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Recent Infection, Sexually Transmitted Infections and Transmission Clusters Frequently Observed Among Persons Newly-Diagnosed with HIV in San Francisco

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Abstract

There were 1,311 newly-diagnosed HIV cases in San Francisco between 2005 and 2011 that were linked to care at publicly-funded facilities and had viral sequences available for analysis. Of the 214 cases characterized as recently-infected with HIV at time of diagnosis, 25% had a recent sexually transmitted infection (STI) diagnosis (vs. 10% among longer-standing HIV infections, $p<0.001$) and 57% were part of a phylogenetic transmission cluster (vs. 42% among longer-standing HIV infection, $p<0.001$). The association observed between recent HIV infection and having a STI diagnosis during the interval overlapping likely HIV acquisition points to potential opportunities to interrupt HIV transmission.

Keywords

HIV; recent infection; acute infection; sexually transmitted infections; phylogenetics; transmission clusters

Introduction

The majority of new HIV infections are thought to be transmitted by individuals who are unaware they are infected.[1,2] With approximately 20% or fewer persons living with HIV in the United States unaware of their infection status, the leading edge of the epidemic may be concentrated in a few transmission chains or clusters at any point in time.[3] Transmission clusters are defined as HIV infections that share sufficient viral genetic similarity to suggest a recent common source of infection or a chain of transmission. Prior studies have suggested

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that transmission clusters may contribute disproportionately to the rate of ongoing transmission.[4-7] Meanwhile, the association between HIV and other sexually transmitted infections (STIs) has been proposed to be causally related to acquisition or transmission or as a marker for engaging in condomless sexual intercourse and having multiple partners in a short period of time.[8-11] Therefore, characterizing the intersection of recent HIV infections, transmission clusters and incident STI may point to particularly efficient opportunities for prevention efforts. We examined the correlates associated with the stage of infection at time of diagnosis among new HIV cases in San Francisco.

Methods

We characterized San Francisco residents who were newly-diagnosed with HIV from 2005 through 2011, linked to care at publicly-funded facilities and had viral sequences available. Study data were obtained from the ARI-UCSF Laboratory of Clinical Virology (LCV), the San Francisco Department of Public Health (SFDPH) Laboratory, the SFDPH HIV/AIDS Case Registry and the SFDPH STD Case Registry. The LCV conducts HIV-1 drug resistance testing for publicly-funded and community-based clinics in San Francisco. The LCV database was matched to the HIV/AIDS Case Registry to obtain demographic and risk characteristics information. Matches to the STD Case Registry and SFDPH Laboratory dataset were conducted to obtain documentation of STI diagnoses and acute and recent HIV infection status, respectively.

Data on the demographic and risk characteristics of cases included gender, age, race/ethnicity and HIV transmission category. Clinical characteristics included stage of HIV infection at time of diagnosis and history of STIs. Recent HIV infection was defined as: 1) having a negative antibody test result within 6 months of HIV diagnosis based on self-reported data from HIV testing intake forms; and/or 2) presenting with acute infection; that is, being HIV antibody negative and HIV-RNA positive at time of HIV diagnosis. STIs reportable to the case registry included Chlamydia, gonorrhea, syphilis and non-gonococcal urethritis. Recent STI diagnosis was defined as being diagnosed with a reportable STI within the 6 months preceding HIV diagnosis. Cases could be diagnosed with a specific STI more than once and could be diagnosed with one or more STIs concurrently.

HIV transmission cluster membership was determined based on viral RNA sequences. Viral population sequencing of plasma viral RNA generated full protease and portions of the reverse transcriptase reading frames (TRUGENE HIV-1 Genotyping Assay, Siemens, Malvern, PA). All available viral sequences were included in the phylogenetic analysis. Viral sequences were aligned using ClustalW (in BioEdit 7.1.3.0) and adjusted manually. Sixty-seven codons known to be associated with drug resistance were excluded.[12] A phylogeny was reconstructed using FastTree 2.1.5, with the generalized-time-reversible model of nucleotide substitution and a single substitution rate per cite (GTR+CAT). Transmission clusters were defined as having Shimodaira-Hasegawa node support greater than 0.90 and mean pairwise genetic distance less than 0.03 substitutions per site, a definition that is consistent with other similar published studies.[13-15]

Associations between recent HIV infection and demographic factors, HIV transmission risk, STI diagnosis and being part of a transmission cluster were evaluated using multivariate logistic regression. Data matching and statistical analyses were performed using SAS 9.3. The study received approval from the Institutional Review Board at the University of California, San Francisco.

Results

A total of 3,699 San Francisco residents were newly-diagnosed with HIV in San Francisco from 2005 through 2011, of whom 3,060 were linked to care at publicly-funded facilities and 1,311 had viral sequences from clinical resistance testing available for phylogenetics analysis. The 1,311 newly-diagnosed cases were mostly male, white, men who have sex with men (MSM), as detailed in Table 1. Median age was 36 years old (IQR 28, 44), ranging from 17 to 73 years old. Four hundred and seventeen cases (32%) had history of a STI diagnosis, with the most common being Chlamydia (n=384), gonorrhea (n=338), syphilis (n=201) and non-gonococcal urethritis (n=56). Among the 161 cases diagnosed with a STI within six months prior to HIV diagnosis, the most common STIs were Chlamydia (n=80), gonorrhea (n=64), syphilis (n=23) and non-gonococcal urethritis (n=6). The median time interval between the date of diagnosis and date of the first available blood sample for viral sequencing was 52 days (IQR 18, 364). There were 587 cases (45%) characterized as being part of a HIV transmission cluster; 350 (27%) were in a cluster of 2 or 3 cases and 237 (18%) were in a cluster of 4 or more cases.

There were 214 cases characterized as recent HIV infections; 27 cases were based on viral load testing for acute infection, 34 cases on a documented negative antibody test result within 6 months of HIV diagnosis and 153 cases on patient self-report of a last HIV negative test date within 6 months of HIV diagnosis. Of the 214 recent HIV infections cases, 109 (51%) had a STI history, with the most common being Chlamydia (n=105), gonorrhea (n=89), syphilis (n=43) and non-gonococcal urethritis (n=11). Among the 53 recent HIV infection cases that also had a STI diagnosis within 6 months prior to their HIV diagnosis, the most common STIs were Chlamydia (n=26), gonorrhea (n=24), syphilis (n=6) and non-gonococcal urethritis (n=2). Any history of Chlamydia (OR=2.8 [2.1-3.8]; p<0.0001), gonorrhea (OR=2.4 [1.8-3.3]; p<0.0001) and syphilis (OR=1.5 [1.0-2.2]; p=0.04) was associated with recent HIV infection. Persons with a recent diagnosis of Chlamydia (OR=2.7 [1.6-4.4]; p<0.0001) and gonorrhea (OR=3.3 [2.0-5.7]; p<0.0001) were more likely to be recently-infected with HIV whereas persons with a recent diagnosis of syphilis were not (OR=1.8 [0.7-4.7]; p=0.21). One hundred twenty-three cases with recent HIV infection (57%) were part of a transmission cluster, of which 64 (30%) were in a cluster with 2 or 3 cases and 59 (28%) were in a cluster with 4 or more cases.

The characteristics of being recently-infected with HIV compared to having a longer-standing infection at time of diagnosis are presented in Table 2. Having a recent STI diagnosis (p<0.001), being part of a transmission cluster (p=0.003) and younger age at HIV diagnosis were associated with recent HIV infection. Heterosexuals were less likely to be recently-infected at time of HIV diagnosis (p=0.02) than MSM and people who inject drugs.

There was no association detected between gender, race and ethnicity and being recently-infected with HIV.

Discussions

Many newly-diagnosed HIV cases in San Francisco had a history of an STI diagnosis, were part of a transmission cluster and were younger in age. These characteristics were even more prevalent among those cases that were recently-infected at time of HIV diagnosis. A quarter of recent HIV infection cases were also recently diagnosed with a STI, particularly Chlamydia and gonorrhea. More than half of recent HIV infections were found within a phylogenetic transmission cluster. Nearly half of recently-infected individuals were less than 30 years old at the time of their HIV diagnosis, the vast majority were MSM. Along with the potential attributable fraction of HIV due to undiagnosed infection, these factors help narrow the target to interrupt on-going transmission.

A primary aim of this analysis was to characterize the clustering of related viral sequences at a population level rather than to identify individual transmission linkages. HIV infections diagnosed soon after acquisition were more likely to be found within a detected phylogenetic transmission cluster. Infections not linked to a phylogenetic transmission cluster harbored a virus that was less closely related to other sequences in the study sample, possibly because persons with potentially related viruses were receiving care at private facilities in San Francisco or at facilities outside of San Francisco or are undiagnosed infections.

The study sample was limited to individuals who received care at publicly-funded facilities, which represented over 80% of all newly-diagnosed HIV cases during the study period. The associations observed among this sample may differ compared to individuals receiving care at private facilities or with private providers and persons who are not linked to care. Self-reports of a negative antibody test result within 6 months of HIV diagnosis could not be confirmed. However, our prior research found HIV-1 incidence estimates derived from laboratory-based assays and self-reported HIV testing history yielded comparable results.[16] HIV transmission cluster linkages may have been underestimated since we would be unable to detect linkages that are mediated through a third party with viral sequences not available for analysis. Long intervals between time of infection and time of sampling for viral sequencing may affect cluster identification. However, given the median time interval between the date of diagnosis and date of the first available blood sample for viral sequencing was less than 2 months, the amount of genetic drift within an individual is likely to have limited impact on our cluster identification.

Our study findings point to intervention opportunities to interrupt HIV transmission. Recent HIV infection was associated with being diagnosed with a STI during the time interval when HIV transmission most likely occurred. Therefore, our finding highlights the value of integrating HIV and STI testing services, screening for acute HIV infection among newly-diagnosed STI cases, early initiation of antiretroviral treatment (eiART), increased use of STI partner services and use of HIV pre-exposure prophylaxis (PrEP) by uninfected members of these sexual networks where the risk for HIV infection is most acute.

The identification of HIV transmission clusters may further help to focus prevention efforts. The high rate of clustering observed among recently-infected persons indicates that recent infection may be associated with increased risk of onward transmission of HIV. This finding is consistent with the evidence of increased transmission risk related to unawareness of infection status and high viral load in acute and early untreated infection and does not support a paradigm of many infections arising sporadically from long-standing infections. Information on whether individuals were screened for syphilis and on negative test results were not available, which may partially account for the observed lack of association between recent infection and syphilis. Data were not available on whether or not individuals were screened for syphilis or if the screening results were negative, which may account in part for the observed lack of association between recent infection and syphilis. Recently-infected individuals may be reached through intervention programs such as partner services and risk reduction counseling for persons living with HIV to reduce the risk of further spread of infection. These findings also point towards the need for further studies to elucidate the factors associated with HIV transmission clusters and ways to reach them in real time with individual- and social-level interventions.

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Table 1

Demographic characteristics, HIV transmission category and any sexually transmitted infection (STI) history of newly-diagnosed HIV persons, San Francisco, 2005-2011 (N=1,311)

	N	%
Gender		
Male	1,098	84
Female	150	11
Transgender	63	5
Age		
≤ 24	178	14
25-29	233	18
30-39	399	30
40-49	151	12
≥ 50	151	12
Race/Ethnicity		
White	562	43
Hispanic/Latino	356	27
Black	250	19
Asian/Pacific Islander	96	7
Other/Unknown	47	4
HIV Transmission Risk		
Men who have sex with men	1,009	76
People who inject drugs	147	11
Heterosexual	120	9
Other/Unknown	35	3
Any STI History		
None prior to HIV diagnosis	894	68
≤ 6 months prior to HIV diagnosis	161	12
> 6 months prior to HIV diagnosis	256	20
HIV Transmission Cluster		
Member of a cluster with 2-3 cases	350	27
Member of a cluster with ≥ 4 cases	237	18
Not member of a cluster	724	55

Table 2

Characteristics of newly-diagnosed persons with recent HIV infection compared to longer-standing HIV infection at time of diagnosis, San Francisco, 2005-2011 (N=1,311)

	All HIV Infections	Recent HIV Infections	Longer-standing HIV Infections	Odds Ratio (95% CI)	P value	Adjusted OR (95% CI)	P value
Total	**N=1,311**	**N=214**	**N=1,097**				
Gender							
Female	11%	9%	12%	0.7 (0.4-1.2)	0.20	2.0 (0.9-4.7)	0.10
Transgender	5%	5%	5%	0.9 (0.5-1.9)	0.84	0.8 (0.4-1.7)	0.65
Male	84%	86%	83%	Referent	-	Referent	-
Age at HIV diagnosis (years)							
≤ 24	14%	21%	12%	4.8 (2.3-9.8)	< 0.0001	3.6 (1.7-7.6)	0.0009
25-29	18%	23%	17%	3.8 (1.8-7.7)	0.0003	2.7 (1.3-5.7)	0.009
30-39	30%	30%	30%	2.7 (1.4-5.5)	0.004	2.2 (1.1-4.6)	0.03
40-49	26%	21%	28%	2.1 (1.0-4.2)	0.04	1.8 (0.9-3.7)	0.12
≥ 50	12%	5%	13%	Referent	-	Referent	-
Race/Ethnicity							
Black	19%	14%	20%	0.7 (0.5-1.1)	0.12	1.0 (0.6-1.6)	> 0.99
Hispanic/Latino	27%	29%	27%	1.0 (0.7-1.5)	0.87	1.0 (0.7-1.5)	0.84
Asian/Pacific Islander	7%	8%	7%	1.1 (0.7-2.0)	0.63	1.1 (0.6-2.0)	0.67
Other/Unknown	4%	5%	3%	1.3 (0.6-2.8)	0.43	1.4 (0.7-3.1)	0.36
White	43%	44%	43%	Referent	-	Referent	-
HIV Transmission Risk							
Men who have sex with men	76%	86%	75%	1.6 (1.0-2.7)	0.08	1.9 (0.9-4.0)	0.12
Heterosexual	9%	3%	11%	0.4 (0.1-1.0)	0.05	0.3 (0.1-0.9)	0.02
Other/Unknown	4%	3%	3%	1.5 (0.4-4.1)	0.44	1.7 (0.6-4.9)	0.36
People who inject drugs	11%	8%	12%	Referent	-	Referent	-
Recent STI Diagnosis							
≤ 6 months prior to HIV diagnosis	12%	25%	10%	3.0 (2.1-4.4)	< 0.0001	2.4 (1.7-3.6)	< 0.0001
> 6 months/none prior to HIV diagnosis	88%	75%	90%	Referent	-	Referent	-
HIV Transmission Cluster							
Linked to a cluster with ≥ 2 cases	45%	57%	42%	1.8 (1.4-2.5)	< 0.0001	1.8 (1.3-2.4)	0.0003

		All HIV Infections	Recent HIV Infections	Longer-standing HIV Infections	Odds Ratio (95% CI)	P value	Adjusted OR (95% CI)	P value
Total		**N=1,311**	**N=214**	**N=1,097**				
	Not linked to a cluster	55%	43%	58%	Referent	-	Referent	-