Using Molecular HIV Surveillance Data to Guide Public Health Practice in NYC

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Discussion with UCHAPS colleagues
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Plan for Today

• Background: the NYC HIV epidemic
• Background: laboratory reporting enabling Molecular HIV Surveillance
• Genesis of “phylo project”, which uses MHS to guide public health practice
• Update, process and outcomes
  – Surveillance
  – Field Services/DIS
Background—The HIV Epidemic in NYC

- PCP and KS among young MSM reported to *MMWR* June and July 1981
  - First verified case is a perinatal transmission backdated to a 1977 city birth
- Diagnoses peaked at 12,737 in 1993
  - Steady decline
- Deaths peaked at 8,341 in 1994
  - Dramatic drop between 1995 and 1996 with introduction of HAART including PI
- 2,520 new diagnoses in 2015
  - 71% initiated care within 90 days of initial diagnosis
  - 83% of cases in care were suppressed on their last VL
- Registry now contains cumulative total of 240,082 cases and >10 million laboratory reports
History of the HIV Epidemic, NYC 1981-2015

- AIDS case reporting mandated by NYS
- CDC AIDS case definition (23 OIs) implemented
- HIV-related cause of death reporting begins
- AIDS case definition expanded (CD4 <200, 26 OIs)
- HAART introduced
- NYS expands AIDS reporting to include HIV
- NYS HIV reporting law takes effect
- HIV surveillance expands to include all HIV-related laboratory reports
- NYS mandates routine offer of HIV test
- ART for all PLWHA recommended

PLWHA=People living with HIV/AIDS

* Data on 2015 deaths are incomplete.
NYS Laws that Underpin MHS

• **1981**: MMWR reports PCP and KS. AIDS surveillance begins.
• **1983**: NYS mandates named AIDS case reporting
• **1997**: NYS mandates newborn screening
• **2000**: NYS mandates named HIV reporting and reporting of WB+, CD4<500 and detectable VL
• **2005**: NYS mandates electronic reporting and adds *all* VL and CD4 values, genotypes
• **2010**: NYS mandates:
  - Offer of voluntary HIV testing to patients at every health care encounter
  - Proactive linkage to care for all newly diagnosed persons
    • Baseline labs should include genotype
Background—Genotype Reporting

• Nucleotide sequence from all genotypes ordered by NYC physicians is reportable to surveillance

• The NYC sequence archive
  – Dates from June 1, 2005
  – Contains 150,240 sequences representing 67,487 unique individuals

• 57.8% of new cases are genotyped within 3 months of diagnosis; this early genotype is hypothesized to represent (the closest we can get to) their transmission virus
How we got started

• In 2012, we started working with colleagues at UCSD who had developed a computationally efficient means of genetic network construction that estimates the genetic distance between sequences in the NYC genotype archive.

• This cluster construction method was in its infancy then, and is now CDC’s standard means of ascertaining close genetic relationships among the transmission viruses of newly diagnosed persons.

• We began by looking back at our existing data and realized….long gestation…. 
Molecular HIV Surveillance Data Flow

- Patient receives HIV diagnosis
- Patient presents for care
- Physician orders genotype
- Genotype processed at laboratory
- Laboratory reports:
  - Polymorphisms and resistance profile → doctor
  - Nucleotide sequence → NY State DOH
  - NYC providers’ sequences → NYC
- NYC cleans, deduplicates, concatenates, aligns, matches to registry
- NYC sends out (Stanford, UCSD) for analysis
- NYC receives resistance interpretation and cluster
Timeline from Diagnosis to Data

- Red arrow is long – 4 months at best
  - Patient must get into care (71% within 3 mos)
  - Dr must order baseline genotype (54% in 2015)
  - Sequence must be reported to state (1-4 mos)
  - State must parse out NYC and send to us (1 mo)
  - Clean, deduplicate, concatenate, align, match (1 wk)
  - Send to Stanford for analysis, send to UCSD for cluster
  - Receive results, add to eHARS, create analysis files

- Why does the long red arrow matter?
- Time frame: OK for analysis (see →)
  - No good for public health intervention (e.g., AHl and partner notification, linkage or return to care)
**RISK FACTOR PREDICTS GEOGRAPHIC SPREAD WITHIN NEW YORK CITY HIV-1 TRANSMISSION NETWORK AND BEYOND**

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1University of California, San Diego, 2Veterans Affairs San Diego Healthcare System, 3Vanderbilt Department of Health and Human Hygiene

**BACKGROUND**

1HIV transmission networks inferred from sequence data can be used to identify risk groups for targeted interventions.

Transmission disparities spread over larger geographic areas may require different methods of intervention than geographically localized crashes.

**NETWORK CONSTRUCTION INFORMATION**

- SNP: 1,412 individual's or putative single nucleotide polymorphism.

- Phylogenetic tree: Maximum likelihood method.

- Neighbor-joining tree: Minimum evolutionary tree method.

- Distance matrix: Jukes-Cantor distance.

**RESULTS**

- The transmission network was constructed using the Neighbor-Joining method with 1,412 individuals.

- The network was then pruned to remove nodes that were not connected to the main transmission path.

- The resulting network consisted of 135 connected components, with the largest component containing 72 nodes.

**CONCLUSIONS**

- This study highlights the importance of using transmission networks to identify risk groups for targeted interventions.

- The results suggest that transmission networks can be used to identify risk groups for targeted interventions.

- Further studies are needed to validate these findings and to determine the effectiveness of targeted interventions.
Transmitted Antiretroviral Drug Resistance in New York State, 2006-2008: Results from a New Surveillance System

Adam C. Roedhead1, Daniel E. Gordon2, Zhongyan Wang2, Bridget J. Anderson1, Kathleen S. Brussou2, Maria A. Kuznetsova3, Lisa A. Fargione1, Lou C. Smith4, Lucie V. Torian5

1The New York City Department of Health and Mental Hygiene, HIV Epidemiology and Field Service Program, New York, New York, United States of America, 2The New York State Department of Health, Bureau of HIV/AIDS Epidemiology, Albany, New York, United States of America

Abstract
Background: HIV-transmitted drug resistance (TDR) is a public health concern because it has the potential to compromise antiretroviral therapy (ART) at the population level. In New York State, high prevalence of TDR in a local cohort and a multicase resistant case cluster led to the development and implementation of a statewide surveillance system.

Methods/Results: We conducted a cross-sectional analysis of the 13,189 cases of HIV infection that were newly diagnosed and reported in New York State between 2006 and 2008, including 4,139 with HIV genotypes drawn within 3 months of initial diagnosis and electronically reported to the new resistance surveillance system. We assessed compliance with DHHS recommendations for genotypic resistance testing and estimated TDR among new HIV diagnoses.

Principal Findings: Of 13,189 new HIV diagnoses, 3,985 (30%) had laboratory evidence of utilization of related medical care, and 4,139 (31%) had a genotypic pattern within 3 months of initial diagnosis. Of these, 11.3% (95% confidence interval 0.9, 16.1) had no evidence of TDR. The proportion with mutations associated with any antiretroviral regimen in the NRTIs (nAIDS=43%, nNRTIs=61%, nPIs=81%), the proportion with mutations associated with resistance to any regimen (nAIDS=18%, nNRTIs=31%, nPIs=44%), and the proportion with mutations associated with any regimen (nAIDS=21%, nNRTIs=31%, nPIs=44%) were all significantly higher than expected. Approximately 1% (297/3985; 95% CI 0.7, 1.5) were assigned to high transmission risk. Conversely, approximately 1% (34/3985; 95% CI 0.6, 1.4) were assigned to low transmission risk. These differences were significant (p<0.001). The analyses showed that the median time to high transmission risk was 14 days, and the median time to low transmission risk was 4 days.

Conclusions/Significance: TDR appears to be more evenly distributed and stable among newly diagnosed HIV patients in New York State. Multicase TDR is rare. Less than half of new diagnoses initiating care are receiving a genotype by drug regimen guidelines.

Social and Genetic Networks of HIV-1 Transmission in New York City

Joel O. Wertheim1, Sergei L. Kasakovski Pond2, Lisa A. Fargione1, Sanjiv R. Mehta1, Ben Murrell1, Sharmilla Shah1, Dwayne M. Smith1, Konrad Sheffler1, Lucie V. Torian1

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Abstract

TRANSMITTED DRUG RESISTANCE

<table>
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<th>Year of Diagnosis</th>
<th>Total Diagnoses</th>
<th>Tested within 3 months</th>
<th>Not Tested within 3 months</th>
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<td>2011</td>
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[Table 11.1: Number of new HIV diagnoses with a genotype within 3 months of diagnosis, NYC 2008-2012]

[Figure 11.1: Proportion of new HIV diagnoses with transmitted drug resistance (TDR), NYC 2008-2012]

To the Editors:

Readers of 2 articles recently published in *AIDS*—1,2 may be interested in the transmitted drug resistance (TDR) observed during the first 5 full calendar years of routine population-based genotype surveillance in New York City.

Supported by a Cooperative Agreement with the Centers for Disease Control and Prevention, 5U08-09, 202, R02-CDC-U002325839.

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www.jids.com | e119
Shortening the Red Arrow

- What if diagnosis and genotype data were available at the same time? or almost...
- We could shorten the red arrow to a few days
- Field personnel would have data they need for PS now
- One solution: *Point-of-diagnosis genotyping*
  - DOH bought a sequencer, trained staff, got certified
  - Now sequencing all HIV tests from the DOH STD clinic network immediately upon diagnosis (not sure if old or new dx)
  - Sequence routed to epi, epi sends to UCSD for cluster
  - Epi gives data on viremic/OOC cluster members to FSU
  - FSU interviews index and viremic/OOC in network, offers testing to undiagnosed named partners, offers return to care to OOC, offers adherence support to viremic in care
Background – DIS to All New Diagnoses

• Every new case in NYC (N=2400/yr) is contacted and offered an interview with partner notification and voluntary testing (84% accept)

• Question 1: Do named partners comprise the index patient’s entire sexual and social network?

• Answer: No
  – The average patient names 0.5 partners
  – The virus of 22% of patients in NYC overall, 54% of MSM, and 62% of patients diagnosed in STD and LGBT clinics clusters genetically with one or more other genotypes in surveillance, i.e., has a genotype that is similar at a specified concordance cutoff (our local cutoff is 1.5%)
  – We are also missing all of the “singletons”
Named vs. Genetic Partners

• Question 2: do patients name plausible transmission partners, i.e., does their named partner’s virus have a similar genotype?

• Answer: sometimes (59%)

• Outcome varies by risk factor:
  – HET men and women: 77% name at least one partner whose genotype is similar
  – IDU: 38% name a partner with a similar genotype
  – MSM: 42% named a partner with a similar genotype

• Limitation: we do not have genotypes on the entire prevalence pool, so networks are never fully mapped
  – There are many apparent singletons in our archive
Expanding PS to Genetic Partners

• Hypothesis: Expanding partner services to include genetic as well as named partners has potential to slow cluster growth and ultimately to slow incidence
Special Phylo Project
New Diagnoses in the SHCs

• Rolled out Feb 1, 2016
• Focuses on persons testing HIV+ in the DOHMH Sexual Health Clinics
  – In 2016, the NYC Public Health Laboratory built capacity to perform point-of-diagnosis genotyping
  – SHCs diagnose ~250 cases/year
  – Majority are new diagnoses (do not match to an existing registry record
  – SHCs represent ~10% of new diagnoses citywide
Workflow of “Phylo Project” Laboratory to Surveillance

• Surveillance receives STD index genotype from PHL
  – Lag time between diagnosis at SHC and report of genotype to surveillance is 1 month

• Surveillance, with assist from UCSD, cleans and aligns sequence, pings against NYC sequence pool, computes pairwise genetic distance between the index sequence and the earliest sequence of each other member of the pool (soon to expand to all sequences)

• If <1.5% discordant bases, report cluster

• Here are examples from 2012-2016
What does the pairwise concordance output look like?

Tables showing edges/degrees and distances
Cluster diagrams
## Example of a Table from 2 MSM Clusters

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<th>NodeID</th>
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Example of a Table We Create from Surveillance

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Clusters come in various shapes and sizes

Here is a kite cluster from 2012 with HET man as bridge between MSM, IDU and UNK

This cluster now has 49 members and is no longer a kite
The ‘kite’ in 2016
MSM ‘hive’ cluster with multi-edge hubs and a multi-edge UNK
MSM ‘hive’ cluster with one HET female (TG?), two HET men and an IDU
This cluster of HET women was built in 2012
The same HET female cluster in 2016
2012 MSM ‘molecule cluster’ with a bridge person

This cluster now has 101 members
The ‘molecule’ in 2016
Which Partners Receive Outreach in the SHC Pilot Phylo Project?

How we triage cases for outreach:

• Index clusters with at least one other person
• Select all 1-degree genetic partners (≤1.5% discordant bases)
• Provide DIS if:
  – Out of care ≥13 months
  – Last VL was detectable and >1500 copies
Workflow of our pilot project: Laboratory to Surveillance

• Surveillance receives STD index genotype from PHL
  – Lag time between diagnosis at SHC and report to HEFSP is ~1 month

• Surveillance/UCSD cleans and aligns sequence, pings against NYC sequence pool, computes pairwise genetic distance between the index sequence and the earliest sequence of each other member of the pool (soon to expand to all sequences)

• If <1.5% discordant bases, report cluster

• For example…
Cluster with 4 New Diagnoses in 2017, 4 in 2015

PhyloID: PHL0000262

Sex: Male  Date collected: 07/03/2017
Race: Black  Age: 27
# linked partners: 6  # linked viremic: 1
# linked priority cases: 4  # linked out-of-care: 3
Cluster ID: 57  Cluster status: Permanent
STD target rank: 56  STD target percentile: 70.52
Full Network target rank: 61  Full network target percentile: 98.34

Figure 2: Transmission cluster 57 shape and cluster growth plot. Case PHL0000262 diagnosed in an STD clinic is shown in white with red label. Other STD cases are shown in white. For Frozen Database cases, color denotes transmission risk factor and shading denotes viremia status. Shape denotes sex. Label denotes year of diagnosis. See Legend for details.
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Cluster with 6 new diagnoses 2016-17

PhyloID: PHL0000269

Sex: Male  Date collected: 07/12/2017  Age: 54
Race: White

# linked partners: 7  # linked viremic: 2
# linked priority cases: 3  # linked out-of-care: 2

Cluster ID: 1978  Cluster status: Permanent
STD target rank: 141  STD target percentile: 26.78
Full Network target rank: 210  Full network target percentile: 94.29

Figure 5: Transmission cluster 1978 shape and cluster growth plot. Case PHL0000269 diagnosed in an STD clinic is shown in white with red label. Other STD cases are shown in white. For Frozen Database cases, color denotes transmission risk factor and shading denotes viremia status. Shape denotes sex. Label denotes year of diagnosis. See Legend for details.
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Work Flow
Surveillance → Field Services

• Individuals in cluster are matched to surveillance data for demographics, risk factor, last care date, last VL

• Out of care and viremic members with 1-degree (≤1.5% discordant bases) genetic separation from index sent to FSU
  – FSU verifies care and viral status

• Cases assigned to field staff on monthly basis
Closing in on the most recent, most epidemiologically relevant sections

• We re-drew these two clusters using both the permissive 1.5% cutoff and the tighter 0.5% cutoff
  – 1.5% shows the history of cluster growth
    • See the staircase on the right
  – 0.5% zooms in on the more recent pairs

• Here are the results

• We are presently constructing the phylogenetic trees that will better elucidate evolutionary time and distance
Cluster # 57
Surveillance Data Flow to FSU

432 total individuals in the dataset

112 not tested/pending

320 total sequences

168 total clusters containing 2771 members

174/2771 (6%) are OOC (13+ mos) and within 1 degree

123/2771 (5%) are viremic (1500+) and within 1 degree
## Out of Care Cases: Outcomes (As of September 1, 2017)

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*No CD4/VL ≥9 months
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<tr>
<td><strong>Outcomes among closed cases</strong></td>
<td></td>
</tr>
<tr>
<td>Facilitated more consistent HIV care</td>
<td>6</td>
</tr>
<tr>
<td>Concluded all effort (chart review + provider conference)</td>
<td>24</td>
</tr>
<tr>
<td>Deceased</td>
<td>2</td>
</tr>
<tr>
<td>Not viremic (per viral loads obtained after case investigation initiated)</td>
<td>8</td>
</tr>
<tr>
<td>In study</td>
<td>1</td>
</tr>
<tr>
<td>Moved/Out of jurisdiction</td>
<td>1</td>
</tr>
</tbody>
</table>
OOC Cases: Observations and Challenges

• Out of care cases identified as part of phylogenetic clusters were assigned to be investigated and receive outreach per the routine OOC protocol
• The focus of OOC work is re-engagement in care
• Reasons for OOC are assessed for and ancillary social services needs, such as housing, health insurance applications or substance use counseling are addressed through referrals
• Partner services are offered, but historically the yield among prevalent cases has been low
• Provider outreach to discuss phylogenetic cluster investigation has not been incorporated in the current model – “Dear Colleague” letter will be drafted and rolled out as part of future phylogenetics work with OOC persons
Viremic Cases: Challenges

- Viremic patients are in HIV care
- The potential range of services that DOHMH can offer them depends on the type of provider/facility where they receive care
- Necessary to approach provider (delicately) for consultation in assistance with investigation of public health importance
- Fieldwork is time consuming and detailed – chart review and supplemental information on mental health, ART history, adherence, substance use, comorbidities, housing, incarceration and other socioeconomic and cultural factors affecting viremia are documented
- Coordinating provider conference can sometimes take several weeks (in some cases, provider is not responsive)
Viremic Cases: Observations and Successes

• Viremic patients tended to have larger underlying issues, e.g., substance use, mental health, unstable employment and housing and require intensive and ongoing social worker/case management services
• Almost all cases were in care at facilities with integrated HIV care and case management
• Investigations have resulted in stronger DOHMH-provider collaboration – providers have been forthcoming and receptive to DOHMH intervention and supplemental assistance
• FSU DIS were successful in assisting some providers with outreach to difficult patients
Viremic Cases: Observations and Successes, Continued

• In consultation with provider, FSU DIS facilitated improved HIV care seeking for six viremic patients:
  – Made future appointments with their HIV care provider or facilitated personal outreach by provider
  – Encouraged them to keep appointments
  – Offered assistance with transportation and/or sent them Metrocards
  – Linked or re-linked them to providers’ case management services
  – Ensured that their HASA applications were complete

• In addition, DIS talked about partners, attempted to elicit partners, educated on PEP and PrEP, condom use, viral suppression and STI care and sent condoms and HIV home test kits to patients to give to partners or associates
Practical Challenges

- Will people agree to talk to us (1st time, 2\textsuperscript{nd} time)?
- Will the second interview yield more information or any useful information for public health action?
  - Will we get previously unnamed partners?
  - Will people accept RTC and adherence support?
- How best do we enhance possibility that this viremic person can achieve suppression?
  - Work with doctor to see what is needed – delicate discussion
  - Patient may be unhappy with care +/- or may have MH/SA
  - Refer to adherence support services with proven track record
  - Tailor the support to the patient’s preferences and needs
  - Track the patient’s VL over time to measure success or failure
  - Track the cluster’s subsequent growth – did the outreach work?
How to Evaluate Our Work

• Did cluster growth slow or stop?
• Are the new positives seen in the cluster prevalent or incident positives?
  – Good outcome: more prevalent cases were diagnosed *and/or genotyped*, and thus there is more complete mapping of clusters
  – Bad outcome: more incident cases, new AHI
• Were OOC persons successfully returned to care?
• Did viremic persons achieve suppression?
If you must triage cases or clusters – ask these questions

- What is the cluster’s history of growth, and what growth phase (geometric, exponential) is it in at present? It is on the way up or is it flat, spent?
- How many persons in this cluster are currently viremic, and what positions do they occupy in the cluster (central, peripheral, bridging)?
- How many new acute HIV infections are in the cluster and what positions do they hold?
- What variables and statistics best predict forward growth?
- What other factors should be considered -- geography, risk factor, age, race/ethnicity?
Thanks to:

• Our Core and Molecular HIV Surveillance staff and our colleagues at UCSD
• Our Field Services Unit
• Our colleagues at the Public Health Laboratory
• NYS Department of Health for management of the genotype reporting system
The “Next Gen” of Phylo work in NYC:
Focus on HLMSM

• Hispanic and Latino men who have sex with men (HLMSM) accounted for 1,766 new HIV diagnoses between 2013 and 2015
  – 22% of all new diagnoses in NYC

• Among these newly-diagnosed HLMSM:
  – 75% were aged 20-39
  – 52% were born outside the US
    • 17% were born in South America
    • 14% were born in Central America
    • 11% were born in the Caribbean
    • 7% were born in Puerto Rico
Networks of MSM and HLMSM

- MSM networks are more geographically dispersed compared to heterosexual risk networks.
- MSM index cases are less likely to name genetically plausible transmission partners during PS interviews.
- More MSM fall into known genetic clusters than do NYC PLWHA in general.
- HLMSM are as likely as MSM overall (54%) to be members of genetic clusters.
- 61.5% of newly diagnosed HLMSM are genotyped at baseline.
  - Compared to 58.4% of MSM overall, and 46% of all new NYC diagnoses.
Scale of field investigation work for 17-1711

- In 2015 and 2016, there were 3,220 members of clusters that contained newly diagnosed HLMSM in NYC
  - 539 (17%) were viremic
  - 728 (23%) were out of care

- This is a total of 1,267 additional clients projected to be triaged for possible outreach.