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Predictors of HIV Molecular Cluster Membership and Implications for Partner Services

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Abstract

Public health surveillance data used in HIV molecular cluster analyses lack contextual information that is available from partner services (PS) data. Integrating these data sources in retrospective analyses can enrich understanding of the risk profile of people in clusters. In this study, HIV molecular clusters were identified and matched to information on partners and other information gleaned at the time of diagnosis, including coinfection with syphilis. We aimed to produce a more complete understanding of molecular cluster membership in Houston, Texas, a city ranking ninth nationally in rate of new HIV diagnoses that may benefit from retrospective matched analyses between molecular and PS data to inform future intervention. Data from PS were matched to molecular HIV records of people newly diagnosed from 2012 to 2018. By conducting analyses in HIV-TRACE (TRAnsmission Cluster Engine) using viral genetic sequences, molecular clusters were detected. Multivariable logistic regression models were used to estimate the association between molecular cluster membership and completion of a PS interview, number of named partners, and syphilis coinfection. Using data from 4,035 people who had a viral genetic sequence and matched PS records, molecular cluster membership was not significantly associated with completion of a PS interview. Among those with sequences who completed a PS interview ($n = 3{,}869$), 45.3% ($n = 1{,}753$) clustered. Molecular cluster membership was significantly associated with naming 1 or 3+ partners compared with not naming any partners [adjusted odds ratio, aOR: 1.27 (95% confidence interval, CI: 1.08–1.50), $p = .003$ and aOR: 1.38 (95% CI: 1.06–1.81), $p = .02$]. Alone, coinfection with syphilis was not significantly associated with molecular cluster membership. Syphilis coinfection was associated with molecular cluster membership when coupled with incarceration [aOR: 1.91 (95% CI: 1.08–3.38), $p = .03$], a risk for treatment interruption. Enhanced intervention among those with similar profiles, such as people coinfected with other risks, may be warranted.

Keywords: HIV, cluster detection and response, partner services, molecular surveillance, syphilis coinfection

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Introduction

HIV burdens some geographic communities more than others, resulting in differential social and fiscal impacts. In the United States, major metropolitan areas are most affected, and the South has the highest rate of people newly diagnosed with HIV.[1] Similar viral genetic sequences among people may indicate putative transmission partners,[2] moreover groups of people with related HIV sequences may indicate a cluster of linked transmission events.[3] Interrupting disease transmission by curtailing growth of molecular clusters may be impactful because HIV transmission rates within molecular clusters are exceptionally high.[4] Harnessing molecular cluster analysis to inform intervention in the South presents an opportunity to further focus prevention efforts where HIV is most concentrated.

Houston, Texas is the largest Southern city with over 2.3 million residents,[5] and the metro area ranks ninth in rate of new HIV diagnoses.[6] The majority of Houston falls within Harris County, a county lagging behind both the United States and Texas in retention in care and viral suppression.[7] In Texas, HIV genetic sequences became reportable to surveillance in 2010, allowing for the systematic collection of molecular data by health departments,[8] including the Houston Health Department (HHD).

The HHD is responsible for partner identification and notification (''partner services'' or ''PS'') among people newly diagnosed with HIV and/or other priority sexually transmitted diseases (STD) in Houston/Harris County. When a person is successfully interviewed, a Disease Intervention Specialist (DIS) elicits information about sexual (and for HIV, needle-sharing) partners and social network members who may be at risk. The DIS then attempts partner notification: confidentially notifying people of a potential exposure and offering services, such as testing. Despite robust data collection during this process, results of matched interview and HIV-1 genetic sequence data have rarely been published in the context of a major Southern U.S. city.

Although PS has been utilized since the 1930s,[9] effectiveness may wane if members of growing molecular clusters are unwilling to complete interviews and unwilling or unable to name partners. PS has expanded to include linkage to HIV medical care or, for those who are HIV negative, a referral to preexposure prophylaxis (PrEP). Continued transmission, as evidenced by molecular cluster membership, could indicate differential uptake of PS among cluster versus noncluster members, whereby interruption of transmission through antiretroviral therapy (ART) or PrEP has not occurred. Therefore, we sought to determine if PS uptake through completion of an interview differed for molecular cluster members versus individuals not in molecular clusters, and whether data collected during PS could be used to improve current PS or HIV prevention services.

A better understanding of risk information obtained at the time of HIV diagnosis through the conduct of PS, such as coinfection with syphilis, number of named partners, incarceration history, and drug use may also assist in discovery of differences between molecular cluster and noncluster members. An analysis of Houston and Chicago men who have sex with men (MSM) revealed an association between HIV/syphilis coinfection and membership in a social network with others living with HIV or coinfected.[10] We seek to build upon this work, moving from social relatedness to genetic relatedness, by uncovering associations between syphilis coinfection and molecular cluster membership. The more we understand about the risk profile of members of transmission networks, the better we can plan and implement effective and efficient preventative efforts. Research has demonstrated the value of combining sequence and PS data to better understand transmission networks,[3,11] and we will report outcomes of this strategy for the first time in the large, Southern city of Houston.

Materials and Methods

Positive HIV/STD test results and new diagnoses are reported to the HHD by medical providers and/or laboratories. New diagnoses of HIV are investigated, and pertinent demographic, transmission risk, and clinical data are abstracted from medical records or provider report. During the study period, HIV surveillance data and genetic sequences were entered into the Enhanced HIV/AIDS Reporting System (eHARS). Reactive syphilis test results and PS data were stored in STD*MIS.

Individual-level matching between eHARS and STD*MIS datasets was conducted through a combination of automated and manual review. Automated matching utilized a modified version of an SAS program from previous research that constructs combinations of first name, last name, and birth date.[12] Exact matching was attempted, and inexact matches were possible through phonetic matching. All Texas eHARS records ($n = 176{,}156$) entered by January 1, 2019 were processed and a total of 87,543 records (49.7%) matched (see Supplementary Digital Content on record matching). Demographic variables and laboratory information were populated from surveillance records, while syphilis coinfection, number of named partners, incarceration history, drug use, and other risk factors were obtained from PS records (see Supplementary Digital Content on variables of interest).

The cohort for this study was persons who were reported through surveillance as living with HIV and entered in eHARS by January 1, 2019. For inclusion, each person must have been newly diagnosed between January 1, 2012 through December 31, 2018 and resided in Houston, Kingwood (annexed suburb), and/or Harris County at the time of diagnosis or at some point after diagnosis. If a person met these residential criteria but had sequences reported from elsewhere in Texas, those sequences were still included in analyses (e.g., if a person was diagnosed in Houston but their sequence was from a Dallas, TX facility/provider, the sequence would be included). Anyone under 13 years of age at diagnosis or with perinatal transmission risk was excluded.

HIV-TRACE (TRAnsmission Cluster Engine) is a tool available to researchers for analysis of HIV genetic sequences.[13,14] A secure, specialized version is available to health departments. HIV-TRACE determines the relatedness of sequences by calculating pairwise genetic distances, a measure of similarity. Smaller genetic distances indicate less time has elapsed since two HIV strains diverged.[13,14] A putative transmission network is created and, by selecting a recommended genetic distance threshold, clusters of recent transmission can be detected. A molecular cluster was defined as: at least two people who had sequences with a level of genetic similarity meeting a predefined distance threshold

(≤1.5%; 0.015 substitutions/site) using HIV-TRACE. This distance corresponds to what has been observed between epidemiological linked partners in a U.S. surveillance system.[3] When a person had more than one sequence of suitable length, all sequences were considered in the analysis[15] by collapsing them into a person-node in the network.

Any person who did not have at least one HIV-1 genetic sequence from the *pol* region of suitable length (i.e., ≥500 nucleotides) was excluded. The *pol* region consists of the ''genomic region encoding the viral enzymes protease, reverse transcriptase, and integrase.''[16] This region was selected by the developers of HIV-TRACE because insertions/deletions in comparison to a reference sequence is rare, allowing efficient pairwise alignment.[14] The selected genetic distance threshold (≤1.5%; 0.015 substitutions/site) has been previously validated with HIV-TRACE using protease and reverse transcriptase,[14] therefore, integrase sequences were excluded from analysis.

Multivariable logistic regression models were used to estimate the association between molecular cluster membership and predictors of interest: completion of a PS interview for HIV, number of named sex and needle-sharing partners (defined as ''initiable'' partners with enough information to attempt notification), and syphilis coinfection at the time of diagnosis. Syphilis coinfection followed established methodology,[17] defined as a syphilis diagnosis ±45 days of the HIV diagnosis date. Also following previously published methodology, subpopulation was defined using sex assigned at birth, current gender, and transmission category to create mutually exclusive categories.[18]

An initial model (''PS Participation'') was constructed to determine whether completion of a PS interview was associated with molecular cluster membership. The population of interest was all individuals who matched between eHARS and STD*MIS (i.e., a match in partner services) and had a sequence. The offering or conduct of PS could not be determined for unmatched individuals, therefore, they were excluded from further analyses. Any variable assessed only through interview was excluded because a response would be systematically missing for anyone without an interview. The independent variable of interest, interview completion, was retained in the model regardless of significance in the subsequent model.

Then, the second model (''PS Risks'') was estimated to assess the association between number of partners and syphilis coinfection with molecular cluster membership. The population of interest for this model was all individuals who matched between eHARS and STD*MIS, had a sequence, and completed a PS interview. Covariates were considered for inclusion based on principles of ''purposeful selection of covariates.''[19] Steps included: (1) evaluated each variable in univariable analysis (variables with crude p value <.20 retained for possible inclusion in step 2); (2) fitted multivariable logistic regression model with selected variables from step 1 (full model), compared reduced and full models, fitted reduced models with each variable removed one at a time, and determined importance of each variable by calculating its contribution (compare full to reduced model); (3) retained any excluded variable (one removed to create the reduced model) if the full model had a lower Akaike Information Criterion than the reduced model or if the change in estimates for any of the remaining covariates in the full relative to the reduced model was >10%.

Covariates initially excluded in step 1 were reexamined in step 3 and evaluated in the same manner. The independent variables of interest, coinfection with syphilis, and number of named partners, were retained regardless of significance. Subpopulation was also determined *a priori* as a variable of importance and retained.

SAS® 9.4 was used for all analyses. Effect modification was initially determined through automated selection (stepwise with entry set at $p < .25$ and removal set at $p < .05$) and confirmed by visual diagnostics. This study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston (UTHealth) and adhered to relevant confidentiality regulations. As per Centers for Disease Control and Prevention (CDC) guidance to health departments, HIV sequence data reported to surveillance programs are not released to public repositories.

Results

Sample characteristics

A total of 10,548 persons were newly diagnosed with HIV between January 1, 2012 and December 31, 2018 and met study criteria. All sequences closely matching (≤1.5%) a laboratory control, HXB2, were deemed potential contaminants and removed ($n = 10$). When narrowed to individuals with valid sequence data, the sample was reduced to 5,442 people (51.6%) and 7,842 sequences. Among individuals with more than one sequence, the median time between the first and last sequence was 357 days. In total, 42.9% of people ($n = 2,336$) clustered within 560 molecular clusters. The mean molecular cluster was 4.2 members (median = 2, standard deviation = 5.1, min = 2, max = 51); 53.4% ($n = 299$) of molecular clusters were dyads.

As shown in Figure 1, 74.1% ($n = 4,035$) of individuals with a valid sequence matched to PS data. The cohort for the PS Participation Model consisted of people matching to PS records ($n = 4,035$) because the primary independent variable of interest was interview completion. Conversely, the cohort for the PS Risks Model consisted of people matching to PS records who also completed a PS interview ($n = 3,869$), which allowed utilization of risk factor and drug use variables. In each cohort, about 45% of people were in a molecular cluster.

PS participation model

The majority of the 4,053 people in the PS Participation Model cohort were under 40 years of age at interview attempt (72.3%), Black (45.5%) or Hispanic (35.4%), MSM (56.6%), and diagnosed before 2017 (87.7%). Over 28% of people were diagnosed with HIV late as evidenced by an AIDS diagnosis within 1 year of their HIV diagnosis. People often had a first CD4 count over 350 cells/μL (51.5%) and a first viral load (VL) of at least 10,000 copies/mL (81.1%). Just 4.1% of the cohort did not have a PS interview completed. All variables were significant by chi-square tests between the groups included and excluded from molecular clusters, except for the variable of interest: interview completion ($p = .52$; Table 1).

For multivariable logistic regression analyses, people were excluded if they had missing values for a covariate in that model; this process resulted in a sample size of 3,982 people

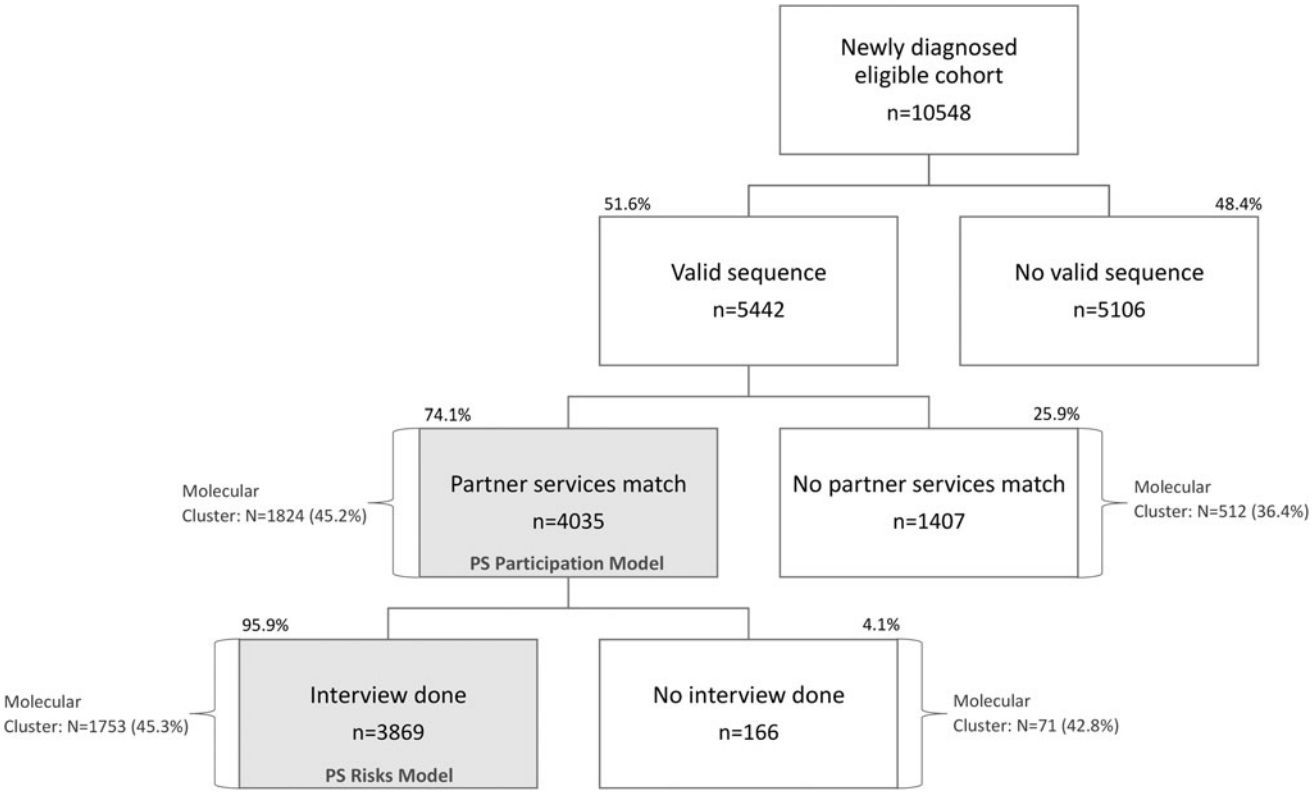

FIG. 1. Cohort composition by model.

(Table 3). After controlling for all covariates, there was no significant difference in odds of molecular cluster membership among Hispanic, Black, or White people. MSM had 1.5 times as high odds of molecular cluster membership [adjusted odds ratio, aOR: 1.53 (95% confidence interval, CI: 1.27–1.85), $p < .0001$]. People diagnosed in both 2015 [aOR: 1.55 (95% CI: 1.24–1.93), $p = .0001$] and 2016 [aOR: 1.43 (95% CI: 1.14–1.80), $p = .002$] had significantly higher odds than those diagnosed in 2012 (ref group). The odds of molecular cluster membership increased with higher levels of first CD4 count or VL. After adjusting for all covariates, interview completion was not significantly associated with higher odds of molecular cluster membership [aOR: 0.88 (95% CI: 0.63–1.23), $p = .45$].

There was effect modification discovered between age at interview attempt and late HIV diagnosis. Among people who were not diagnosed late with HIV, younger age groups (under 40 years) had significantly higher odds of molecular cluster membership compared with those 50+ years of age (ref group). Among people who were diagnosed late, youth, and young adults (under 30 years), also had significantly higher odds of molecular cluster membership.

PS risks model

Descriptive statistics of the cohort for the PS Risks Model are shown in Table 2 with variables from the PS interview included. Approximately 14% of the cohort was coinfected with syphilis at the time of HIV diagnosis. The majority (77.0%) of people named 0 or 1 partner during an interview (mean = 1.1, median = 1, standard deviation = 1.6, min = 0, max = 32). A large proportion reported sex with anonymous partner(s) (50.3%) and meeting partner(s) through the internet or a phone application (31.6%). Drug use was rarely reported other than marijuana use (17.8%), however, 24% reported engaging in sex while intoxicated or high. About 14% of the cohort had previously been incarcerated.

After controlling for all covariates, there was no significant difference in odds of molecular cluster membership among Hispanic, Black, or White people (Table 3). MSM had 1.4 times as high odds of molecular cluster membership [aOR: 1.44 (95% CI: 1.16–1.77), $p = .0008$]. People diagnosed in 2015 [aOR: 1.58 (95% CI: 1.25–1.99), $p = .0001$], 2016 [aOR: 1.44 (95% CI: 1.14–1.82), $p = .003$], and 2017 [aOR: 1.33 (95% CI: 1.01–1.74), $p = .04$] had significantly higher odds than those diagnosed in 2012 (ref group). Like the PS Participation Model, odds increased with higher levels of first CD4 count or VL. Compared with people with no named partners, those with 1 or 3+ named partners had significantly higher odds of molecular cluster membership [aOR: 1.27 (95% CI: 1.08–1.50)], $p = .003$ and aOR: 1.38 (95% CI: 1.06–1.81), $p = .02$] than those with 0 named partners (ref group). Sex with anonymous partner(s) was associated with higher odds, while reported alcohol use was associated with lower odds [aOR: 1.22 (95% CI: 1.03–1.44), $p = .02$ and aOR: 0.60 (95% CI: 0.37–0.95), $p = .03$].

There was effect modification discovered between age at interview attempt and sex while intoxicated/high. Compared with people 50+ years who did not report sex while intoxicated/high, all groups under 40 years had significantly higher odds of inclusion in a molecular cluster. Additionally, effect modification was present between syphilis coinfection

Table 1. Descriptive Statistics: Partner Services Participation Model (N=4,035)

	Cluster=No, n *(row %)*	*Cluster=Yes,* n *(row %)*	*Total,* n *(col %)*	χ^2	p
Age at interview attempt, years				231.62	<.0001
≥50 (ref)	372 (73.5)	134 (26.5)	506 (12.5)		
<24	354 (38.2)	572 (61.8)	926 (23.0)		
24–29	476 (49.4)	488 (50.6)	964 (23.9)		
30–39	593 (57.8)	433 (42.2)	1,026 (25.4)		
40–49	416 (67.9)	197 (32.1)	613 (15.2)		
Race/ethnicity				12.34	.006
White, non-Hispanic (ref)	321 (53.8)	276 (46.2)	597 (14.8)		
Hispanic	738 (51.6)	692 (48.4)	1,430 (35.4)		
Black, non-Hispanic	1,047 (57.1)	788 (42.9)	1,835 (45.5)		
Other, non-Hispanic	105 (60.7)	68 (39.3)	173 (4.3)		
Subpopulation				120.33	<.0001
Cisgender women (ref)	487 (64.8)	265 (35.2)	752 (18.6)		
Cisgender men	508 (66.6)	255 (33.4)	763 (18.9)		
MSM	1,089 (47.7)	1,193 (52.3)	2,282 (56.6)		
PWID	99 (55.3)	80 (44.7)	179 (4.4)		
Transgender women	28 (47.5)	31 (52.5)	59 (1.5)		
Year of HIV diagnosis				18.53	.005
2012 (ref)	471 (60.3)	310 (39.7)	781 (19.4)		
2013	408 (55.8)	323 (44.2)	731 (18.1)		
2014	413 (55.7)	328 (44.3)	741 (18.4)		
2015	338 (50.2)	336 (49.9)	674 (16.7)		
2016	322 (52.5)	291 (47.5)	613 (15.2)		
2017	203 (52.5)	184 (47.6)	387 (9.6)		
2018	56 (51.9)	52 (48.2)	108 (2.7)		
Late HIV diagnosis[a]				93.53	<.0001
No (ref)	1,444 (50.0)	1,443 (50.0)	2,887 (71.6)		
Yes	767 (66.8)	381 (33.2)	1,148 (28.5)		
First CD4 count, cells/μL[b]				114.97	<.0001
<50 (ref)	325 (74.4)	112 (25.6)	437 (10.9)		
50–200	409 (62.9)	241 (37.1)	650 (16.2)		
201–350	446 (52.0)	411 (48.0)	857 (21.4)		
>350	1,013 (49.1)	1,052 (50.9)	2,065 (51.5)		
First VL, copies/mL[b]				7.68	.022
<10,000 (ref)	423 (55.9)	334 (44.1)	757 (18.9)		
10,000–100,000	943 (52.4)	858 (47.6)	1,801 (45.0)		
>100,000	823 (57.1)	619 (42.9)	1,442 (36.1)		
Interview completed				0.41	.520
No (ref)	95 (57.2)	71 (42.8)	166 (4.1)		
Yes	2,116 (54.7)	1,753 (45.3)	3,869 (95.9)		
Total	2,211 (54.8)	1,824 (45.2)	4,035		

Molecular cluster defined as ≥2 people with sequences meeting genetic distance threshold of ≤1.5%.
[a]Late HIV diagnosis = AIDS diagnosis within 1 year of HIV diagnosis.
[b]Only among people without missing values (n=26 missing CD4 count, n=35 missing VL).
MSM, men who have sex with men; PWID, people who inject drugs; VL, viral load.

and incarceration history. People with syphilis coinfection had significantly higher odds only if they also had been incarcerated [aOR: 1.91 (95% CI: 1.08–3.38), p=.03].

Discussion

HIV surveillance data used to construct molecular clusters contain risk information that is transmission centric and lacks critical contextual factors collected in PS, such as how partners met, drug use, and incarceration history. To achieve focused prioritization of cluster response efforts, data integration is necessary to facilitate understanding of the factors associated with molecular cluster membership.

Just as critical as molecular data, the methodology of this study relied on robust PS data. However, PS is only as effective as a client's willingness and ability to participate. We examined if there was a difference in interview completion by molecular cluster membership, which could be a marker of the need for differential strategies to reach this group. We found there was no significant difference in PS interview completion by molecular cluster membership. This finding could be an encouraging indication that this population is

TABLE 2. DESCRIPTIVE STATISTICS: PARTNER SERVICES RISKS MODEL (N=3,869)

	Cluster=No, n *(row %)*	*Cluster=Yes,* n *(row %)*	*Total,* n *(col %)*	χ^2	p
Age at interview attempt, years				224.79	<.0001
≥50 (ref)	350 (73.5)	126 (26.5)	476 (12.3)		
<24	344 (38.2)	557 (61.8)	901 (23.3)		
24–29	459 (49.4)	470 (50.6)	929 (24.0)		
30–39	561 (57.6)	413 (42.4)	974 (25.2)		
40–49	402 (68.3)	187 (31.8)	589 (15.2)		
Race/ethnicity				11.64	.009
White, non-Hispanic (ref)	302 (53.6)	261 (46.4)	563 (14.6)		
Hispanic	712 (51.6)	667 (48.4)	1,379 (35.6)		
Black, non-Hispanic	1,000 (56.8)	761 (43.2)	1,761 (45.5)		
Other, non-Hispanic	102 (61.5)	64 (38.6)	166 (4.3)		
Subpopulation				108.36	<.0001
Cisgender women (ref)	467 (64.4)	258 (35.6)	725 (18.7)		
Cisgender men	463 (66.4)	234 (33.6)	697 (18.0)		
MSM	1,062 (48.0)	1,153 (52.1)	2,215 (57.2)		
PWID	96 (55.5)	77 (44.5)	173 (4.5)		
Transgender women	28 (47.5)	31 (52.5)	59 (1.5)		
Year of HIV diagnosis				19.78	.003
2012 (ref)	453 (60.5)	296 (39.5)	749 (19.4)		
2013	392 (55.5)	315 (44.6)	707 (18.3)		
2014	391 (56.0)	307 (44.0)	698 (18.0)		
2015	316 (49.7)	320 (50.3)	636 (16.4)		
2016	307 (52.4)	279 (47.6)	586 (15.1)		
2017	201 (52.2)	184 (47.8)	385 (10.0)		
2018	56 (51.9)	52 (48.2)	108 (2.8)		
Late HIV diagnosis[a]				89.63	<.0001
No (ref)	1,388 (50.0)	1,391 (50.1)	2,779 (71.8)		
Yes	728 (66.8)	362 (33.2)	1,090 (28.2)		
First CD4 count, cells/μL[b]				107.77	<.0001
<50 (ref)	299 (74.0)	105 (26.0)	404 (10.5)		
50–200	396 (63.4)	229 (36.6)	625 (16.3)		
201–350	425 (51.8)	396 (48.2)	821 (21.4)		
>350	979 (49.1)	1,015 (50.9)	1,994 (51.9)		
First VL, copies/mL[b]				8.43	.015
<10,000 (ref)	410 (56.2)	320 (43.8)	730 (19.0)		
10,000–100,000	902 (52.1)	830 (47.9)	1,732 (45.2)		
>100,000	783 (57.0)	590 (43.0)	1,373 (35.8)		
Number of named partners				20.16	.0002
0 (ref)	871 (58.3)	623 (41.7)	1,494 (38.6)		
1	804 (54.2)	680 (45.8)	1,484 (38.4)		
2	284 (51.5)	267 (48.5)	551 (14.2)		
3+	157 (46.2)	183 (53.8)	340 (8.8)		
Syphilis coinfection				5.53	.019
No (ref)	1,848 (55.5)	1,485 (44.6)	3,333 (86.1)		
Yes	268 (50.0)	268 (50.0)	536 (13.9)		
Incarceration history[b]				1.83	.177
No (ref)	1,799 (55.2)	1,463 (44.9)	3,262 (86.1)		
Yes	274 (52.0)	253 (48.0)	527 (13.9)		
Met partner on internet or app[b]				61.09	<.0001
No (ref)	1,535 (59.0)	1,067 (41.0)	2,602 (68.4)		
Yes	545 (45.4)	655 (54.6)	1,200 (31.6)		
Sex with anonymous partner[b]				40.78	<.0001
No (ref)	1,131 (59.8)	759 (40.2)	1,890 (49.7)		
Yes	947 (49.5)	965 (50.5)	1,912 (50.3)		
Sex while intoxicated or high[b]				3.46	.063
No (ref)	1,600 (55.5)	1,283 (44.5)	2,883 (76.0)		
Yes	473 (52.0)	437 (48.0)	910 (24.0)		

(*continued*)

TABLE 2. (CONTINUED)

	Cluster = No, n *(row %)*	*Cluster = Yes,* n *(row %)*	*Total,* n *(col %)*	χ^2	p
Exchanged drugs/money for sex[b]				0.04	.842
No (ref)	1,954 (54.7)	1,620 (45.3)	3,574 (94.1)		
Yes	124 (55.4)	100 (44.6)	224 (5.9)		
Sex with PWID[b]				0.08	.781
No (ref)	2,006 (54.8)	1,653 (45.2)	3,659 (96.4)		
Yes	74 (53.6)	64 (46.4)	138 (3.6)		
Alcohol use				1.68	.196
No (ref)	2,059 (54.5)	1,717 (45.5)	3,776 (97.6)		
Yes	57 (61.3)	36 (38.7)	93 (2.4)		
Crack or other cocaine use				0.24	.624
No (ref)	1,944 (54.6)	1,618 (45.4)	3,562 (92.1)		
Yes	172 (56.0)	135 (44.0)	307 (7.9)		
Marijuana use				3.56	.059
No (ref)	1,761 (55.4)	1,418 (44.6)	3,179 (82.2)		
Yes	355 (51.5)	335 (48.6)	690 (17.8)		
Prescription medication use[c]				0.002	.963
No (ref)	2,079 (54.7)	1,722 (45.3)	3,801 (98.2)		
Yes	37 (54.4)	31 (45.6)	68 (1.8)		
Total	2,116 (54.7)	1,753 (45.3)	3,869		

Molecular cluster defined as ≥2 people with sequences meeting genetic distance threshold of ≤1.5%.
[a]Late HIV diagnosis = AIDS diagnosis within 1 year of HIV diagnosis.
[b]Only among people without missing values ($n = 25$ missing CD4 count, $n = 34$ missing VL, $n = 80$ missing incarceration history, $n = 67$ missing met partner on internet or app, $n = 67$ missing sex with anonymous partner, $n = 76$ missing sex while intoxicated or high, $n = 71$ missing exchanged drugs/money for sex, $n = 72$ missing sex with PWID).
[c]Nonprescribed or recreational use.
MSM, men who have sex with men; PWID, people who inject drugs; VL, viral load.

being reached at a similar level as noncluster members using traditional health department approaches or, alternatively, that PS has disrupted transmission that would have otherwise been detected through molecular cluster analysis. Further research on the effectiveness of PS to disrupt transmission and reduce growth in molecular clusters is recommended to inform selection of appropriate interventions in cluster response efforts.

In the present study, an increase in partner count did not always correspond to higher odds of molecular cluster membership, diverging from a previous study where an association between number of sex partners and transmission was detected through molecular cluster analysis.[15] An unknown, and possibly confounding factor was how many people may have been unable or unwilling to provide enough information to initiate a partner for follow-up. These individuals would appear in our study as having zero partners. A systematic review published in 2007 determined that, on average, 67% of named partners were found and notified of HIV exposure.[20] In a more recent study of syphilis in Texas, MSM with and without HIV had increasing proportions of PS interviews deemed ''no partner initiated'' from 2013 to 2016. Proportions were higher among MSM with HIV and ranged from 35.8% to 42.8% of early syphilis interviews.[21] This increasing trend limits effectiveness of PS, and in our study, anonymous sex was associated with molecular clustering. We suggest that a further study of partner count, regardless of whether partners are initiable, may be beneficial.

Despite the elevated risk of HIV transmission associated with syphilis,[22,23] we found that coinfection was only significantly associated with molecular cluster membership among people who had a history of incarceration. Delays in establishing health care postincarceration could increase risk among this population and their network. After release from a Texas prison, just 30% of people with HIV filled a prescription for ART within 60 days and only 5% avoided treatment interruption.[24] Delays in HIV treatment and/or syphilis screening postincarceration may facilitate ongoing transmission, which could contribute to molecular clustering.

We detected significant predictors of molecular cluster membership beyond the primary variables of interest. MSM had higher odds of molecular cluster membership. This finding supports prior work from North Carolina where transmission was ''dominated by MSM''[25] and from a region of Tennessee where active cluster members were more likely to be MSM.[26] Concurrency among MSM played a significant role in molecular clustering elsewhere[27] and could be considered in future analyses. While other localities have also detected outbreaks or clusters among people who inject drugs,[28,29] this group does not yet appear to play a large role in structuring molecular clusters in Houston.

We did not find that the Hispanic population was significantly more likely to cluster. This was an unanticipated discovery because phylodynamic methods identified the Hispanic population as a critical source and recipient of transmission in Houston.[18] These seemingly contradictory findings suggest that adjusting for risk information gathered in PS, such as sex with anonymous partner(s), may better explain molecular cluster membership than surveillance data alone.

Table 3. Multivariable Logistic Regression Models: Partner Services Participation Model (N=3,982) and Partner Services Risks Model (N=3,703)

	Model: PS participation, no cluster (n=2,177) vs. cluster (n=1,805)		*Model: PS risks, no cluster (n=2,024) vs. cluster (n=1,679)*	
	aOR (95% CI)	p	*aOR (95% CI)*	p
Race/ethnicity				
White, non-Hispanic (ref)				
Hispanic	1.10 (0.90–1.35)	.362	1.12 (0.90–1.39)	.317
Black, non-Hispanic	0.86 (0.70–1.05)	.138	0.88 (0.71–1.09)	.240
Other, non-Hispanic	0.65 (0.45–0.94)	.022	0.63 (0.43–0.92)	.018
Subpopulation				
Cisgender women (ref)				
Cisgender men	1.08 (0.86–1.35)	.505	1.02 (0.80–1.30)	.878
MSM	1.53 (1.27–1.85)	<.0001	1.44 (1.16–1.77)	.0008
PWID	1.30 (0.92–1.85)	.143	1.16 (0.79–1.71)	.443
Transgender women	1.56 (0.90–2.71)	.115	1.56 (0.87–2.80)	.135
Year of HIV diagnosis				
2012 (ref)				
2013	1.19 (0.96–1.48)	.116	1.21 (0.97–1.51)	.100
2014	1.16 (0.94–1.44)	.168	1.14 (0.91–1.44)	.249
2015	1.55 (1.24–1.93)	.0001	1.58 (1.25–1.99)	.0001
2016	1.43 (1.14–1.80)	.002	1.44 (1.14–1.82)	.003
2017	1.29 (0.99–1.68)	.057	1.33 (1.01–1.74)	.040
2018	1.38 (0.90–2.12)	.145	1.37 (0.88–2.14)	.163
First CD4 count, cells/μL				
<50 (ref)				
50–200	1.58 (1.20–2.10)	.001	1.57 (1.16–2.10)	.003
201–350	1.94 (1.38–2.72)	.0001	2.19 (1.64–2.92)	<.0001
>350	2.17 (1.53–3.06)	<.0001	2.39 (1.81–3.15)	<.0001
First VL, copies/mL				
<10,000 (ref)				
10,000–100,000	1.22 (1.02–1.46)	.034	1.23 (1.02–1.49)	.031
>100,000	1.35 (1.10–1.65)	.004	1.31 (1.06–1.63)	.013
Interview completed				
No (ref)				
Yes	0.88 (0.63–1.23)	.449	—	—
Number of named partners				
0 (ref)				
1	—	—	1.27 (1.08–1.50)	.003
2	—	—	1.21 (0.98–1.50)	.083
3+	—	—	1.38 (1.06–1.81)	.017
Met partner on internet or app				
No (ref)				
Yes	—	—	1.08 (0.91–1.28)	.387
Sex with anonymous partner				
No (ref)				
Yes	—	—	1.22 (1.03–1.44)	.019
Alcohol use				
No (ref)				
Yes	—	—	0.60 (0.37–0.95)	.030
Age at interview attempt at Late HIV diagnosis[a]=No				
≥50 (ref), No (ref)				
<24, No	2.53 (1.87–3.42)	<.0001	—	—
24–29, No	1.66 (1.23–2.24)	.0009	—	—
30–39, No	1.38 (1.03–1.86)	.034	—	—
40–49, No	0.97 (0.70–1.36)	.872	—	—

(*continued*)

TABLE 3. (CONTINUED)

	Model: PS participation, no cluster (n = 2,177) vs. cluster (n = 1,805)		*Model: PS risks, no cluster (n = 2,024) vs. cluster (n = 1,679)*	
	aOR (95% CI)	p	*aOR (95% CI)*	p
Age at interview attempt at Late HIV diagnosis[a] = Yes				
≥50 (ref), No (ref)				
<24, Yes	3.12 (1.94–5.04)	<.0001	—	—
24–29, Yes	1.63 (1.05–2.54)	.031	—	—
30–39, Yes	1.09 (0.72–1.66)	.683	—	—
40–49, Yes	0.83 (0.53–1.31)	.432	—	—
Age at interview attempt at Sex while intoxicated or high = No				
≥50 (ref), No (ref)				
<24, No	—	—	4.18 (3.07–5.68)	<.0001
24–29, No	—	—	2.44 (1.81–3.28)	<.0001
30–39, No	—	—	1.75 (1.31–2.34)	.0002
40–49, No	—	—	1.25 (0.91–1.72)	.161
Age at interview attempt at Sex while intoxicated or high = Yes				
≥50 (ref), No (ref)				
<24, Yes	—	—	2.55 (1.76–3.71)	<.0001
24–29, Yes	—	—	1.95 (1.33–2.84)	.0006
30–39, Yes	—	—	2.17 (1.50–3.15)	<.0001
40–49, Yes	—	—	1.42 (0.86–2.33)	.170
Syphilis coinfection at Incarceration history = No				
No (ref), No (ref)				
Yes coinfection, No	—	—	0.88 (0.71–1.09)	.234
Syphilis coinfection at Incarceration history = Yes				
No (ref), No (ref)				
Yes coinfection, Yes	—	—	1.91 (1.08–3.38)	.026

Molecular cluster defined as ≥2 people with sequences meeting genetic distance threshold of ≤1.5%.

For the purposes of multivariable analysis, people were removed if missing values present (PS Participation Model: $n = 53$; PS Risks Model: $n = 166$).

[a]Late HIV diagnosis = AIDS diagnosis within 1 year of HIV diagnosis.

aOR, adjusted odds ratio; CI, confidence interval; PS, partner services.

Higher CD4 counts and VLs were associated with molecular cluster membership. Such relationship between molecular clusters and VLs and/or CD4 counts has been found previously.[15,26,30] Le Vu et al. simulated multiple clustering methods and recognized that people more recently infected are more likely to be genetically closer to their source of infection, therefore, CD4 count and VL are likely to be associated with molecular clustering. Accordingly, these factors may be less informative in conclusions about onward transmission risk,[31] and molecular clustering may be biased toward people diagnosed earlier in their infection.[32]

Age tended to interact with other variables dependent on the covariates included in the model. Previous research has also found younger age as a factor fueling molecular cluster membership or cluster growth,[26,30,33] although interaction with other risks appears a novel finding. This suggests that age alone may not be as effective in prioritizing cluster response efforts compared with other risk factors, further emphasizing the importance of PS data in models of molecular cluster membership.

Surprisingly, alcohol use was associated with lower odds of molecular cluster membership, and other drugs queried had no significant effect. Comparable studies assessing alcohol use and noninjection drug use by molecular cluster members were not found, but critical reviews and original articles both have demonstrated evidence that appears contrary to our findings. Alcohol use is associated with HIV incidence,[34] and experimental studies have drawn causal links between alcohol use and sexual risk-taking intentions.[35] A possible explanation for our unexpected finding is that DIS ascertained drug and alcohol use overall, not use specifically preceding sexual encounters. We were also unable to detect amounts or frequency, and there may be a dose–response effect. This hypothesis was supported by our model; there was significantly higher odds of molecular cluster membership for the interaction between age and sex while intoxicated/high. Additional research examining alcohol use timing and amount is necessary to further elucidate the relationship with molecular cluster membership.

Another area for further exploration is concerning evidence of delays in diagnosis: over 28% of people included in our models received a late diagnosis of HIV. This finding is consistent with prior research in Texas (27%), and in Houston, unemployment was found to have a positive association.[36] Interventions to increase focused and timely testing and further distill drivers of delays may be a particular area of opportunity for HIV prevention efforts in Houston.

This study was reliant on sequence data reported through routine surveillance and is subject to several limitations. These data are generated as a result of drug resistance testing,

which must be ordered by a medical provider and is most often performed upon entry into HIV medical care.[13] Because molecular cluster detection is limited to people who have sequences, this methodology primarily represents people with HIV who have engaged in care. Sensitivity analyses did reveal that some individuals in our setting were more likely to have sequences than others (Supplementary Table S1 and Supplementary Table S2, Supplementary Digital Content). Finally, conclusions from molecular cluster detection should be interpreted with caution. Clustering does not indicate that transmission occurred between molecularly linked individuals. We do not know if there are individuals missing in the network who are not yet diagnosed and/or who have not yet had a sequence performed and reported to the health department. Therefore, while these analyses are a helpful tool in understanding patterns of transmission, the network is incomplete and directionality between individuals cannot and should not be inferred.

Conclusion

Implications for PS

Our methods and results can be translated to real-world application, including building upon existing mechanisms for interruption of transmission. We found that some people with particular risk profiles were more likely than others to belong to molecular clusters. A likely sign of recent transmission, molecular cluster membership, signals that these groups be considered as priority for prevention resource allocation. Especially in regions where public health need exceeds the resources of PS, retrospective analyses such as these may present a mechanism to better focus resource-intensive field efforts by DIS.

Instead of reactionary approaches after molecular cluster detection, a systems-level approach could revolutionize PS—an activity already in desperate need of a revamp.[37] With regular retrospective analyses, health departments could enhance PS for people fitting the risk profiles of those most likely to cluster in their jurisdiction. For example, if syphilis coinfection among those with incarceration history is associated with molecular cluster membership, health departments could shift workloads to allow a higher level of service intensity when seeking partners of similar clients in the future. Such systematic changes would not rely on continued (re-)engagement of cluster members, an example of surveillance data for ''direct prevention'' that has come under scrutiny.[38] While this solution would entail a retrospective approach to inform prevention efforts among future clients, molecular cluster detection is already structured as a retrospective endeavor with many members likely in care (as evidenced by presence of a genetic sequence). We believe a preventative approach offers an alternative to reinterviewing or differential engagement with cluster members and their social/sexual networks, which may inadvertently stigmatize people.

Now surpassing 40 years since the HIV epidemic began in the United States, we reflect on the plethora of options available to effectively end new HIV infections. We can confidently proclaim that viral suppression means no risk of onward sexual transmission.[39] For those who are at risk for HIV, we can now offer prevention in the form of PrEP.[40] Moreover, we should not overlook another powerful advance: greater understanding stemming from innovative uses of data. To most effectively focus prevention efforts, genetic sequence and PS data can be analyzed to identify and characterize clusters where HIV is rapidly transmitted. With a limited pool of resources for public health intervention, this tool may present an opportunity to evolve our existing response efforts.

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Supplementary Material

Supplementary Digital Content
Supplementary Table S1
Supplementary Table S2

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