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The Relationship Between the Human Immunodeficiency Virus-1 Transmission Network and the HIV Care Continuum in Los Angeles County

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Background. Public health action combating human immunodeficiency virus (HIV) includes facilitating navigation through the HIV continuum of care: timely diagnosis followed by linkage to care and initiation of antiretroviral therapy to suppress viral replication. Molecular epidemiology can identify rapidly growing HIV genetic transmission clusters. How progression through the care continuum relates to transmission clusters has not been previously characterized.

Methods. We performed a retrospective study on HIV surveillance data from 5226 adult cases in Los Angeles County diagnosed from 2010 through 2014. Genetic transmission clusters were constructed using HIV-TRACE. Cox proportional hazard models were used to estimate the impact of transmission cluster growth on the time intervals between care continuum events. Gamma frailty models incorporated the effect of heterogeneity associated with genetic transmission clusters.

Results. In contrast to our expectations, there were no differences in time to the care continuum events among individuals in clusters with different growth dynamics. However, upon achieving viral suppression, individuals in high growth clusters were slower to experience viral rebound (hazard ratio 0.83, $P = .011$) compared with individuals in low growth clusters. Heterogeneity associated with cluster membership in the timing to each event in the care continuum was highly significant ($P < .001$), with and without adjustment for transmission risk and demographics.

Conclusions. Individuals within the same transmission cluster have more similar trajectories through the HIV care continuum than those across transmission clusters. These findings suggest molecular epidemiology can assist public health officials in identifying clusters of individuals who may benefit from assistance in navigating the HIV care continuum.

Keywords. HIV; care continuum; molecular epidemiology; transmission network; cluster; Cox proportional hazard; gamma frailty.

Key to successful control of human immunodeficiency virus (HIV) is ensuring that individuals newly diagnosed with HIV are linked to care, achieve viral suppression via antiretroviral therapy (ART), and remain in care to prevent recurrence of viremia. Successful navigation through this HIV continuum of care [1, 2] ensures that people living with HIV have greatly reduced risk of transmitting the virus [3, 4]. Rapid linkage to care and adherence to ART improves individual long-term health prognosis [5], and achieving viral suppression virtually eliminates risk of onward viral transmission [6, 7]. These tenets guide HIV public health activities worldwide [5, 8–10].

Molecular epidemiology can identify and characterize genetic clusters of HIV transmission [11, 12], which can assist in prioritizing cases for public health services (e.g., linkage or re-linkage to care to help individuals achieve sustained suppression of viral replication) [13–15]. These clusters are comprised of individuals whose HIV is sufficiently genetically similar as to imply direct or indirect epidemiological connections among their members [16, 17]. The frequency of clustering is most strongly associated with reported transmission risk and demography [17–20]; however, other factors such as sampling density and time between infection and diagnosis can substantially influence clustering propensity [21–23]. Nonetheless, in the US surveillance setting, HIV genetic clusters with evidence of recent transmission are disproportionately likely to give rise to subsequent cases of HIV [18, 19] and can have transmission rates 8 times the national average [24]. Furthermore, people in these growing transmission clusters with unsuppressed viral replication are associated with future incident HIV infections [25]. We hypothesize that individuals most likely to be associated with future cluster growth (i.e., those in rapidly growing clusters at the time of HIV diagnosis) will take longer to progress through the HIV care continuum.

Here we incorporate molecular HIV surveillance data from Los Angeles County (LAC) in analyses of predictors

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of time to events in the care continuum employing both semiparametric and parametric frailty survival models.

METHODS

Data Source

The Division of HIV and STD Programs (DHSP) in LAC Department of Public Health (DPH) has been conducting mandatory named-based HIV surveillance since 2006, which includes reporting results of viral load (VL) and $CD4^+$ T-cell count laboratory tests, as well as human immunodeficiency virus type 1 protease and reverse transcriptase (*pol*) genetic sequences generated during routine antiretroviral drug resistance testing [26]. All reported HIV cases in LAC are stored in the Enhanced HIV/AIDS Reporting System (eHARS); approximately 10–14% of people living with HIV in LAC are undiagnosed [27]. Additional case-level metadata in eHARS include date, age, and ZIP code at diagnosis, current ZIP code, vital status, race/ethnicity, sex at birth, and transmission risk factor. HIV transmission risk categories were assigned in a hierarchical order: people who inject drugs (PWID), men who have sex with men (MSM), heterosexual contact, and unidentified risk. MSM who reported injection drug use were grouped with PWID. Cases with no reported risk were classified as "unknown risk" [28]. Stage of infection at HIV diagnosis was defined using the first $CD4^+$ count postdiagnosis: ≥500 cells/mL, 200–499 cells/mL, and < 200 cells/mL. Socioeconomic status was assessed at the level of residential ZIP code at diagnosis: the fraction of the population living below the 100% federal poverty level [29].

Inclusion Criteria

We performed a population-based retrospective study using HIV/AIDS surveillance data from LAC DPH on 22 398 individuals who resided or received HIV care in LAC and had a reported HIV *pol* sequence. We restricted our statistical analysis to the 5226 cases diagnosed from January 2010 through December 2014, representing 75% of all cases diagnosed during these years (Supplementary Table 1). This time-period was chosen to minimize gaps or delays in reporting prior to 2010 and to ensure at least 2 years of follow-up laboratory data. It also predates the era of cluster-based investigations in LAC. Included cases also met the following criteria: (i) a reported HIV *pol* genotype; (ii) diagnosed in and current resident of LAC; (iii) ≥ 13 years of age at HIV diagnosis; (iv) detectable first VL (≥200 copies/mL); and (v) complete month and year reported for time of diagnosis and VL/$CD4^+$ lab results. Our final data set was enriched for older individuals, Latinos, MSM, and individuals with later disease stage at diagnosis (Supplementary Table 1).

Transmission Network

A molecular transmission network was constructed using HIV-TRACE [30] from 22 398 individuals whose HIV *pol* sequences were reported to LAC DPH between 2006 through 2016; characteristics of this network were previously described [31]. To build the network, cases were linked to each other in the transmission network if their pairwise genetic distance was ≤ 0.015 substitutions/site. This threshold is in accordance with the expected divergence between sequences within an individual [32] and the genetic distance inferred between named HIV risk partners [33]. Linked cases were combined into clusters, wherein all members of a cluster are linked to at least 1 other member of that cluster.

Cluster Growth

For each individual, on the date of their diagnosis, we determined the size of their cluster (i.e., only including members linked through cases diagnosed at or prior to that date). Cluster growth was measured by calculating the number of newly diagnosed cases linked in a cluster in the previous year divided by the square root of the cluster size. People with a reported HIV sequence but unclustered in the network had a cluster growth value of 0. This cluster square root growth metric, referred to as cluster growth for the remainder of this article, is a reliable predictor of future cluster growth in a US HIV surveillance setting [18]. Cluster growth at diagnosis was categorized as high (≥75th percentile), medium (>50th to < 75th percentile), and low (≤50th percentile).

Outcome Measures

We assessed time to each event in the HIV care continuum and potential failure in treatment adherence at the individual level using the date of laboratory test as a proxy for medical office visit for the following endpoints: (i) months from diagnosis to receipt of care (i.e., first VL or $CD4^+$ after diagnosis); (ii) months from care to viral suppression (i.e., first VL < 200 copies/mL); (iii) months from diagnosis to viral suppression; and (iv) months from viral suppression to viral rebound (i.e., first postsuppression VL ≥ 1500 copies/mL). Inclusion in statistical analysis required having a reported HIV sequence and at least 1 follow-up VL/$CD4^+$ measurement after reaching a previous continuum event.

Statistical Analyses

Ordinal logistic regression was used to compare cases diagnosed in high growth clusters with cases in medium and low growth clusters. Parametric and semiparametric models were constructed to adjust for covariates in STATA 15.1, College Station, TX: StataCorp LP.

Semiparametric Modeling

Separate Cox proportional hazard models [34] with robust standard errors were built to analyze times between events in the care continuum. All cases were followed until death or the administrative censoring date of December 2016. To investigate the impact of delayed reporting or interruptions in engagement in care, we performed sensitivity analyses that restricted consideration to only individuals who had at least one follow-up

visit within 1 year after initial linkage to care. Viral suppression can occur any time between last VL ≥ 200 copies/mL and first VL < 200 copies/mL, and viral rebound can occur anytime between last VL < 200 copies/mL and first subsequent VL ≥ 1500 copies/mL. Therefore, we repeated the restricted analysis using methods that accommodate interval censoring [35] to account for our inability to observe exact event dates of achieving viral suppression or viral rebound; only the interval in which the event occurred is observed. To evaluate whether the time interval relationship between cluster growth and time to viral suppression was modified by time to linkage to care, we tested for interaction between cluster growth and linkage to care within 2 months after diagnosis. Model fit for Cox models were assessed using Schoenfeld and Cox-Snell residuals.

Parametric Shared Frailty Model

To identify the appropriate survival model and account for heterogeneity between transmission clusters, we conducted additional parametric analyses using exponential, Weibull, log-logistic, and log-normal baseline hazard functions in a shared gamma frailty [36, 37] framework. The log-normal distribution provided the best fit according to Akaike's information criterion (AIC) (Supplementary Table 2). Sensitivity analysis of the frailty variance to exclusion of covariates and nonclustered individuals were also conducted.

RESULTS

Individuals included in our analysis of the care continuum were predominantly male (91%), Hispanic/Latino (51%), and MSM (71%) (Table 1). The adjusted odds of being in a high growth cluster (≥75th percentile) at date of diagnosis, compared with being in a medium or low growth cluster, were higher for males and cases with $CD4^+$ ≥500 cells/mL at diagnosis (Table 1). Adjusted odds of being in a high growth cluster was lower for individuals ≥ 30 years old at diagnosis, blacks compared with whites, and cases with unidentified transmission risk compared with MSM.

We investigated the time between events in the HIV care continuum: (i) diagnosis to linkage to care, (ii) linkage to care to viral suppression, and (iii) viral suppression to viral rebound. Of cases linked to care, 92% achieved viral suppression and 26% experienced viral rebound postsuppression (Table 2); Median time from diagnosis to care was < 1 month, care to suppression was 5 months, and diagnosis to suppression was 6 months. The majority of individuals achieved suppression within 2 visits after receiving care (Supplementary Figure 1). The greater number of consecutive visits prior to viral suppression is associated with a longer time to suppression (Supplementary Figure 2), supporting the belief that longer observed times to suppression are not driven primarily by the visit schedule.

Cluster Growth and Time to Care Continuum Events

Investigation of the effect of cluster growth at HIV diagnosis on time to events in the care continuum revealed no significant differences in the time to each event between cases in medium and low growth clusters at time of diagnosis (Cox proportional hazards; Figure 1 and Table 3). However, in contrast to our initial hypothesis, cases in high growth clusters at diagnosis were more rapidly linked to care (adjusted hazard ratio [HR] 1.06; $P = .028$) and achieved suppression more rapidly after diagnosis (HR 1.08; $P = .034$), compared with cases in low growth clusters. Upon achieving viral suppression, cases in high growth clusters were slower to rebound (HR 0.83; $P = .011$), compared with cases in low growth clusters.

The time from diagnosis to suppression was modified by an indicator of linkage to care within 2 months of diagnosis (Cox proportional hazards model; $P < .05$). Among the 988 cases (19%) not linked to care within 2 months, cases in the medium (HR 1.26, $P = .005$) and high (HR 1.29, $P = .003$) growth clusters achieved suppression faster than cases in low growth clusters (Figure 2). However, there was no significant difference in the time to viral suppression between individuals who were linked to care within 2 months of diagnosis. Therefore, the faster average time from diagnosis to suppression for cases in high growth clusters is likely attributable to the small fraction of cases not linked to care within 2 months of diagnosis (Figure 1).

To assess sensitivity of results to analytical method, we compared results from a Cox regression with those from a multivariable logistic regression of the odds of being linked to care in 2, 6, and 12 months. Results of these models were consistent; among cases not linked to care within 2 months of diagnosis, those in high growth clusters at diagnosis had increased odds of being linked to care in 6 ($P = .007$) and 12 ($P = .004$) months compared with cases in low growth clusters at diagnosis (Supplementary Table 3).

Excluding Out-of-Care Cases and Interval Censoring

To ensure these results were not primarily driven by cases who fell out of care, we repeated the Cox regression but including only cases with a follow-up visit within 1 year after being linked to care (Table 3). In the restricted analyses, the relationships between cluster growth at diagnosis and (i) diagnosis to care, (ii) care to suppression, and (iii) suppression to rebound were unchanged. However, the time from diagnosis to suppression was no longer significant ($P = .30$). This result suggests that the difference in time from diagnosis to suppression may be driven by cases diagnosed in low growth clusters who disproportionately fell out of care. The same pattern was observed when we restricted this analysis to only cases linked to care within a year of being diagnosed. Furthermore, to account for the inherent difference between event time (i.e., viral

Table 1. Characteristics of Cases in the Los Angeles County HIV Transmission Network Diagnosed in High, Medium, and Low Growth Clusters Using Multivariable Ordinal Logistic Regression[a]

Attributes	Total n (%)[2]	Low Cluster Growth n (%)[b]	Medium Cluster Growth n (%) [b]	High Cluster Growth n (%) [b]	AOR[c]	95% CI
Total population	5226 (100)	2621 (100)	1301 (100)	1304 (100)	–	–
Birth sex						
Male	4749 (91)	2317 (88)	1203 (92)	1229 (94)	1.30	1.02–1.67
Female	477 (9)	304 (12)	98 (8)	75 (6)	Ref.	–
Age at diagnosis						
13–19	177 (3)	59 (2)	58 (4)	60 (5)	1.25	.94–1.66
20–29	1813 (35)	730 (28)	482 (37)	501 (46)	Ref.	–
30–39	1493 (29)	772 (29)	370 (28)	351 (27)	0.65	.57–.74
40–49	1100 (21)	645 (25)	266 (21)	189 (15)	0.52	.45–.61
50–59	521 (10)	329 (13)	102 (8)	88 (7)	0.49	.40–.60
60+	122 (2)	86 (3)	21 (2)	15 (1)	0.35	.24–.53
Race/ethnicity						
White	1124(21)	557 (21)	288 (22)	279 (21)	Ref.	–
Black/African American	1040 (20)	574 (22)	237 (18)	229 (18)	0.79	.67–.95
Hispanic/Latino	2655 (51)	1264 (48)	695 (53)	696 (53)	1.07	.92–1.23
Asian/Pacific Islander	240 (5)	134 (5)	46 (4)	60 (5)	0.80	.61–1.06
Other[d]	167 (3)	92 (4)	35 (3)	40 (3)	0.75	.55–1.04
Poverty level at ZIP code of diagnosis[e]						
25th percentile	487 (9)	249 (10)	115 (9)	123 (9)	Ref.	–
50th percentile	989 (19)	474 (18)	246 (19)	269 (21)	1.00	.81–1.24
75th percentile	1332 (26)	711 (27)	316 (24)	305 (23)	0.83	.68–1.02
>75th percentile	2418 (46)	1187 (45)	624 (48)	607 (47)	0.97	.80–1.18
$CD4^+$ count at diagnosis						
≥500 cells/mm^3	1561 (30)	681 (26)	438 (34)	442 (34)	1.88	1.62–2.18
200–499 cells/mm^3	2247 (43)	1030 (39)	587 (45)	630 (48)	1.80	1.57–2.06
<200 cells/mm^3	1412 (27)	908 (35)	274 (21)	230 (18)	Ref.	–
Missing	6 (<1)	2 (<1)	2 (<1)	2 (<1)	2.36	.55–10.07
Transmission risk						
MSM	3729 (71)	1741 (66)	979 (75)	1009 (77)	Ref.	–
PWID[f]	224 (4)	113 (4)	59 (5)	52 (4)	0.96	.74–1.25
Heterosexual sexual contact	155 (3)	95 (4)	34 (3)	26 (2)	0.86	.59–1.28
Unidentified	1118 (22)	672 (26)	229 (17)	217 (17)	0.77	.66–.89

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; MSM, men who have sex with men; PWID, people who inject drugs.

[a]Likelihood ratio test of proportional odds assumption was performed to assess whether the associated log odds is equal to that comparing high and medium growth clusters to low growth clusters ($P = .187$).

[b]Column percentages.

[c]Adjusted odds ratio comparing cases in high growth clusters at diagnosis compared with cases in low and medium growth clusters at diagnosis.

[d]Includes American Indian/Alaskan Native, multiracial, or unknown race/ethnicity.

[e]Fraction of population in ZIP code of diagnosis living below 100% of the federal poverty level.

[f]PWID includes MSM who reported injection drug use.

suppression or rebound) and visit time (i.e., the date of laboratory test), the analysis was repeated using methods that accommodate interval censoring; results of these restricted models were unchanged.

Cluster Membership Predicts Time to Care Continuum Event

We then explored the relationship between cluster growth and outcomes in the care continuum using parametric models. The times from diagnosis to care, care to suppression and diagnosis to suppression were, once again, were not significantly different among cases diagnosed in low, medium, and high growth clusters in the log-normal gamma frailty model (Table 4). However, time from suppression to rebound remained significantly longer for cases diagnosed in high growth clusters (adjusted time ratio [TR] 1.38; $P < .001$). These results were robust to inclusion only of individuals with at least one follow-up visit within 1 year after first linkage to care (TR 1.36; $P = .002$). For comparison, the frailty model was also conducted with the commonly used Weibull distribution [38], and the time ratio results were qualitatively similar to those obtained from a log-normal baseline hazard (Supplementary Table 4).

We then investigated the role of heterogeneity among genetic clusters in time to events in the care continuum (i.e., treating cluster membership as a random effect) using a shared gamma

Table 2. Proportion of Individuals That Progressed to Each Event in the Care Continuum and the Median Survival Time to Each Event

	All Cases				Restricted to Cases With Follow-up Visit Within 1 year After Initial Linkage to Care			
Continuum Interval	Total Cases at Start[a]	Total Cases at End[b]	% Reached Outcome	Median Months to Outcome (IQR)[c]	Total Cases at Start[a]	Total Cases at End[b]	% Reached Outcome	Median Months to Outcome (IQR)[c]
Diagnosis to care	5,226	5,225	100%	0 (0–1)	4,944	4,944	100%	0 (0–1)
Care to suppression	5,204	4,791	92%	5 (3–10)	4,944	4,604	93%	5 (3–9)
Diagnosis to suppression	5,226	4,791	92%	6 (4–13)	4,944	4,604	93%	6 (4–12)
Suppression to rebound	4,646	1,223	26%	15 (7–28)	4,482	1,176	26%	15 (7–28)

Abbreviation: IQR, interquartile range.

[a]Cases with at least 1 viral load after the beginning of each interval are eligible.

[b]Cases not meeting the end point are censored.

[c]Median survival times.

frailty model. Along every event interval in the care continuum, the variance of the cluster random effect was highly significant (Table 4). This finding was also observed when we restricted the analysis to individuals with at least 1 follow-up visit within a year of first linkage to care.

To ensure the variance of cluster random effect was not driven by the 2035 cases (39%) that did not cluster in the HIV transmission network, we performed additional sensitivity analyses for the outcome of time from diagnosis to suppression. These analyses included only cases linked genetically to at least one other case diagnosed from 2010 through 2014 (i.e., cluster size ≥ 2). The variance remained highly significant using both log normal and Weibull baseline hazard models ($P < .001$; Supplementary Table 5).

Even after adjusting for individual level confounders (i.e., birth sex, age at diagnosis, race/ethnicity, $CD4^+$ count at diagnosis, and transmission risk), the variance of the cluster random effect remained significant ($P < .001$); the magnitude of the estimate effect was reduced by a third (Supplementary Table 5). For all events in the HIV care continuum, event times were more similar within than across transmission clusters (Supplementary Figure 3).

DISCUSSION

We characterized the relationship between the HIV transmission network and the care continuum using HIV surveillance data from individuals diagnosed and residing in Los Angeles County. The timing of progression to events in the HIV care continuum was more similar among individuals who were members of the same transmission cluster than among individuals in different transmission clusters. For example, individuals in clusters with members that take longer to achieve viral suppression are themselves more likely to take longer to

Table 3. Adjusted Hazard Ratios for Months to Events in the Continuum of Care by Cluster Growth

		Cox Proportional Hazard					
		All Cases			Restricted to Cases With Follow-up Visit Within 1 year After Initial Linkage to Care		
Continuum Interval	Cluster Growth	HR[a]	95% CI	*P*	HR[a]	95% CI	*P*
Diagnosis to care	Low	Ref.	–	–	Ref.	–	–
	Medium	1.04	.99–1.10	.084	1.05	.99–1.11	.066
	High	1.06	1.01–1.12	.028	1.07	1.01–1.12	.024
Care to suppression	Low	Ref.	–	–	Ref.	–	–
	Medium	0.98	.91–1.05	.489	0.99	.93–1.07	.934
	High	1.03	.96–1.11	.357	0.98	.92–1.06	.661
Diagnosis to suppression	Low	Ref.	–	–	Ref.	–	–
	Medium	1.01	.94–1.08	.749	1.04	.97–1.11	.318
	High	1.08	1.01–1.16	.034	1.04	.97–1.11	.302
Suppression to rebound	Low	Ref.	–	–	Ref.	–	–
	Medium	0.98	.85–1.13	.806	0.99	.86–1.13	.837
	High	0.83	.72–.96	.011	0.84	.73–.97	.018

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Adjusted hazard ratio adjusted for age at diagnosis, race/ethnicity, poverty level at ZIP code of diagnosis, transmission risk category, birth sex, and $CD4^+$ count at diagnosis.

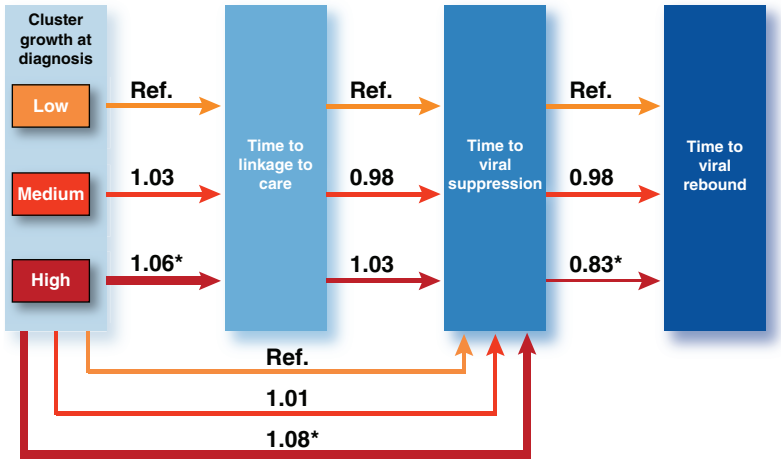

Figure 1. Flow diagram of the human immunodefiency virus care continuum based on cluster growth at diagnosis. Values indiciate adjusted hazard ratios, with low cluster growth at diagnosis serving as the reference category. Arrows show path between care continuum events (i.e., diagnosis to care). Thick arrows denote significantly increased rate of progression between care continuum events; thin arrows denote significantly slower rate of progression between care continuum events. Asterisks indicate significance at $P < .05$ in the Cox proportional hazards model.

achieve suppression. This effect extends beyond what is captured by demographic, laboratory, and transmission risk surveillance data, which themselves tend to be assortative across the transmission network [39]. Therefore, epidemiological connections informed by genetic linkage can potentially inform future progression through the care continuum. We suggest that public health services related to linkage-to-care, viremia support, and return-to-care could be prioritized for individuals in clusters whose other members have failed to timely reach events in the care continuum or have fallen out-of-care.

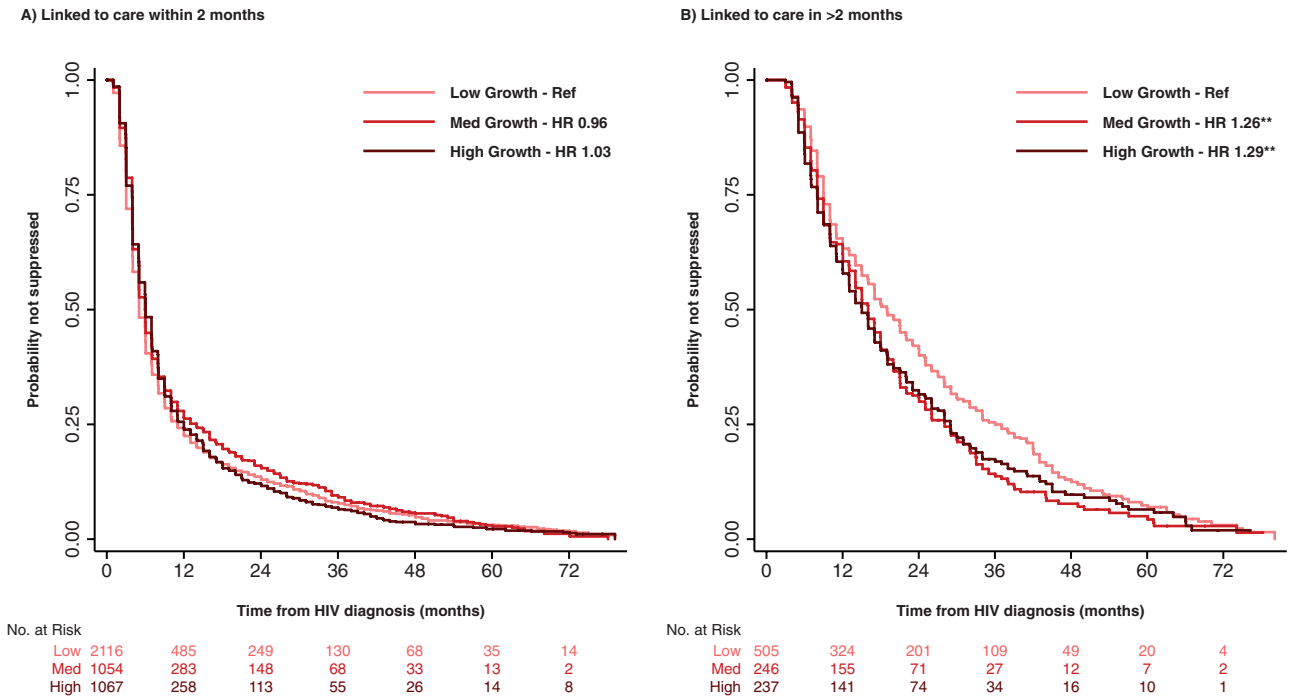

Figure 2. Kaplan-Meier survival estimates and adjusted HRs of time from diagnosis to viral suppression by linked to care in 2 months. Median months from diagnosis to suppression is 5 (IQR 3–11), 6 (IQR 4–14), and 6 (IQR 4–12) if linked to care in 2 months for low, medium and high growing clusters, respectively. Median months from diagnosis to suppression is 19 (IQR 9–36), 16 (IQR 8–28), and 15 (IQR 8–29) if linked to care >2 months after diagnosis for low, medium and high growing clusters, respectively. There was no significant difference in hazards for cases linked to care within 2 months. For cases linked to care in >2 months after diagnosis, medium and high growing clusters reached suppression 26–29% faster ($P < .01$) compared with low growing clusters, after adjusting for age at diagnosis, race/ethnicity, poverty level at ZIP code diagnosis, transmission risk category, birth sex, and $CD4^+$ at diagnosis. Abbreviations: HIV, human immunodeficiency virus; HR, hazard ratio; IQR, interquartile range.

Table 4. Adjusted Time Ratios for Months to Events in the Continuum of Care by Cluster Growth Accounting for Genetic Heterogeneity (i.e., Membership in Same Transmission Cluster) Using Gamma Frailty Model

		Log Normal Gamma Shared Frailty							
		All Cases				Restricted to Cases With Follow-up Visit Within 1 year After Initial Linkage to Care			
Continuum Interval	Cluster Growth	TR[a]	95% CI	θ[b]	*P*	TR[a]	95% CI	θ[b]	*P*
Diagnosis to care	Low	Ref.	…			Ref.	…		
	Medium	0.98	.85–1.14		.848	0.98	.84–1.14		.770
	High	0.91	.77–1.07		.252	0.93	.79–1.09		.355
				0.11	<.001			0.11	<.001
Care to suppression	Low	Ref.	…			Ref.	…		
	Medium	1.07	.99–1.14		.061	1.05	.98–1.12		.162
	High	1.04	.96–1.11		.349	1.07	.99–1.15		.053
				0.28	<.001			0.28	<.001
Diagnosis to suppression	Low	Ref.	…			Ref.	…		
	Medium	1.04	.97–1.11		.229	1.02	.96–1.09		.473
	High	0.99	.92–1.07		.873	1.02	.95–1.10		.519
				0.22	<.001			0.25	<.001
Suppression to rebound	Low	Ref.	…			Ref.	…		
	Medium	1.10	.91–1.31		.321	1.09	.91–1.32		.345
	High	1.38	1.14–1.68		.001	1.36	1.12–1.66		.002
				0.13	.005			0.12	.007

Abbreviations: CI, confidence interval; TR, time ratio.

[a]Time ratios > 1 indicate slower time to event, whereas time ratios < 1 indicates accelerated time to event.

[b]Theta is the variability of the gamma frailty across groups of cluster estimated from the data with a mean of 1.

Our results do not support the hypothesis that continued expansion of rapidly growing clusters is associated with prolonged viremia due to slower progression through the care continuum. In fact, we estimated that individuals in rapidly growing clusters at diagnosis took 17% longer to experience postsuppression viral rebound. Furthermore, among individuals who took longer than 2 months after diagnosis to be linked to care, those in rapidly growing clusters at diagnosis became virally suppressed 29% faster. LAC DPH did not initiate cluster investigation and response until after 2016, so these findings are not influenced by cluster-based interventions. We acknowledge that cluster growth is influenced by access to and engagement with care, including HIV testing: a higher proportion of cases in low growth clusters had $CD4^+$ count < 200 copies/mm^3 at diagnosis. The shorter time to viral rebound for cases in low growing clusters may be related to this decreased engagement with care.

The HIV care continuum is typically evaluated at a population level over a fixed time period (e.g., 51% of people living with HIV in the US were virally suppressed in 2015 [1]). However, the HIV transmission network comprises individuals who may or may not be linked to care or virally suppressed at any given time point. This discrepancy informed our study design: our approach focused on the time from linkage to care to virologic suppression, rather than on the proportion of people who successfully transition from linkage to suppression in the next year. Furthermore, our study design did not permit analysis of retention in care, which relies on reported laboratory results whose completeness is around 80% [40]. Hence, missing lab results are an unreliable indicator of care status. In addition, relocation outside of LAC results in erroneous designation of out-of-care status. Therefore, the relationship between out-of-care status and the transmission network would be better assessed at the state or federal level.

Our conclusions are limited to individuals with reported laboratory data. Cluster growth cannot be assessed for individuals without a reported HIV sequence, and characterizing progression through the care continuum relies on reported laboratory data. Nonetheless, among observable cases, our results demonstrate the underlying relationship between shared membership in an HIV transmission cluster and progression through the care continuum.

We described the relationship between the HIV transmission network and the rate of progression through the HIV continuum of care in Los Angeles County. Planned efforts to reduce HIV incidence through the *Ending the HIV Epidemic* initiative [10] would benefit from further study of this relationship.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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