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Transmission Cluster of Multiclass Highly Drug-Resistant HIV-1 Among 9 Men Who Have Sex With Men in Seattle/King County, WA, 2005–2007

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Abstract

Background—From 2005 through 2007, Seattle health care providers identified cases of primary multiclass drug-resistant (MDR) HIV-1 with common patterns of resistance to antiretrovirals (ARVs). Through surveillance activities and genetic analysis, the local Health Department and the University of Washington identified phylogenetically linked cases among ARV treatment-naïve and -experienced individuals.

Methods—HIV-1 *pol* nucleotide consensus sequences submitted to the University of Washington Clinical Virology Laboratory were assessed for phylogenetically related MDR HIV. Demographic and clinical data collected included HIV diagnosis date, ARV history, and laboratory results.

Results—Seven ARV-naïve men had phylogenetically linked MDR strains with resistance to most ARVs; these were linked to 2 ARV-experienced men. All 9 men reported methamphetamine use and multiple anonymous male partners. Primary transmissions were diagnosed for more than a 2-year period, 2005–2007. Three, including the 2 ARV-experienced men, were prescribed ARVs.

Conclusions—This cluster of 9 men with phylogenetically related highly drug-resistant MDR HIV strains and common risk factors but without reported direct epidemiologic links may have important implications to public health. This cluster demonstrates the importance of primary resistance testing and of collaboration between the public and private medical community in identifying MDR outbreaks. Public health interventions and surveillance are needed to reduce transmission of MDR HIV-1.

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Keywords

HIV; HIV-1; multiple drug resistance; disease clustering; highly active antiretroviral therapy

INTRODUCTION

Primary acquired HIV-1 drug resistance among antiretroviral (ARV)-naïve individuals has been found in 10% or more of newly HIV-1 diagnosed individuals in North America.^{1–4} Knowledge of primary resistant strains on a population level can be useful for prevention and care decisions.^{1,5} Primary resistance may correlate with adverse outcomes, including a more rapid CD4-positive T lymphocyte (CD4) decline early in the course of disease.^{6–8} Drug resistance testing in patients newly diagnosed with HIV-1 is recommended where the prevalence of primary resistance is greater than 5%⁹ and at initiation of HIV-1 care.¹⁰

If a drug-resistant HIV-1 strain is transmitted over a long period of time it suggests the strain has a high level of fitness; similarly, if a drug-resistant HIV-1 strain is transmitted to multiple individuals, it suggests the strain has relatively high infectivity. Clusters can be instructional regarding transmission chains and host versus viral characteristics and their impact on outcomes such as CD4 count, viral load (VL), progression to AIDS, and mortality.¹¹ Clusters also permit investigations of potential superinfections among HIV-1-infected partners.¹² Community characteristics and risk behaviors associated with these transmissions can be identified, and public health actions initiated in response.

The Centers for Disease Control and Prevention has partnered with Public Health–Seattle & King County (PHSKC) to conduct primary HIV-1 ARV drug resistance surveillance among treatment-naïve individuals since 2003.⁴ Medical providers in Seattle also identified and reported cases of primary multiclass drug-resistant (MDR) HIV-1 infections. We used these and other data to investigate a cluster of 9 individuals with phylogenetically related drug-resistant HIV-1.

METHODS

Variant, Atypical, and Resistant HIV Surveillance and HIV/AIDS Surveillance

Variant, Atypical, and Resistant HIV Surveillance (VARHS) is a laboratory-based sentinel surveillance system in King County. VARHS collects (1) remnant sera from positive HIV-1 diagnostic tests, submitting them for genotypic testing, and (2) genotype test results from clinical practice. The 4 laboratories that participate identify approximately one half of the estimated annual 350–400 new HIV-1 diagnoses in King County. VARHS eligibility requires an initial confidential diagnosis of HIV-1 no more than 90 days before the collection of a specimen for genotypic testing and no previous use of ARV. A history of ARV use is sought by medical record review, patient interview, or from the reporting medical provider. Remnant sera were sent to the University of Washington or Stanford University for genotypic testing.

Genotypic Drug Resistance Tests

We classified drug resistance according to the Stanford HIV-1 Drug Resistance Database algorithm (<http://hivdb.stanford.edu>, accessed January 2008) and defined drug resistance as intermediate or high-level resistance unless otherwise specified. Possible and low-level resistance were not included because their clinical significance is unknown. MDR was defined as high-level genotypic ARV resistance in 2 or more of the 3 major ARV classes: protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs).

MDR Cluster Investigation

Starting in February 2007, after the first 4 cluster cases were found, PHSKC asked providers to report individuals with MDR HIV-1 regardless of VARHS eligibility. Thus, the cluster of MDR cases were identified through VARHS, provider outreach, and laboratory quality assurance activities. The University of Washington and Stanford genotyping laboratories independently conducted phylogenetic analyses for quality assurance purposes. To ensure that highly similar resistance patterns are from distinct individuals rather than being contaminated or mislabeled specimens, both laboratories routinely investigated similar viruses labeled as being from different people. MDR in ARV-naïve individuals was investigated by submitting a second specimen from the individual for genotypic and/or phenotypic testing. Mutations presented for the cluster were those from the International AIDS Society USA,¹³ with additional mutations proposed as important for resistance surveillance.¹⁴ Additional investigations on cluster cases included the following: collecting the results of confirmatory genotypic and phenotypic resistance tests, replication capacity (RC), and envelope gene sequencing for fusion inhibitor sensitivity. RC testing (Monogram Biosciences, South San Francisco, CA) measures the ability of the virus to replicate in the absence of ARVs; 100% is the median value for wild-type (nonresistant) viruses. Partner counseling and referral service (PCRS) interviews for people with primary MDR HIV-1 were conducted by trained disease investigators using semistructured questionnaires to identify and offer testing to all potentially exposed partners. PCRS investigators seek both named and unnamed sexual and injection drug equipment-sharing partners as occasionally index patients have some way of contacting anonymous partners. Additional data regarding substance use and sexual partners were obtained from health care providers and medical record reviews. Resistance testing was recommended for HIV-1-infected partners.

Phylogenetic Analyses

Using ClustalX,¹⁵ MDR cluster sequences were aligned with 53 other randomly selected, local VARHS subtype B sequences from people diagnosed with HIV-1 in 2006. Three subtype B reference sequences were included. The sequences were trimmed with MacClade (v4.08, Sinauer Associates, Inc, 2005) to include the region of the HIV-1 protease (PRO) gene from amino acids 5 to 99 and the reverse transcriptase (RT) gene from amino acids 38 to 229, excluding PRO 46, 54, 82, and 90 and RT 67, 69, 70, 103, 181, 215, and 219. These sites of ARV resistance were removed from phylogenetic analyses to avoid potential confounding due to convergent evolution from similar ARV selective pressure. Neighbor-joining (Hasegawa-Kishino-Yano-1985 model) and maximum likelihood (general time-reversible with a proportion of invariable sites and gamma-distributed rate variation model and tree-bisection-reconnection swapping algorithm) phylogenetic trees and distance matrices were created using PAUP v4.0b10.¹⁶ In addition, we compared MDR cluster sequences with the Los Alamos HIV-1 Database (<http://www.hiv.lanl.gov>, accessed April 2007), Stanford HIV-1 Drug Resistance Database (accessed April 2007), and the University of Washington Clinical HIV-1 database using the Blast algorithm (<http://www.hiv.lanl.gov>, accessed April 2007).

Statistical Analyses

Average phylogenetic distances of PRO and RT genetic sequences of cluster and noncluster individuals were compared using a Wilcoxon rank sum test performed with JMP® (version 5.1.2, SAS Institute, Cary, NC, 2004).

Protection of the Identity of Individuals and the Security of Data

The cluster was investigated under HIV/AIDS surveillance authority and was not considered research as no experimental procedures were used. No data which could identify individuals are presented.

RESULTS

In 2006, we identified 2 cases of primary MDR among newly HIV-1 diagnosed, ARV-naïve individuals with similar genotypic results predicting sensitivity to none of the PIs or NNRTIs, and only 2 of the 7 reported NRTIs. By December 2007, 5 additional ARV-naïve and 2 ARV-experienced cases with similar resistance profiles were reported to PHSKC by providers ($n = 6$) and/or genotyping laboratories ($n = 1$). Eight subjects had subsequent genotypic resistance tests with confirmatory results, eliminating the possibility of laboratory error.

The Stanford Database interpretations for the 7 ARV-naïve cluster members are presented in Figure 1. Lamivudine and emtricitabine (FTC) were the only ARVs interpreted as susceptible. Major mutations, Table 1, are notable for the absence of M184I/V among ARV-naïve cluster members. Two cluster members' viruses had enfuvirtide susceptibility testing and both tested as sensitive. Three had RC testing with results of 5%, 34%, and 112%.

Relatively consistent phenotypic test results were received for 3 cluster members—with more consistency for PI and NNRTI than NRTI. All 3 phenotypic results indicated sensitivity to abacavir; 1 had 5 additional NRTIs test as susceptible, including lamivudine and FTC. All 3 had phenotypic results confirming no NNRTI susceptibility (none were tested for efavirenz). One subject's virus demonstrated susceptibility to ritonavir-boosted indinavir; and another cluster member (1 of the treatment-experienced individuals) had susceptibility to 3 ritonavir-boosted PIs (indinavir, tipranavir, and darunavir).

All 9 cases were men who have sex with men (MSM) reporting recent use of methamphetamine and sex with multiple, mostly anonymous partners. One injected methamphetamine and 7 denied injecting the drug, and method of methamphetamine use was unknown for 1. Six also reported use of erectile dysfunction drugs, 4 reported use of amyl nitrate (poppers), and 4 reported using club drugs (2 used ecstasy/methylenedioxymethamphetamine, 1 used GHB, gamma hydroxy butyrate, and 1 used both). Cluster members reported meeting recent sexual partners through the Internet, bath-houses, and sex parties. Comorbidities at time of HIV diagnosis included syphilis ($n = 3$), gonorrhea ($n = 2$), chlamydia ($n = 1$), and methicillin-resistant *Staphylococcus aureus* ($n = 3$). Eight of the 9 men were whites; decade of age ranged from 20s through 40s (median = 40 years).

The CD4 counts closest to the time of HIV-1 diagnosis for the treatment-naïve cluster members ranged from 300 to 700 (median 519) cells per microliter and plasma VL ranged from less than 2000 to more than 100,000 (median 17,700) viral copies per milliliter. To date, only 1 treatment-naïve individual, whose CD4 count fell into the 300s, has received ARV therapy. He remains on a 3-class regimen consisting of FTC, tenofovir, darunavir, ritonavir, and raltegravir. He has now had 2 undetectable VL tests, and his CD4 count has increased by more than 200 cells per microliter. Plasma VL and CD4 count since diagnosis of MDR HIV are shown in Figures 2 and 3.

Phylogenetic analysis (Fig. 4) confirmed that the viruses from the 9 individuals were very similar strains of HIV-1, having an average *pol* genetic distance of 1.1% (SD = 0.6; median = 0.9). These viruses are genetically more similar than viruses from randomly selected local 2006 HIV-1 cases ($n = 53$) that had an average distance of 6.9% (SD = 1.7, median = 6.7) ($P < 0.0001$).

The date of HIV-1 diagnosis for the 7 ARV-naïve cases ranged from late 2005 through late 2007. Follow-up since MDR diagnosis ranges from 2 to 25 months. Four had evidence of recent HIV-1 infection, with a prior negative HIV-1 test ranging from 5 to 18 months earlier. One was diagnosed with acute HIV-1 seroconversion syndrome when he was ill and initially had an indeterminate Western blot. MDR was diagnosed in less than 3 months after HIV-1

diagnoses for the ARV-naïve men and in more than 10 years after HIV-1 diagnoses for the others.

PCRS data confirmed that all cluster members were distinct individuals and elicited 5–40 partners in the year before HIV-1 diagnosis. Of these, no more than 5 partners were located for each cluster member. Identified sexual partners did not overlap between cases, although the anonymous nature of their sexual encounters precluded such identifications. Two were in primary nonmonogamous relationships with noncluster MSM. All sexual partners contacted through PCRS were either not infected with HIV-1 or had a non-MDR HIV-1 strain.

One of the ARV-experienced individuals was diagnosed with HIV-1 in the mid 1980s, treated with 3 major classes of ARV (PI, NNRTI, and NRTI), and never achieved sustained VL suppression. He remains on a salvage 3-class ARV regimen and has a stable clinical course and CD4 counts between 200 and 300 cells per microliter. The other was diagnosed with HIV-1 in the early 1990s and had more than a decade of undetectable VLs with 2 NRTI drugs plus 1 NNRTI. In early 2007, an unexpected increase in plasma VL (close to 20,000 copies/mL) prompted ARV resistance testing and identified mutations similar to those of cluster members. His resistance mutations included M184I. Modifications of his ARV regimen were associated with a decrease in his VL, but not full suppression of viral replication (plasma VL 2000–7000 copies/mL). His CD4 count was approximately 500 at 10 months post-MDR diagnosis.

DISCUSSION

Provider reports and expanded surveillance for HIV-1 drug resistance in King County detected 7 ARV-naïve and 2 ARV-experienced MSM with highly drug-resistant and phylogenetically linked strains of HIV-1. The detection of this large cluster of MDR HIV-1 suggests that some MDR strains can be transmitted to multiple individuals over a prolonged period, given favorable circumstances. Follow-up has not detected rapid disease progression, and those on ARV therapy have done well clinically with partial to full suppression of VL.

To our knowledge, this is the largest cluster of transmitted MDR HIV-1 reported to date. Although many other clusters have been described, including clusters with transmitted drug resistance, none reported the level of resistance we describe.^{17–19} It is possible that there are additional cluster members either undiagnosed or diagnosed and not reported. Future surveillance activities may benefit from the participation of additional laboratories to approach full population-based primary ARV drug resistance surveillance coverage.

Some drug-resistant viruses do not transmit as easily as wild-type viruses,²⁰ although the transmission efficiency may vary by specific genetic mutation patterns.²¹ Drug-resistant strains may select for adaptive mutations that enhance fitness, allowing replication to proceed similarly to wild-type viruses.²² As we found, RC of drug-resistant strains is variable.²²

The clinical impact of primary drug resistance is not completely understood, with both more rapid and slower disease progression reported. Adverse clinical outcomes include a faster CD4 decline early in disease^{6–8} and, after ARV initiation, an increased time to viral suppression (<500 copies/mL) and a shorter period of sustained viral suppression.²³ Still, drug resistance does not necessarily accelerate disease progression and may even slow disease progression if the viral fitness is compromised.²⁴

Transmission of drug-resistant HIV-1 has numerous public health implications. Concern about becoming infected with a resistant strain of HIV-1 may prompt individuals to reduce risk behavior and increase HIV-1 testing and, for HIV-1-infected individuals, prompt patients to discuss ARV adherence and resistance with their medical providers. Public health authorities should monitor ARV resistance testing among providers to see that recommended guidelines

are being followed.^{9,10} Knowledge of the prevalence of ARV resistance in the community is useful for prevention and health planning, for example, choosing ARV regimens for post-exposure prophylaxis.

Use of methamphetamine is associated with more sexual partners, high-risk behaviors, and acquisition of sexually transmitted infections, including HIV-1.^{25–27} Methamphetamine use has also been correlated with drug-resistant HIV-1 and with NNRTI drug resistance.²⁸ Methamphetamine use together with erectile dysfunction agents increases high-risk sexual behavior.²⁹

This MDR strain does not seem to be highly virulent (based on intermediate VL levels and RC), but may be persistent (transmissions being diagnosed for more than a minimum of 24 months), and given the number of individuals infected with this strain, may also be easily transmitted. Furthermore, although it would be difficult to prove without stored sera available for additional testing, 1 of the ARV-experienced individuals may have contracted this strain of HIV due to a superinfection despite being on ARV therapy at the time with good viral suppression, as measured by consistently undetectable VL.

In summary, we observed a cluster of MDR HIV-1 transmitted for more than a 2-year period, but not associated with rapid clinical or laboratory decline. Local surveillance for ARV drug resistance, including epidemiologic and phylogenetic investigations, was critical in identifying this cluster. Population-based surveillance and natural history studies of HIV-1 drug resistance are needed to understand the impact of ARV drug resistance on treatment. Methamphetamine and erectile dysfunction drug use among members of the cluster may provide targets for surveillance, intervention activities, and research to assess the impact of use of these agents on the risk of infection with drug-resistant HIV-1 and their relationship to clinical outcomes.

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FIGURE 1.

Stanford database interpretations of genotypic tests among 7 ARV-naïve members of a cluster with primary or transmitted MDR HIV-1 in Seattle, WA, 2005–2007. Interpretation of genotypic mutations based on Stanford Database

(<http://hivdb.stanford.edu/pages/algs/HIVdb.html>), accessed January 25, 2008. Pls: ATV, atazanavir; DRV, darunavir; FPV, fosamprenavir; IDV, indinavir; LPV, lopinavir + ritonavir; NFV, nelfinavir; SQV, saquinavir; TPV, tipranavir NRTIs: 3TC, lamivudine; ABC, abacavir; AZT, azidothymidine (or ZDV, zidovudine); D4T, stavudine; DDI, didanosine; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate NNRTIs: DLV, delavirdine; EFV, efavirenz; NVP, nevirapine; ETV, etravirine. HIGH = high level of resistance predicted, little or no response to this ARV expected; INT, intermediate = a lower level of resistance predicted than for HIGH; LOW = ARV use may result in a suboptimal response; SUSCEPTIBLE = no evidence of resistance.

FIGURE 2.

CD4+ lymphocyte values of 9 members of an MDR HIV-1 cluster in Seattle, WA, 2005–2007. Solid lines indicate ARV-naive individuals and dashed lines represent ARV-experienced individuals. The highlighting indicates CD4+ lymphocyte testing after initiating ARV therapy.

FIGURE 3.

Plasma VL values of 9 members of an MDR HIV-1 cluster in Seattle, WA, 2005–2007. Solid lines indicate ARV-naïve individuals and dashed lines represent ARV-experienced individuals. The highlighting indicates plasma VL testing after initiating ARV therapy.

FIGURE 4.
Maximum likelihood phylogenetic tree demonstrating relatedness of 9 MDR HIV-1 cases in Seattle, WA, 2005–2007. Treatment-experienced individuals in the cluster are identified by an “E.”

TABLE 1

Major Mutations Present Among 7 ARV-Naïve Members of a Cluster With Primary or Transmitted MDR HIV-1 in Seattle 2005–2007

Major PRO gene mutations for PIs
L33F M46I, M46L, or M46I/L I47V (1) I54L (6) I54V (1) G73S V82A L90M
Major RT gene mutations for NNRTIs
K103N Y181C
Major RT gene mutations for NRTIs
D67N T69N (5) T69D (2) K70R (4) T215F (5) T215L/V/S/P* (3) K219Q

Bold indicates mutations present for all 7 members of the cluster; otherwise the number of members is given in parentheses. Different mutations at the same site are listed on the same line when the different mutations have identical interpretations (eg, M46I, M46L, and M46I/L); otherwise they are listed separately (eg, I54L and I54V).

* For T215L/V/S/P the 3 include 1 with T215F and other T215 mutations.