HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2024 August 12.

Published in final edited form as:

Clin Infect Dis. 2021 November 02; 73(9): e3244–e3249. doi:10.1093/cid/ciaa1834.

Identification of a Human Immunodeficiency Virus Type 1 and Neurosyphilis Cluster in Vermont

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Abstract

Background.—Rates of syphilis in the United States have more than doubled over the last several decades, largely among men who have sex with men (MSM). Our study characterizes a cluster of neurosyphilis cases among people with human immunodeficiency virus 1 (HIV-1) in Vermont in 2017–2018.

Methods.—Vermont Department of Health disease intervention specialists conduct interviews with newly diagnosed HIV-1 cases and pursue sexual networking analyses. Phylogenetic and network analyses of available Vermont HIV-1 polymerase (*pol*) sequences identified clusters of infection. Fishers-exact and independent *t*-tests were used to compare people with HIV-1 within or outside an identified cluster.

Results.—Between 1 January 2017 and 31 December 2018, 38 residents were diagnosed with HIV-1 infection. The mean age was 35.5 years, 79% were male and 82% were White. Risk factors for HIV-1 included MSM status (79%) and methamphetamine use (21%). Eighteen cases (49%) had HIV-1 viral loads (VLs) >100 000 copies/mL and 47% had CD4 cell counts <200/mm^3. Eleven of the 38 (29%) had positive syphilis serology, including four (36%) with neurosyphilis. Sexual networking analysis revealed a ten-person cluster with higher VLs at diagnosis (90% with VLs > 100 000 copies/mL vs 33%, $P = 0.015$). Phylogenetic analysis of *pol* sequences showed a cluster of 14 cases with sequences that shared 98%–100% HIV-1 nucleotide identity.

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Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC) or any of the authors' affiliated institutions.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Presented in part: 2020 Conference on Retroviruses and Opportunistic Infection. Boston, MA, 10 March 2020. Abstract 1051.

Conclusions.—This investigation of newly infected HIV-1 cases in Vermont led to identification of a cluster that appeared more likely to have advanced HIV-1 disease and neurosyphilis, supported by phylogenetic and network analyses.

Keywords

syphilis; neurosyphilis; HIV-1

Syphilis incidence in the United States has been rising steadily over the past 2 decades. In the United States, there were approximately 8700 cases of syphilis in 2005 followed by more than 35 000 in 2018, the highest rate since 1993 [1-3]. Since 1950, syphilis has been linked with sexual practices among men who have sex with men (MSM) [4]. Despite public health efforts to promote safer sex, the use of methamphetamine, a highly addictive psychoactive stimulant associated with decreased inhibition and enhanced sexual desire, became popular within MSM communities in the 1990s and 2000s [5].

Several case reports and retrospective chart reviews suggest a strong association between newly diagnosed cases of human immunodeficiency virus type 1 (HIV-1) and ocular syphilis, a form of neurosyphilis [6-8]. Additional national interest in neurosyphilis followed the clusters of cases in 2014–2015 in Seattle, Washington, and San Francisco, California, occurring largely among MSM living with HIV-1 [9]. Our study characterizes a recent cluster of neurosyphilis cases among individuals living with HIV-1 in Vermont, which prompted exploration of sexual partnerships, specific sexual behaviors, and other transmission dynamics to help explain HIV-1/syphilis coinfection in Vermont.

METHODS

The Vermont Department of Health (VDH), as part of standard surveillance, collects all laboratory testing results for HIV-1 and syphilis. HIV-1 data reported to the VDH are housed in the enhanced HIV/AIDS Reporting System Surveillance System. Under the Reportable and Communicable Diseases Rule [10], laboratories are required to report specific HIV-1–related laboratory results, including positive fourth-generation antigen/ antibody testing that indicates possible HIV-1 infection, CD4 counts ≤200 cells/mm^3 and/or ≤14% of total lymphocytes, and all HIV-1 viral load (VL) results, including those below the assay limit of detection. Syphilis serologies are similarly captured, including *Treponema pallidum*-specific immunoglobulin G antibodies, rapid plasma reagin, fluorescent treponemal antibody absorption, and Venereal Disease Research Laboratory (VDRL) reactive tests on serum and cerebrospinal fluid (CSF) samples.

VDH disease intervention specialists (DISs) interview newly diagnosed cases of HIV-1 and syphilis to explore risk factors for infection acquisition and transmission, identify sexual contacts, and ensure engagement into clinical care. DISs follow the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Guidelines for treatment and to coordinate access to care within appropriate clinical settings [11]. Finally, DISs contact all HIV-1 and syphilis cases to explore specific risk behaviors, including sexual practices and illicit drug use. This information is then entered into the VDH Electronic Disease Surveillance System.

All newly diagnosed cases of HIV-1 in Vermont from 1 January 2017 to 31 December 2018, inclusive, were reviewed. As most cases were followed at the University of Vermont Medical Center (UVM-MC), we collected clinical data through medical record review. This study received institutional review board approval from both the VDH/Agency of Human Services and UVM-MC. Information compiled for each case included demographic data and other contact tracing data including risk factors for HIV-1 acquisition, HIV-1 polymerase (*pol*) genotype sequence from antiretroviral drug resistance testing, HIV-1 VL and CD4 counts at the time of diagnosis, syphilis testing, and clinical information associated with the diagnosis and management of HIV-1 and syphilis infections.

Identifying syphilis stages as well as ocular syphilis, a form of neurosyphilis, included review of syphilis serology and CSF VDRL results, treatment history, and, when available, medical specialty notes. Because some syphilis patients declined lumbar puncture and/or formal ophthalmological evaluation, the diagnosis of neurosyphilis and ocular syphilis was made clinically. Laboratory-confirmed syphilis cases were defined as neurosyphilis if patients fulfilled diagnostic criteria for syphilis with demonstrated signs and/or symptoms that involved the central nervous system. Ocular syphilis cases were based on laboratory-confirmed syphilis and endorsement of new visual signs and/or symptoms (eg, blurry vision, light sensitivity).

We used phylogenetic analysis of available Vermont HIV-1 *pol* sequences to identify infection clusters [12]. Briefly, while DISs pursued newly reported cases of HIV-1 infection from January 2017 to December 2018, the full phylogenetic dataset included all Vermont *pol* sequences from January 2016 to December 2018 generated at commercial laboratories. Additional related *pol* sequences identified in a search of the GenBank database using Basic Local Alignment Search Tool (BLAST) software and HIV-1 subtype J *pol* sequences as an outgroup were included in the analysis. We aligned sequences using the Molecular Evolutionary Genetics Analysis software [13] and performed maximum likelihood phylogenetic analysis with FastTree v2.1 [14]. Trees were visualized using FigTree v1.4 [15]. Phylogenetic clusters were defined when HIV-1 *pol* sequences shared nucleotide identity of greater than 98% and node support greater than 0.99. HIV-1 subtyping was done using COMET [16].

We used MicrobeTrace [17] to visualize epidemiologic and HIV-1 *pol* sequence data to explore transmission dynamics of the large cluster of cases identified via phylogenetic analysis [18]. Genetic networks were constructed using a Tamura-Nei genetic distance (*d*) cutoff of 1.5% followed by application of a nearest neighbor algorithm (NNA) in MicrobeTrace. The NNA traverses the *d* matrix and finds the closest links among all distance pairs and adds a link when it finds the lowest *d* between the pairs while maintaining cluster connectivity. When there are multiple links to different cases, the NNA identifies multiple equal low distances between the pairs. This approach is particularly useful for understanding the historical context of an entire cluster [19].

Descriptive statistics were used to summarize patient characteristics including sex, age, race and ethnicity, county of residence, and disease-specific details. Fisher exact and independent *t* tests were used to compare cluster vs noncluster groups.

RESULTS

Between 1 January 2017 and 31 December 2018, 38 Vermont residents with a new HIV-1 diagnosis were identified. This represented a notable increase from 18 new HIV-1 cases between 1 January 2015 and 31 December 2016 [20]. The number of new cases living with HIV-1 in 2017–2018 per month, with or without concomitant syphilis, is shown in Figure 1.

Characteristics of these 38 HIV-1 cases are listed in Table 1. The median age was 35.5 years, 79% were male, and 82% identified as White. Approximately 42% of cases resided in the primary urban county of Chittenden, including Burlington. Risk factors for HIV-1 acquisition included MSM status (79%) and methamphetamine use prior to sex in the past 6 months (21%). Eighteen cases (49%) had HIV-1 VLs > 100 000 copies/mL, and 47% had CD4 cell counts <200/mm^3. Eleven (30%) newly diagnosed HIV-1 patients had a positive syphilis serology test. Of these 11 syphilis patients, 4 (36%) met clinical criteria for either neurosyphilis or ocular syphilis. Risk factors for concomitant HIV-1 and syphilis infection included injection drug use, methamphetamine use, and MSM status (data not shown).

Further investigation of sexual partnerships and illicit drug use revealed a cluster of 10 cases living with HIV-1. Of these cases (Table 1), 8 (80%) were MSM and 7 (70%) reported methamphetamine use. At diagnosis, 7 (70%) had CD4 cell counts <200/mm^3 and 3 (30%) had signs or symptoms suggestive of either neurosyphilis or ocular syphilis. Comparing individuals within or outside of the epidemiologic cluster (Table 1), the only statistically significant difference between the 2 groups was that those in the cluster were more likely to have higher HIV-1 VLs at diagnosis (90% with VLs > 100 000 copies/mL vs 33%, P = .015).

To understand if these 10 cases were part of an HIV-1 transmission cluster, we performed phylogenetic analysis of 105 Vermont and 100 GenBank reference *pol* sequences from 2016 to 2018. We identified a 14-member cluster and a 2-member cluster with strong support (Figure 2). The 14-person cluster contained the 10 DIS-identified cases from 2017–2018 and an additional 4 cases who did not report contacts to a DIS. The 14 *pol* sequences shared 98%–100% HIV-1 nucleotide identity. The 4 new cases (K–N) were all MSM. Cases K–M were diagnosed with HIV-1 in 2018. Case N was diagnosed with HIV-1 in 2016 and reported intravenous drug use. Sequences in the 2-member cluster shared 99.5% nucleotide identity and were from syphilis-uninfected MSM with HIV-1 infection diagnosed in 2018. All Vermont sequences in our dataset were HIV-1 B subtypes except for 8 non-B subtypes that did not cluster.

MicrobeTrace network analysis confirmed the 14-member cluster identified using phylogenetic inference (Figure 3). The network results further illustrate that exclusion of the HIV-1 *pol* sequences from persons who did not report contact with others in the analyses would have missed their linkage to the cluster. Specifically, exclusion of case N diagnosed with HIV-1 in 2016 would have significantly reduced our understanding of the transmission network in this investigation. Case N had the most total links (n = 6), the most links with other cases with syphilis (n = 5), and the most links to persons who reported methamphetamine use (n = 4) in the network. Cases K, L, and M were located on the outer

edges of the network and had only 1 link to another case. Nonetheless, they represent the leading edge for potential continued growth of the network. At a 0.5% genetic distance threshold, the 14-member cluster disassociates into 2 dyads (A and C; H and M) and 10 singletons (not shown).

DISCUSSION

Our investigation in the rural state of Vermont identified 38 new HIV-1 cases in 2017–2018 and a 14-person cluster of HIV-1 cases (1 diagnosed in 2016) with 9 syphilis coinfections. Syphilis infection is known to increase HIV-1 acquisition by at least 2-to 5-fold, likely through both biological and behavioral factors [21-24]. Some studies suggest that syphilis among individuals living with HIV-1 may increase HIV-1 VL and suppress CD4 count [25, 26]. Indeed, we found higher HIV-1 VLs in the cluster that syphilis could be augmenting. Consequently, clinical guidance on the care of patients living with HIV-1 prompts syphilis screening [27]. Considerable research supports that the rise in syphilis cases is largely secondary to an increase in some sexual behaviors, including condomless anal sex among MSM and communities that engage in illicit substance abuse, including methamphetamine [28, 29]. Consistent with trends noted in the past 2 decades across the United States, individuals newly diagnosed with HIV-1 and neurosyphilis in Vermont tended to be MSM, with a prominent proportion reporting recent methamphetamine use. The emergence of a cluster with advanced HIV-1 and concomitant diagnoses of neurosyphilis prompted joint efforts between disease surveillance and clinicians.

Studies from US urban settings support that there are both behavioral and biological elements that promote HIV-1 and syphilis coinfection, including condomless sex and, in some settings, serosorting (choosing sex partners based on HIV-1 serological status) and having multiple sex partners [30]. Any identification of clusters prompts discussion of the role of social networks in communities of MSM. Sexual networks with high prevalence of HIV-1 and syphilis occur commonly in densely urban US communities [31]. Less is known about sexual networks in less urban and rural settings in the context of HIV-1 risk among largely White MSM communities.

Identification of the cluster was strongly supported by both network and phylogenetic analyses of available HIV-1 *pol* sequences from Vermont. Inclusion of *pol* sequences from persons who did not report contact to a DIS expanded the cluster by 28.5%, from 10 to 14 cases. Similar results have been reported in other studies, demonstrating the utility of molecular sequences for better monitoring transmission of HIV-1 for improved public health prevention responses [32, 33]. Our finding that this large cluster disassociates at a lower genetic distance threshold into 2 pairs supports that most of the HIV-1 transmissions likely occurred in the more recent past, consistent with diagnoses from 2016 to 2018 [34]. Importantly, inclusion of an HIV-1 *pol* sequence collected in 2016 identified a historical link with syphilis infection to the cluster. This case also had the most HIV-1 genetic linkages in the transmission network and could have been an important person for public health prevention efforts if identified earlier.

The findings detailed here underscore the importance of routine syphilis screening among individuals living with HIV-1, especially during initial engagement in medical care, as well as the benefits of coupling with DIS investigation with Molecular HIV Surveillance (MHS) in rural settings. Advanced manifestations of syphilis can occur at any stage after the primary infection. Early detection is important for improved health outcomes and prevention of further infections. Even in a low incidence rural area such as the state of Vermont, the risks involved with untreated syphilis were apparent as this report indicates.

DIS investigation of a cluster of acute HIV-1 infection led to identification of several cases with comorbid neurosyphilis. Prior to this investigation, Vermont had not used MHS, but the tool proved very useful. MHS enhanced the investigation to genetically link cases to the cluster where links had not previously been determined, confirm suspected linkages, and had ancillary implications in the investigation of the syphilis cases. Ultimately, through the partnership of community infectious diseases providers and the Department of Health and its resources, a vulnerable population was quickly identified, and the spread of complications was contained and minimized.

Notable strengths of this study include describing incidence and associated behaviors with HIV-1 and syphilis infection in a largely rural setting. Focusing on both a notable increase in new HIV-1 cases and identifying a cluster led to the coordination of a sophisticated public health investigation, close local clinical engagement, and formal networking with CDC experts on describing the phylogenetic and network characteristics of this cluster. A limitation of our study is that only a minority of patients underwent formal consultations with neurology or ophthalmology specialists to help confirm their neurosyphilis or ocular syphilis infections. Our findings of roughly 30% of individuals diagnosed with ocular syphilis per clinical discretion (visual symptoms along with reactive syphilis serologies) appear more prominent than findings reported by Marra and colleagues earlier this decade. They reported a 6.0% prevalence of ocular syphilis in a cohort of individuals living with both HIV-1 and syphilis [35]. This difference likely reflects that most cases of formally diagnosed ocular syphilis rely on funduscopic examination by an ophthalmologist, with findings typically of uveitis, retinitis, neuroretinitis, or optic neuritis. Our study relied, instead, on clinical impression of disease based on subjective symptoms.

In summary, we found a high incidence of neurosyphilis infection among individuals in Vermont newly diagnosed with HIV-1. Dedicated public health efforts are needed to educate and out-reach to certain communities, including MSM and those engaged in methamphetamine use, on consistent condom use toward prevention of sexually transmitted infections, including syphilis and HIV-1 preexposure prophylaxis. Our findings also support the use of HIV-1 sequences in cluster detection and response, which is a key pillar of the national Ending the HIV Epidemic initiative [36].

Acknowledgments.

The authors thank Ellsworth M. Campbell for assistance with network analyses and Abigail Crocker for statistical analyses.

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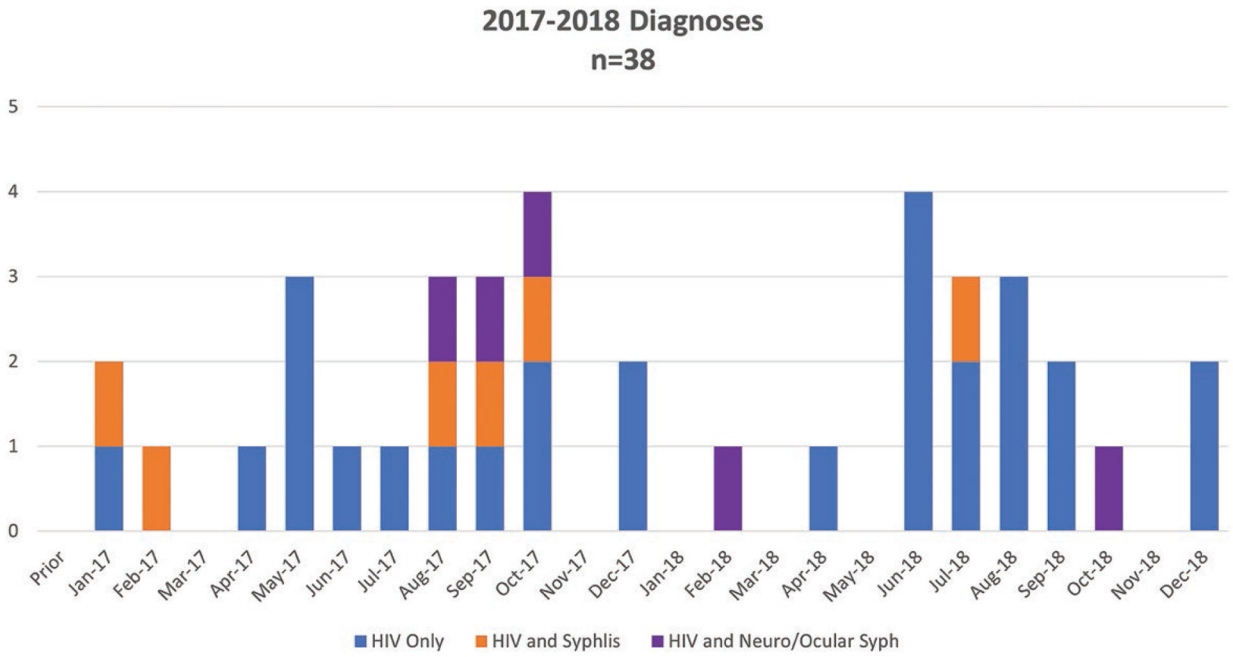

Figure 1.

Number of individuals living with HIV-1 with or without concomitant syphilis in 2017–2018, by month. Abbreviations: HIV-1, human immunodeficiency virus type 1; Neuro, neurosyphilis; Syph, syphilis.

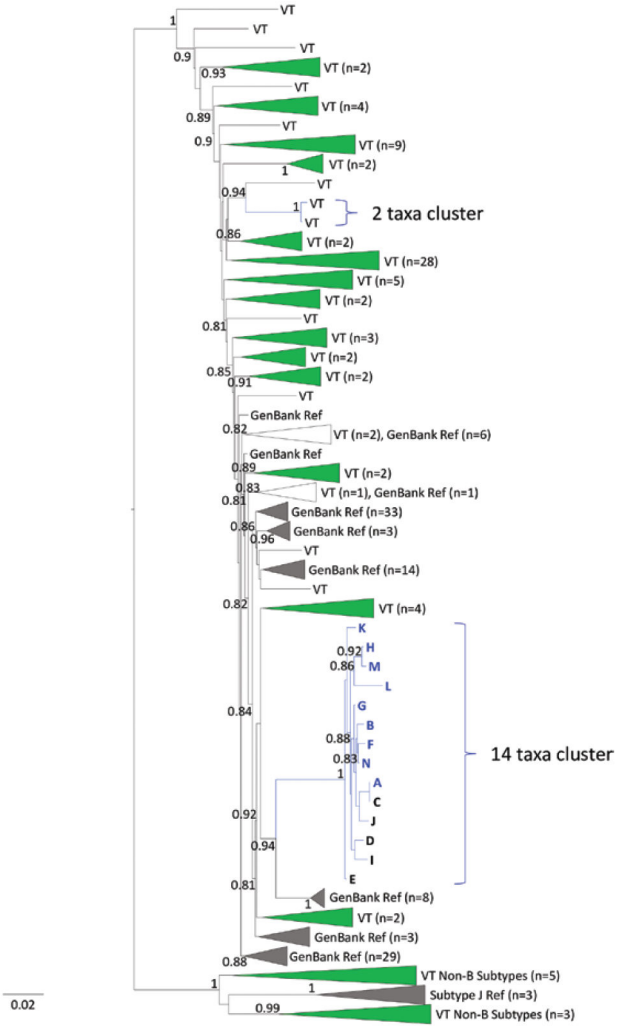

Figure 2.

Identification of a large cluster of persons living with both human immunodeficiency virus type 1 (HIV-1) and syphilis. Phylogenetic relationships inferred with maximum likelihood analysis using HIV-1 polymerase sequences from 105 persons from Vermont, 100 reference sequences identified at GenBank, and 3 subtype J reference sequences. Shimodaira–Hasegawa probabilities >0.8 are provided at phylogenetic tree nodes. Cases in the 14-member cluster with syphilis diagnoses are in blue text and tree branches. Large Vermont (green), reference (gray), and mixed clades (white) are collapsed as triangles for clarity. Number of clade taxa are provided in parentheses. Scale bar indicates number of nucleotide substitutions per site. Abbreviation: VT, Vermont.

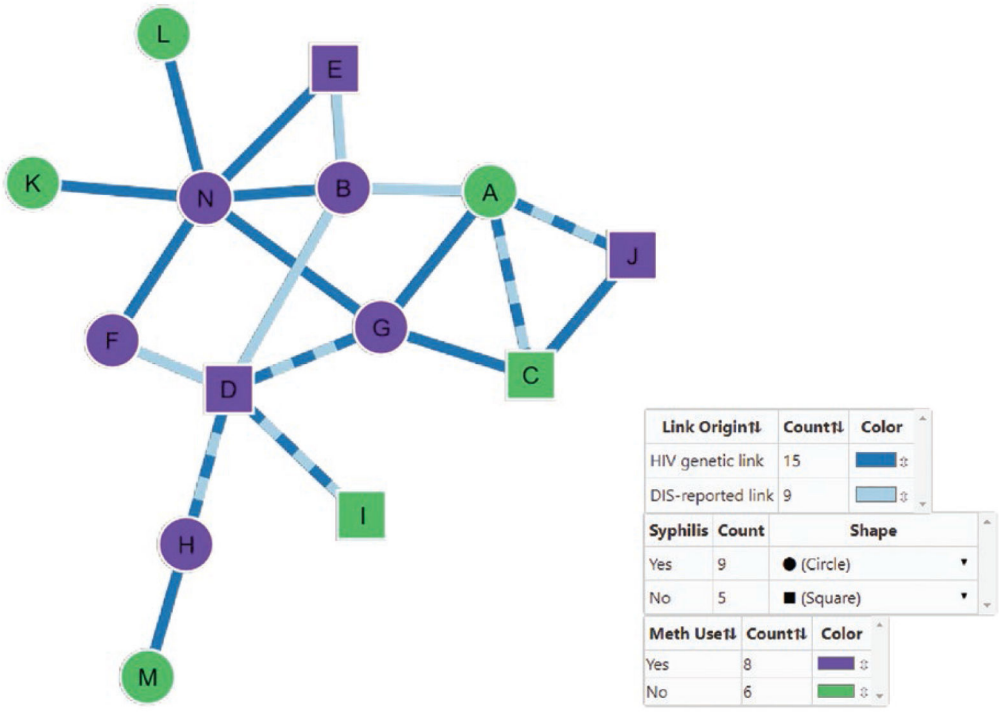

Figure 3.

HIV-1 genetic and contact tracing networks of a large 14-member cluster. HIV-1 polymerase sequences and associated epidemiologic data were combined and visualized using MicrobeTrace. A genetic distance cutoff of 1.5% was used to infer the genetic network that was then filtered using a nearest neighbor algorithm in MicrobeTrace. Network linkages with only either HIV-1 genetic links or contact tracing links are indicated with dark and light blue lines, respectively. Dashed blue lines indicate both a reported contact tracing and HIV-1 genetic link. Circles and squares represent cases diagnosed with and without syphilis infection, respectively. Cases that reported using and not using methamphetamine are indicated in the network with purple and green nodes, respectively. Abbreviations: DIS, disease intervention specialist; HIV-1, human immunodeficiency virus type 1; meth, methamphetamine.

Table 1.

Demographic and Clinical Characteristics of Cases Living With Human Immunodeficiency Virus Type 1 Identified in 2017–2018, Overall and According to Cluster Status

Characteristic	Overall (N = 38), n (%)	In Cluster (N = 10), n (%)	Not in Cluster (N = 28), n (%)	*P* Value
Age, y				
Median (25%–75%)	35.5 (26–50)	31.5 (30–34)	38 (25.5–51.5)	.476
Sex				
Female	8 (21)	1 (10)	7 (25)	.653
Male	30 (79)	9 (90)	21 (75)	
Race				
Black	4 (11)	0 (0)	4 (14)	.301
White	31 (82)	10 (100)	21 (75)	
Asian	3 (8)	0 (0)	3 (11)	
Geographic location				
Chittenden County	16 (42)	5 (50)	11 (39)	.228
Other	22 (58)	5 (50)	17 (61)	
Risk factors				
Men who have sex with men, yes	30 (79)	8 (80)	22 (79)	>.99
Methamphetamine[a]	8 (21)	7 (70)	1 (4)	
Persons who inject drugs, yes	4 (12)	1 (11)	3 (12)	>.99
Human immunodeficiency virus type 1 viral load, copies/mL				
<1000	2 (5)	0 (0)	2 (7)	.015
1000–10 000	1 (3)	0 (0)	1 (4)	
10 000–100 000	16 (43)	1 (10)	15 (56)	
>100 000	18 (49)	9 (90)	9 (33)	
CD4 category, mm^3				
<200	18 (47)	7 (70)	11 (39)	.311
200–500	8 (21)	1 (10)	7 (25)	
500+	12 (32)	2 (20)	10 (36)	
Syphilis				
Primary or secondary	11 (30)	5 (50)	6 (22)	.125

Characteristic	Overall (N = 38), n (%)	In Cluster (N = 10), n (%)	Not in Cluster (N = 28), n (%)	*P* Value
Neuro/ocular	4 (36)	3 (60)	1 (17)	.242

P values calculated using the Fisher exact test.

[a] Unable to calculate *P* value for methamphetamine use given capture of several categories of use (eg, in the past 6 months, lifetime use).