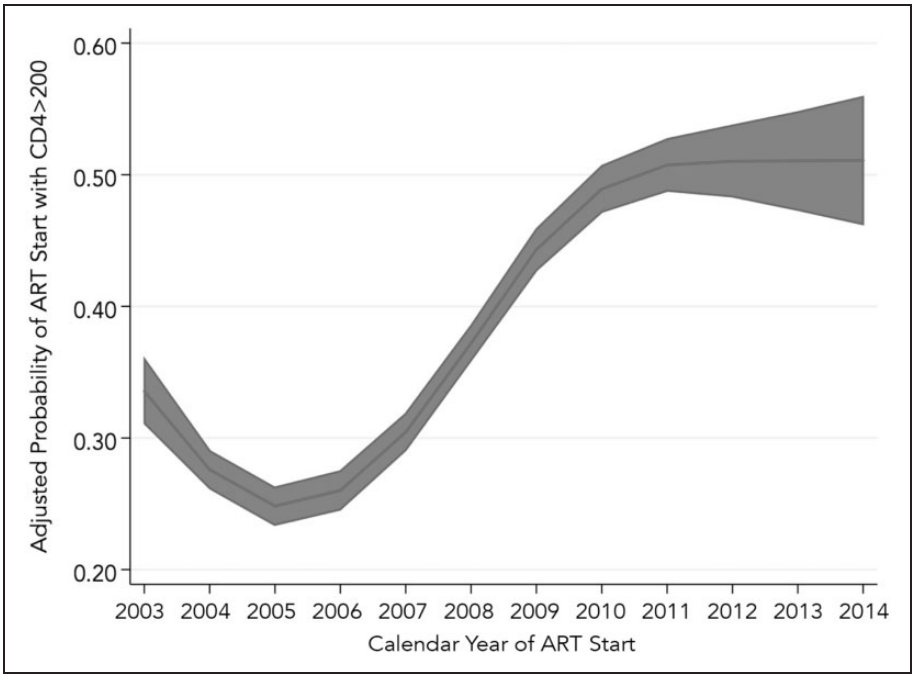

Figure 2. Adjusted probability of ART initiation with a CD4 cell count >200 cells/mm^3, among those initiating ART in CCASAnet, 2003–2014. Probabilities derived from multivariable modified Poisson regression adjusting for age, sex, HIV transmission risk factor, and year of ART initiation; age and year of ART initiation were modeled using restricted cubic splines with four knots. ART: antiretroviral therapy; CCASAnet: Caribbean, Central and South America network for HIV epidemiology.

linked and engaged in care at younger ages. Finally, those with Hetero transmission risk and males initiated later than MSM and females, respectively; this is consistent with other studies finding non-MSM men more likely to present to care with more advanced disease (i.e. lower CD4 counts).[16,17]

In assessing retention immediately following ART_{start}, IDU as HIV transmission risk was associated with the largest significant reduction in retention. The effect size was large (28% reduced probability of retention versus those with Hetero risk) and the unadjusted proportion of those not retained at one year was more than 45%. Though the association was observed in analyses that adjusted for other demographic and clinical characteristics, the influence of unmeasured factors such as psychiatric and mental health comorbidities, structural barriers to care (e.g. criminalization and stigma), and socioeconomic and geographic factors linked to healthcare access (such as income and lack of transportation networks) may be substantial. The IDU risk group was also a small population (<1%) within this cohort, reflecting earlier United Nations estimates of a 0.33% point prevalence of IDU in the general population aged 15–64 in Latin America and the Caribbean.[18] Despite lower prevalence of IDU in Latin America than in Europe (1.26%) or North America (0.66%), these analyses reflect similar inferences as those drawn from related care cascade analyses in our cohort, calling attention to the need to address retention in this risk group and offer targeted responses to the specific needs of this population.[19,20] Younger age also emerged as a significant predictor of poorer retention and viral suppression outcomes, similar to studies in other settings, though the magnitude of these effects was not large.[21,22] This disparity may be related to differences in ongoing healthcare access, risk behaviors, or perhaps active substance use which may be more prevalent in younger populations and which was unaccounted for in these analyses.[23–25] The need for interventions to address substance use and improve screening, particularly in prenatal settings and during prediagnosis engagement in medical care for symptoms, remains a priority.[14,15]

This study had several limitations. First, these results may not be generalizable to persons living with HIV not successfully linked to care, as this population was already engaged in care. More vulnerable populations or those who progressed to death without receiving care may have been excluded, introducing possible bias. Second, there were missing CD4 counts at baseline, affecting the estimation of the ART_{start} at CD4 cell count >200 cells/mm^3 outcome, though this was more pronounced earlier in the study than later (e.g. 27% missing in 2003 versus 9% in 2012); multiple imputation was not used for outcome missingness due to identical covariates available for imputation

Table 2. Factors associated with indicators related to the HIV Cascade of Care after ART_{start} in CCASAnet, 2003–2014: results of multivariable modified Poisson regression.

	ART_{start} at CD4 cell count >200 cells/mm^3 (N = 15,163)		Retained at one year after ART_{start} (N = 17,114)		VL < 200 copies/ml at one year after ART_{start} (N = 6159)	
	aPR	95% CI	aPR	95% CI	aPR	95% CI
Age (versus 35)						
20	**1.35**	(1.25, 1.45)	**0.93**	(0.89, 0.98)	**0.90**	(0.85, 0.97)
25	**1.14**	(1.10, 1.18)	**0.95**	(0.93, 0.97)	**0.95**	(0.92, 0.98)
45	**1.07**	(1.03, 1.10)	**1.05**	(1.03, 1.06)	**1.02**	(1.00, 1.05)
55	**1.07**	(1.01, 1.12)	**1.05**	(1.03, 1.08)	**1.05**	(1.02, 1.09)
65	1.05	(0.96, 1.15)	**1.05**	(1.01, 1.10)	**1.08**	(1.03, 1.15)
Sex						
Male	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Female	**1.22**	(1.17, 1.28)	1.01	(0.99, 1.03)	0.97	(0.93, 1.01)
HIV risk						
MSM	**1.24**	(1.17, 1.31)	1.02	(0.99, 1.05)	**1.05**	(1.01, 1.09)
IDU	0.97	(0.78, 1.20)	**0.82**	(0.71, 0.95)	1.04	(0.93, 1.17)
Hetero	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Other	**1.13**	(1.05, 1.22)	**1.05**	(1.00, 1.10)	**1.07**	(1.02, 1.11)
Year of ART start						
2003	**0.90**	(0.83, 0.97)	**0.95**	(0.92, 0.98)	0.96	(0.91, 1.02)
2004	**0.74**	(0.71, 0.78)	**0.90**	(0.88, 0.92)	**0.83**	(0.80, 0.86)
2005	**0.67**	(0.64, 0.70)	**0.88**	(0.86, 0.90)	**0.77**	(0.74, 0.79)
2006	**0.70**	(0.67, 0.73)	**0.91**	(0.89, 0.93)	**0.79**	(0.76, 081)
2007	**0.82**	(0.80, 0.84)	**0.96**	(0.95, 0.97)	**0.87**	(0.86, 0.89)
2008	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2009	**1.19**	(1.17, 1.21)	0.99	(0.98, 1.00)	**1.12**	(1.11, 1.14)
2010	**1.32**	(1.28, 1.35)	**0.91**	(0.90, 0.92)	**1.20**	(1.18, 1.22)
2011	**1.36**	(1.32, 1.41)	**0.79**	(0.77, 0.81)	**1.22**	(1.19, 1.25)
2012	**1.37**	(1.30, 1.45)	**0.66**	(0.63, 0.69)	**1.21**	(1.17, 1.26)
2013	**1.37**	(1.27, 1.48)	**0.55**	(0.52, 0.59)	**1.20**	(1.14, 1.27)
2014	**1.37**	(1.25, 1.51)	**0.46**	(0.43, 0.50)	**1.19**	(1.11, 1.28)

Bold estimates are statistically significant ($p < 0.05$).

All models adjusted for age and year of ART initiation using restricted cubic splines with four knots; because of this values for 'Age' and 'Year of ART start' denote comparisons between those exact ages/years (not categories or category endpoints) and the respective reference age/year.

Haiti excluded from viral suppression outcome due to unavailable HIV-1 RNA testing at the site during the study period

aPR: adjusted prevalence ratio; ART: antiretroviral therapy; CCASAnet: Caribbean, Central and South America network for HIV epidemiology; Hetero: heterosexual contact; IDU: injection drug use; VL: viral load; MSM: men who have sex with men; 95% CI: 95% confidence interval.

being used in the final model for the outcome. Finally, these data are serial cross-sections, and it may be possible that individuals followed for longer periods would have exhibited different retention or viral suppression likelihoods as they experienced greater exposure to the healthcare system; however, assessments of retention and viral suppression immediately following ART_{start} have been shown to be important prognostic markers of future outcomes, with worse retention typically occurring within the first year of treatment.[26]

Despite these limitations, this remains a valuable evaluation of critical cascade of care outcomes in lower- and middle-income settings in the Western Hemisphere. These findings provide a basis for cautious optimism that, despite persisting disparities affecting younger, male, and IDU populations, there are general improvements in the important cascade milestones of earlier ART_{start}, retention on ART, and viral suppression immediately following ART_{start} in Latin America. Once ART is started, focused efforts must be made to keep younger patients and those with IDU history

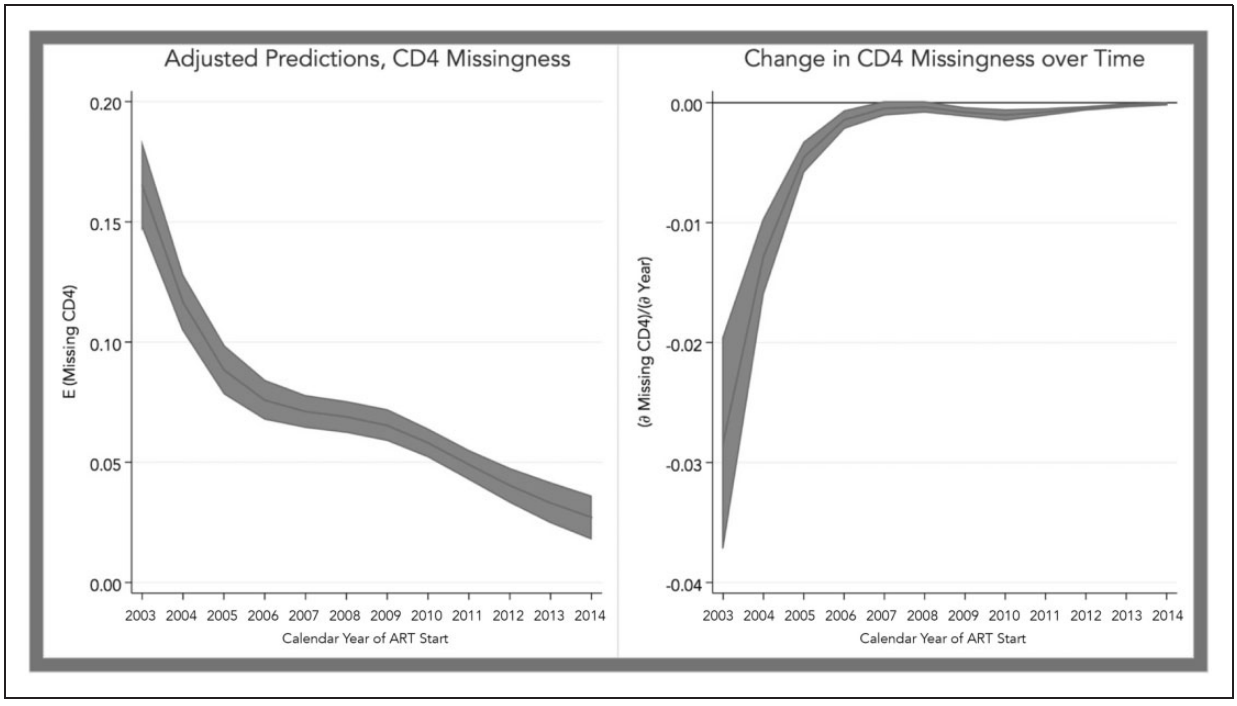

Figure 3. Adjusted probabilities and marginal effects for having a missing CD4+ cell count at ART_{start} by year of ART initiation, CCASAnet, 2003–2014. Probabilities are from linear predictors from multivariable modified Poisson regression of missing CD4+ cell count adjusting for age, sex, HIV transmission risk factor, and year of ART initiation; age and year of ART initiation were modeled using restricted cubic splines with four knots. ART: antiretroviral therapy; CCASAnet: Caribbean, Central and South America network for HIV epidemiology.

engaged in care, to improve goals of sustained viral suppression and attendant survival and transmission benefits.

Acknowledgments

We would also like to acknowledge the patients and these additional personnel at participating CCASAnet sites:
Fundación Huésped, Argentina: Pedro Cahn, Valeria Fink, Omar Sued, Emanuel Dell'Isola, Hector Perez, Jose Valiente, Cleyton Yamamoto
Instituto Nacional de Infectologia-Fiocruz, Brazil: Valdilea Veloso, Paula Luz, Raquel de Boni, Sandra Cardoso Wagner, Ruth Friedman, Ronaldo Moreira.
Universidade Federal de Minas Gerais, Brazil: Jorge Pinto, Flavia Ferreira, Marcelle Maia.
Universidade Federal de São Paulo, Brazil: Regina Célia de Menezes Succi, Daisy Maria Machado, Aida de Fátima Barbosa Gouvêa
Fundación Arriarán, Chile: Maria Fernanda Rodriguez, Gladys Allendes
Les Centres GHESKIO, Haiti: Jean William Pape, Vanessa Rouzier, Adias Marcelin, Christian Perodin.
Hospital Escuela Universitario, Honduras: Marco Tulio Luque.
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico: Juan Sierra Madero, Brenda Crabtree Ramirez, Yanink Caro Vega.
Instituto de Medicina Tropical Alexander von Humboldt, Peru: Eduardo Gotuzzo, Gabriela Carriquiry.
Vanderbilt University Medical Center, USA: Bryan E Shepherd, Timothy Sterling, Karu Jayathilake, Anna K Person, Jessica Castilho, Stephany N Duda, Fernanda Maruri, Hilary Vansell.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the NIH-funded Caribbean, Central and South America network for HIV epidemiology (CCASAnet), a member cohort of the International Epidemiologic Databases to Evaluate AIDS (leDEA) (U01AI069923). This award is funded by the following institutes: National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), the National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), and Office of the Director, National Institutes of Health (OD).

References

1. UNAIDS. AIDSInfo Database, http://aidsinfo.unaids.org/ (accessed 15 August 2016).
2. UNAIDS. *Global AIDS Update 2016*. Geneva: UNAIDS, 2016.
3. Hirnschall G, Harries AD, Easterbrook PJ, et al. The next generation of the World Health Organization's global antiretroviral guidance. *J Int AIDS Soc* 2013; 16: 18757.
4. Gardner EM, McLees MP, Steiner JF, et al. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis* 2011; 52: 793–800.
5. Alonso-González M. *Antiretroviral treatment in the spotlight: a public health analysis in Latin America and the Caribbean*. Pan American Health Organization, ed. Washington: PAHO, 2013, p.52.
6. Avila D, Althoff KN, Mugglin C, et al. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries. *J Acquir Immune Defic Syndr* 2014; 65: e8–16.
7. McGowan CC, Cahn P, Gotuzzo E, et al. Cohort profile: Caribbean, Central and South America Network for HIV research (CCASAnet) collaboration within the International Epidemiologic Databases to Evaluate AIDS (IeDEA) programme. *Int J Epidemiol* 2007; 36: 969–976.
8. Ford MA and Spicer CM. *Monitoring HIV care in the United States: indicators and data systems*. Washington, DC: National Academies Press, 2012.
9. Valdiserri RO, Forsyth AD, Yakovchenko V, et al. Measuring what matters: development of standard HIV core indicators across the U.S. *Department of Health and Human Services*. Public Health Rep 2013; 128: 354–359.
10. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; 159: 702–706.
11. Harrell FE. *Regression modeling strategies with applications to linear models, logistic regression, and survival analysis*. New York: Springer, 2001.
12. Crabtree-Ramírez B, Caro-Vega Y, Belaunzarán-Zamudio F, et al. High prevalence of late diagnosis of HIV in Mexico during the HAART era. Salud publica de Mexico. *SciELO Public Health* 2012; 54: 506–514.
13. Crabtree-Ramírez B, Caro-Vega Y, Shepherd BE, et al. Cross-sectional analysis of late HAART initiation in Latin America and the Caribbean: late testers and late presenters. *PLoS One* 2011; 6: e20272.
14. Martin-Onraët A, Volkow-Fernández P, Alvarez-Wyssmann V, et al. Late diagnosis due to missed opportunities and inadequate screening strategies in HIV infected Mexican women. *AIDS Behav* 2017; 21: 505–514.
15. Maquera-Afaray J, Cvetkovic-Vega A, Cardenas MM, et al. Late diagnosis and advanced disease of HIV in adult patients from a Peruvian social security hospital. *Rev Chilena Infectol* 2016; 33: S20–S26.
16. Yiannoutsos CT, Johnson LF, Boulle A, et al. Estimated mortality of adult HIV-infected patients starting treatment with combination antiretroviral therapy. *Sex Transm Infect* 2012; 88: i33–43.
17. Braitstein P, Boulle A, Nash D, et al. Gender and the use of antiretroviral treatment in resource-constrained settings: findings from a multicenter collaboration. *J Womens Health* 2008; 17: 47–55.
18. Rodríguez CM, Marques LF and Touzé G. HIV and injection drug use in Latin America. *AIDS* 2002; 16: S34–41.
19. Altice FL, Kamarulzaman A, Soriano VV, et al. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. *Lancet* 2010; 376: 367–387.
20. Rebeiro PF, Cesar C, Shepherd BE, et al. Assessing the HIV Care Continuum in Latin America: progress in clinical retention, cART use, and viral suppression. *J Int AIDS Soc* 2016; 19: 20636.
21. Rebeiro P, Althoff KN, Buchacz K, et al. Retention among North American HIV-infected persons in clinical care, 2000–2008. *J Acquir Immune Defic Syndr* 2013; 62: 356–362.
22. Yehia BR, Rebeiro P, Althoff KN, et al. Impact of age on retention in care and viral suppression. *J Acquir Immune Defic Syndr* 2015; 68: 413–419.
23. De Boni RB, Shepherd BE, Grinsztejn B, et al. Substance use and adherence among people living with HIV/AIDS receiving cART in Latin America. *AIDS Behav*. Epub ahead of print 18 April 2016. DOI: 10.1007/s10461-016-1398-6.
24. Vega WA, Aguilar-Gaxiola S, Andrade L, et al. Prevalence and age of onset for drug use in seven international sites: results from the international consortium of psychiatric epidemiology. *Drug Alcohol Depend* 2002; 68: 285–297.
25. Degenhardt L, Whiteford HA, Ferrari AJ, et al. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; 382: 1564–1574.
26. Tassie J-M, Baijal P, Vitoria MA, et al. Trends in retention on antiretroviral therapy in national programs in low-income and middle-income countries. *J Acquir Immune Defic Syndr* 2010; 54: 437–441.