HIV Transmission Hotspot Detection Combining Sexual and Phylogenetic Network Analysis

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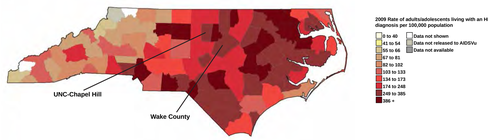
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BACKGROUND

- Contact tracing is the cornerstone of public health HIV test and treat interventions. However, contact tracing is limited by the ability to locate persons for interview and testing. The extent of these limitations is unknown.
- Using molecular approaches may provide new avenues to supplement routine contact tracing, once contact tracing gaps are identified. The main objective of this analysis is to evaluate whether molecular approaches can identify contact tracing gaps in order to supplement it.
- Wake County (Figure 1) is a metropolitan county in NC with a population of approximately 963,000 in 2012-2013, including >2,800 PLWHA [1]; HIV incidence was 16.3 per 100,000 population in 2012 [1].
  - Wake County was chosen as a pilot for this analysis because there is a high number of new infections annually, many HIV patients have available *pol* gene sequences, it is expected that many new patients will have partners outside of the county which allows us to compare contact tracing and sequencing coverage, and we have an ongoing relationship with the Wake County Health Department.

Figure 1. HIV prevalence by NC county in 2009 [2].



METHODS

- The local sexual network was constructed using partner contact tracing for newly diagnosed index cases from 2012-2013 in Wake County and their traceable first-degree partners.
  - Data were abstracted from the NC Department of Health and Human Services HIV database, including Disease Intervention Specialist (DIS) interviews to elicit partnerships; DIS attempt to interview all persons newly diagnosed with HIV across the State of NC.
    - Persons were included as cases if they were newly diagnosed with HIV while residing in Wake County and 18 years of age or older.
    - DIS collect information on contacts that occurred in the last 3 months for persons with acute HIV, in the last 6 months for persons with recent HIV infection, and in the last 12 months for chronic HIV infection.
  - DIS attempt to locate and interview all named contacts (sexual and social) who reside in NC and are not known to be previously infected with HIV.
  - Abstracted data included demographic data, partnership data, data related to HIV testing history, HIV-related lab results, and co-infection with syphilis.
  - The network was created using UCINET v6.587 [3] and visualized using NetDraw v2.155 [4].

Phylogenetic Analyses

- We identified putative transmission clusters using available HIV-1 *pol* sequences from the index cases, their HIV-positive partners, and 15,247 background references sampled in NC.
- Sequences spanned full length PR and partial RT and were derived from drug resistance genotypes performed by LabCorp 1997-2014.
- First available sequences per individual used in all analyses.
- Sequences were aligned using MUSCLE2 and edited manually in Bioedit.
- Probabilistic data matching was used to link sequences to the surveillance data based upon same date of birth, same gender, and date of sequence greater than or equal to date of diagnosis.
- Maximum-likelihood phylogenies were constructed in FastTree with the GTR model. Statistical support of clades was initially assess with local support values [SH-test].
- Putative transmission clusters (TCs) defined as clades with high branch support (>0.90 SH) and maximum pairwise genetic distance <=3.5% between all sequences.
- Clusters were confirmed with Bayesian MCMC approach in BEAST v1.8.2 [5].
- "Study" TCs were defined as TCs that included 2 or more persons (index or HIV-positive partner) from the Wake County partner tracing network that was constructed.

RESULTS

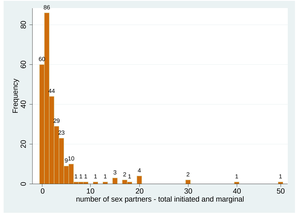
Study Population

- 280 index cases and 383 locatable, unique non-index partners were identified.

Table 1. Characteristics of index cases and partners.

	Index n (%)	Partner n (%)
Gender		
Male	232 (83)	327 (85)
Female	44 (16)	53 (14)
Transgender (M to F)	4 (1)	3 (1)
Race/ethnicity		
non-Hispanic White	69 (25)	120 (31)
non-Hispanic Black	183 (65)	238 (62)
Hispanic	23 (8)	12 (3)
other	5 (2)	8 (2)
unknown	0	5 (1)
Age		
mean (SD)	36 (12)	31 (11)
HIV status		
Positive, with HIV sequence	148 (53)	82 (21)
Positive, no HIV sequence	132 (47)	49 (13)
Negative	0	148 (39)
unknown	0	104 (27)

Figure 2. Sex partners reported by the interviewed index cases (n=225).



- Index Cases (N=280)
  - At diagnosis: 4% acute HIV, 70% chronic HIV (includes 4% recent HIV), 27% concurrent HIV and AIDS diagnosis.
    - 70% (n=195) had no negative previous HIV tests per State HIV database.
    - All 11 acutely-infected patients had a previous test on record, although only 3/11 had a negative test within 1.5 months of the first positive test.
  - 80% of the 280 index cases (n=225) were interviewed by Disease Intervention Specialists.
    - The 225 interviewed index cases reported 854 sex partners and 34 social contacts (4 average contacts per person). 446 contacts (50%) were traceable.
    - Among 225 interviewed: mean number of sex partners in window period is 3.6 +/- 6.0. Range 0-50 (Figure 2).
- Partner HIV stage at diagnosis using the last record (N=168, as 254 partners were of negative or unknown status, may include index cases): 4% acute HIV, 70% chronic HIV (includes 6% recent HIV), 26% concurrent HIV and AIDS diagnosis.

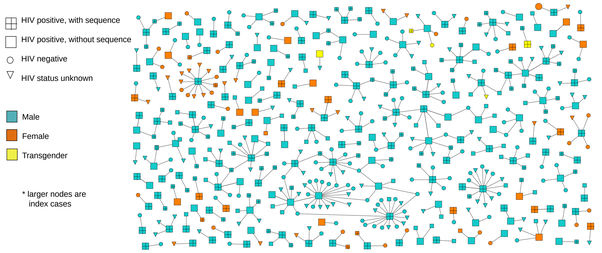
Table 2. Characteristics of index case contacts, where sexual preference is factored from index and sexual partner gender.

			ALL contacts degree			Sex partner contact		
Sexual Preference	**Freq.**	**Percent**	**zero**	**1**	**2 to 19**	**zero**	**1**	**2 to 19**
MSM	392	(59.1)	0	301	91	0	305	87
MSW	50	(7.5)	0	38	12	0	38	12
MSMW	6	(.9)	0	0	6	0	0	6
FSM	73	(11.)	0	64	9	0	67	6
TWM	5	(.8)	0	5	0	0	5	0
No sex contacts	137	(20.7)	104	31	2	137	0	0

Contact Networks

- There were 446 network partnerships (414 sexual and 32 social).
- 663 unique persons in network, including 411 HIV-positive persons.
  - Most persons in the network were Black (64%), MSM (59%), and between ages 25-45 years (IQR).
  - Of the 383 unique non-index partners, 36% resided outside of Wake County.
- The final network was comprised of 137 components of size 2 or greater, with another 104 isolates (Figure 3).
  - Component size 1-65 nodes. 104 isolates (not shown), 75 dyads, 22 triads, and 40 components size 4-65.
- Network largely disconnected. 62% components (n=85) MSM or men who have sex with transgender (MST) only.

Figure 3. Non-singleton nodes in the sexual network (n=559).



Transmission Clusters

- 56% of HIV-positive persons (230/411) had an available *pol* gene sequence (53% of index cases and 63% of HIV-positive partners).
  - Compared to cases without sequences, cases with sequences were similar by sex, had a lower proportion of Black race, and an earlier date of diagnosis.
- 74% of persons with a sequence (171/230) were in a transmission cluster (TC).
  - TC members were more likely to be men, men reporting male contacts vs. having no named partners, and younger.
- In 3 large TC, 75% of sequences were from samples collected 2012-2014, indicating growth after 2012 and therefore significant ongoing transmission (Figure 4 shows cluster 1076).
- There were a total of 118 TCs with at least one person from this Wake County investigation. The TC size with at least one person from this investigation ranged from 2-36 persons, with 804 total sequences from unique persons in those TC (Figure 5).
- The 4 largest TC (range 6-36 members) involved 14 index and 5 partner cases distributed in 11 network components (Figure 6).
- 87 persons were in 34 TC with another person from the study (a "study TC").

Figure 4. Expansion of Cluster 1076 (n=36) over time.

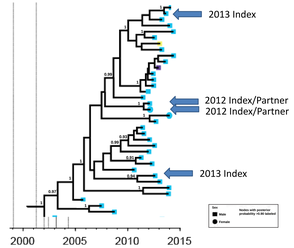
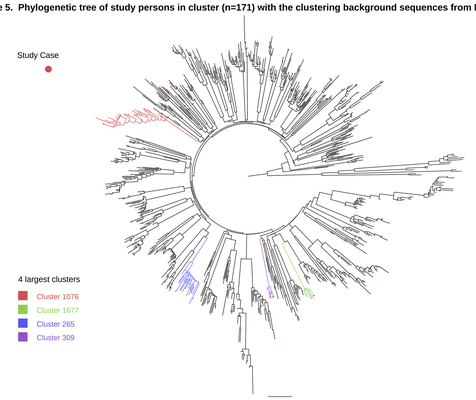
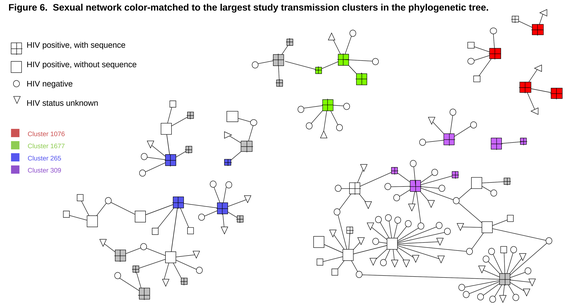


Figure 5. Phylogenetic tree of study persons in cluster (n=171) with the clustering background sequences from NC (n=663).



- Only 52% of persons in a study TC (45/87) were in the same network component as at least one other person in the study TC; the other 48% (n=42) were phylogenetically linked to another person in the study but not identified as being in the same linked group as that person via the network constructed from contact tracing interviews (Figure 6). Both partners in a study TC were in the same network component in every heterosexual pair where both persons had a sequence.

Figure 6. Sexual network color-matched to the largest study transmission clusters in the phylogenetic tree.



CONCLUSIONS

- We were able to identify transmission hotspots among high-risk persons that were not detected through contact tracing.
- Further analysis of the gaps in both sequence data and elicited contact networks is warranted. Contact tracing is limited by persons who cannot be located, refusal bias, and capturing partnerships that may not reflect transmission if significant time occurred between infection and interview. Sequence analysis is limited by inability to infer directionality and unsampled persons who haven't been diagnosed or who do not have a sequence available.
- Combining contact tracing and phylogenetic analysis provides a more complete understanding of HIV transmission.
- Future analysis includes application of mathematical models to the evaluate differences between the phylogenetic and contact tracing networks so that we may find ways to enhance contact tracing with data from HIV sequences.

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