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Transmitted HIV-1 Drug Resistance Among Young Men of Color Who Have Sex With Men: A Multicenter Cohort Analysis

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A B S T R A C T

Background: Given the elevated potential for primary or transmitted drug resistance (TDR) among newly HIV-infected individuals, there is a need for a deeper understanding of the baseline resistance patterns present in young men of color who have sex with men.
Methods: Genotypic data were collected for participants aged 13–24 who were enrolled from seven sites. Univariate and bivariate methods were used to describe the prevalence of TDR and characteristics associated with TDR.
Results: Of the 296 individuals participating in the substudy, 145 (49%) had baseline genotypes. The majority of the individuals were African American (65%) and gay-identified (70%). There was significant variation in genotype availability by site ($p < .001$). Major surveillance drug resistance mutations were present in 28 subjects (19.3%); the majority were non-nucleoside reverse transcriptase inhibitor mutations (12.4%). Subjects with TDR were less likely to have used alcohol on 1 or more days in the prior 2 weeks. Location was not associated with acquisition of TDR.
Conclusions: There was a high rate of TDR in a geographically and racially diverse sample of HIV-infected young men of color who have sex with men. This represents a serious public health concern given the young age of this sample and the potential need for long-term antiretroviral therapy. These findings underscore the critical roles of both early case identification and secondary prevention.

Individuals with antiretroviral (ARV)-resistant HIV who engage in risk behavior place their partners at risk for acquiring a drug-resistant primary HIV infection. This transmitted drug resistance (TDR) has management implications for the newly infected and public health implications at the population level. Retrospective analyses of clinical trials among ARV-naive subjects demonstrate consistently higher rates of virologic failure when TDR was present [1–4]. Being guided by the results of genotypes has been shown to improve virologic outcomes and be cost-effective [5,6]. The slope of $CD4^+$ cell count decline may be greater in the first year after acquisition of TDR, limiting the

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degree of immunologic recovery possible after initial infection [7,8]. Furthermore, resistance mutations acquired during primary infection may persist for many years [9,10], propagating forward transmission of drug-resistant HIV among individuals with undiagnosed or untreated infection [11].

Large-scale epidemiologic surveillance for TDR in North American and European countries with long-established use of ARVs shows that the prevalence has remained relatively stable over the past several years, after initial dramatic increases between the introduction of zidovudine and the advent of highly active antiretroviral therapy (HAART) [3,12–17]. During the years that nucleos(t)ide reverse transcriptase (RT) inhibitors (NRTIs) were the only ARV class available, the prevalence of NRTI resistance rose rapidly, only to decline after the introduction of more completely suppressive combination regimens. Protease inhibitor (PI) resistance has generally remained low (<5%), but the prevalence of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance expanded rapidly within the first several years of use, from .4% in 1998 to approximately 7% by 2006 [18,19].

Assessments of TDR prevalence within subpopulations of the epidemic have mixed results. Studies conducted between 1996 and 1998 on a sample of ARV-naive adolescents from 16 locations in 13 United States (U.S.) cities, in the Reaching for Excellence in Adolescent Care and Health cohort, identified four of 92 (4.3%) subjects with resistance mutations in RT, including one with multiple mutations [20]. In a 2004 study of 55 racially and geographically diverse youth (12–24 years) from 15 sites around the U.S. and Puerto Rico who had acquired HIV in the prior six months, 18% had major mutations, the majority of which conferred resistance to NNRTIs [21].

Blacks and Hispanics are disproportionately affected by the HIV epidemic, with young men who have sex with men (YMSM) being the most affected. In 2006, although about 28% of the U.S. population were blacks and Hispanics, they accounted for approximately two-thirds (66%) of the people with HIV/AIDS [22]. Between 2001 and 2004 in the 33 states with name-based reporting, 17,824 adolescents aged 13–24 were diagnosed with HIV or AIDS. Almost two-thirds were male; of these, 74% were YMSM [23]. In the U.S., YMSM comprise the largest proportion of new HIV infections, and among black and Hispanic men who have sex with men most new infections were in individuals aged 13–29 [24,25]. The potential for such young people to be infected with resistant strains of HIV is of great concern, considering the dwindling pipeline of new ARVs in development and the young age at which these men seroconvert necessitating prolonged exposure to ARVs. Given the elevated potential for HIV ARV resistance among treated populations and transmission of resistant virus to newly infected individuals, there is a need for a deeper understanding of the baseline resistance patterns present in YMSM of color, a group disproportionately affected by the epidemic.

Methods

Study population

Participants for the study were enrolled at one of several Health Resources and Services Administration and/or Special Projects of National Significance (SPNS)-funded demonstration sites throughout the U.S. (Bronx, NY; Chapel Hill, NC; Chicago, IL; Detroit, MI; Houston, TX; Los Angeles, CA; Oakland, CA); each of which had its own outreach, linkage, and retention strategy. Of the eight funded SPNS sites, only seven participated in the resistance substudy. To be eligible for participation in the multisite cohort, participants had to be male (born male or biologically female, but currently self-identified as male); either newly diagnosed as HIV-infected or re-engaging in care (defined as being out of care for ≥6 months); have sex with men, or the intent to have sex with men; self-identify as nonwhite; be between the ages of 13 and 24 years at the time of the first interview; and willing and able to provide full written informed consent and release of medical records. (This includes parent/guardian consent, if required by local institutional review board [IRB]). To be eligible for the resistance substudy, participants had to have a baseline genotype performed before the receipt of any ARV medications. IRBs of Health Resources and Services Administration/HIV/AIDS Bureau (HAB)/SPNS and George Washington University, as well as site-specific IRBs, approved all instruments and protocols.

Data collection

Eligible participants underwent standardized face-to-face interviews by local study staff at baseline, and every 3 months thereafter. Demonstration site administrators were trained at biannual grantee meetings and then provided with an interviewer and abstraction manual to assist in training staff; when needed, evaluation and support faculty conducted site visits for training and quality assurance. All clinical data, including genotypes, were abstracted by trained local personnel. De-identified data were entered into a secure web-based data portal by study staff, quality ensured, and maintained by evaluation center staff.

Interpretation of genotypic resistance data

We defined TDR as the presence of at least one mutation in the 2009 World Health Organization revised listing of surveillance drug resistance mutations (SDRMs) [26]. Developed specifically for TDR surveillance, SDRMs are a more parsimonious set of ARV resistance mutations than the International AIDS Society-USA's list [27,28]. Individual participant records were reviewed to determine the presence or absence of SDRMs. We used the Stanford University HIV Database (http://hivdb.stanford.edu, accessed between May 1 and 10, 2009) to determine the level of ARV resistance conferred by each SDRM detected in the cohort—potential low/low, intermediate, or high.

Statistical analysis

Data collected between June 2006 and March 2009 were analyzed at the George Washington University YES Center, which was the data coordinating and evaluation center. Descriptive statistics were calculated to assess the distribution of continuous variables and determine whether a nonparametric test should be used. Two sets of bivariate comparisons of individual characteristics against either the availability of a genotype or the detection of TDR were conducted. We used Pearson's χ^2 test or Fisher's exact test for nominal and categorical variables, and the Wilcoxon rank-sum test or Students t test for continuous variables, depending on the normality of their distribution. Variation in the prevalence of TDR over time was assessed with the Cochran-Armitage test for trend. Significance was defined as $p <$

Table 1
Demographics and clinical characteristics of HIV-infected young men of color who have sex with men

Characteristic	n	Mean (SD), median (IQR), or %
Age, mean (SD)	296	20.4 (1.9)
Race/Ethnicity, %		
Black	193	65.2
Hispanic	68	23.0
Other/Mixed	35	11.9
Sexual identity, %		
Gay	207	70.4
Bisexual	64	21.6
Insured, %	179	62.8
In school, %	110	37.9
Study Site, %		
East Bay, CA	26	8.8
Los Angeles, CA	58	19.6
Chicago, IL	14	4.7
Detroit, MI	39	13.2
Raleigh/Durham, NC	66	22.3
Bronx, NY	52	17.6
Houston, TX	41	13.9
Months from diagnosis to entry into care, median (IQR)	277	.47 (.17–1.0)
Number of male partners in prior 3 months, median (IQR)	205	2 (1–2)
Most recent CD4, median (IQR)	193	403 (292–588)
Most recent logVL, mean (SD)[a]	180	4.09 (.93)

[a] Five subjects with undetectable viral load not included.

.05 for all analyses. Statistical calculations were made using SAS v.9.1 (SAS Institute, Cary, NC).

Results

Description of the cohort

The mean age of the sample was 20.4 years (Table 1). The majority was African American (65.2%), and most of the participants self-identified as gay (70.4%). Slightly more than one-third (37.9%) of the participants were enrolled in school. Drug use was common, with 54.7% of the sample reporting any drug use (excluding alcohol) in the 3 months before enrollment. The median CD4 count was 403 cells/mm^3 and the mean log viral load was 4.09 copies/mL at entry.

Predictors of genotypic resistance testing

Among the 296 YMSM of color enrolled in the seven participating sites within the SPNS study, 145 (49.0%) had baseline genotypes available for analysis (Table 2). A greater proportion of African American participants had genotypes, as compared to Latino participants or those of mixed races. The number of genotypes did not increase over the study period (p for trend, .28) and there were no significant differences in the number of genotypes ordered before and after 2006 when the U.S. Department of Health and Human Services formally began recommending genotypic drug resistance testing on all persons newly diagnosed with HIV infection. There was significant variation in the genotype availability by site ($p < .001$). The only clinical parameter associated with having a genotype was the mean viral load at study enrollment ($p = .01$), with those having a higher viral load more likely to have a genotype (mean log viral load was 4.2 vs. 3.9 copies/mL, respectively).

Predictors of having TDR

Of the 145 subjects with baseline genotypes available for analysis, SDRMs were present in 28 subjects (19.3%; Table 2). Eighteen (12.4%) had NNRTI mutations, six (4.1%) NRTI mutations, and six (4.1%) PI mutations (Table 3). The most frequently encountered mutation was K103N, detected in samples from 10 participants (6.9%). Two participants demonstrated dual-class resistance to both NRTIs and NNRTIs. Subjects with TDR were less likely to have used alcohol on ≥1 day in the prior 2 weeks. There were no additional statistically significant differences between those with TDR and those without, with respect to other demographic, clinical, or behavioral factors. Location was not associated with acquisition of TDR.

To determine the potential clinical effect of baseline resistance on the efficacy of future therapy, we used the Stanford University HIV Database [29] to classify the level of ARV resistance conferred by each SDRM (Figure 1). Among NRTIs, three samples were resistant to two drugs, two to five drugs, and one to all agents except zidovudine. Among the samples with NNRTI resistance, all 18 demonstrated some level of resistance to the two currently used first-line NNRTIs, efavirenz and nevirapine. Eight samples also had low or intermediate resistance to etravirine [30], a drug often useful in second-line or later stages after failure of first-line NNRTIs. Of the six strains that had reduced susceptibility to PIs, all had reduced sensitivity to six of the eight PIs.

Discussion

These data represent the largest, most geographically and racially diverse U.S. sample of TDR in HIV-infected YMSM reported to date, and have important implications for initial treatment regimens for young persons newly diagnosed with HIV. The overall prevalence of TDR is slightly higher than those recently reported among adult populations [13–17], a finding that is especially concerning given the young age of our sample and the need for lifetime ARV treatment. Furthermore, our population consists of YMSM of color from both rural and urban areas throughout the U.S., reinforcing that TDR cannot be predicted with any confidence when based on any demographic features, risk characteristics, or geographic locations.

Although HAART has successfully transformed HIV into a chronic, manageable disease, treatment alternatives are not limitless and there are consequences (both clinically and psychologically) to losing medication options before one even begins. Despite being considered "ARV naïve," 19% of the cohort had baseline resistance limiting their initial treatment options and 14% had extensive resistance to the only currently available one pill once a day treatment option (the combination of emtricitabine, tenofovir, and efavirenz). Although other once-daily regimens remain, pill burden has both a perceived and an actual effect on adherence to HAART [31–33]. Adherence issues may be even more important for adolescents making the ramifications of a failed regimen even more poignant [1,34]. Although the PI resistance found in this study was somewhat high, most mutations noted only conferred low level resistance and would not limit the use of currently recommended first-line boosted PIs.

This study has direct clinical implications. Almost half (49.0%) of the sample did not have an available baseline genotype, and of these men, almost half (48.3%) were diagnosed with HIV after 2006, when the U.S. Department of Health and Human Services

Table 2
Bivariate comparisons of individual characteristics and genotype availability and transmitted resistance detected, HIV infected young men of color who have sex with men

Characteristic	Genotype obtained (n = 145)		Resistance detected (n = 28)	
	Mean (SD), median (IQR), or n (%)*	p^a	Mean (SD), median (IQR), or n (%)*	p^a
Age, mean (SD)	20.1 (2.0)	.01	19.9 (2.1)	.64
Race/Ethnicity, n (%)				
Black	110 (57)	<.001	22 (20)	.88
Hispanic	21 (31)		3 (14)	
Other/Mixed	14 (40)		3 (20)	
Sexual identity, n (%)				
Gay	99 (48)	.67	19 (19)	.86
Bisexual	32 (50)	.86	4 (13)	.27
Insured, n (%)	94 (53)	.18	16 (17)	.36
In school, n (%)	64 (58)	.01	10 (16)	.35
Study site, n (% resistant)				
East Bay, CA	12 (46)		0 (0)	
Los Angeles, CA	3 (5)		2 (67)	
Chicago, IL	10 (71)		2 (20)	
Detroit, MI	28 (72)	<.001	7 (25)	.2
Raleigh/Durham, NC	52 (79)		11 (21)	
Bronx, NY	11 (21)		1 (9)	
Houston, TX	29 (71)		5 (17)	
Number of male partners in prior 3 months, median (IQR)	1 (1–3)	.92	1 (1–2)	.08
Age at first sex with a male partner, mean (SD)	14.6 (3.4)	.92	14.1 (3.5)	.35
Transactional sex in prior 3 months, n (%)	18 (43.9)	.56	2 (11)	.33
Use of any illicit drug in prior 3 months, n (%)	77 (47.5)	.58	14 (18)	.71
Alcohol use ≥1 day in prior 2 weeks, n (%)	72 (46)	.02	8 (11)	.03
Months from diagnosis to entry into care, median (IQR)	.47 (.23–1.0)	.96	.23 (.17–.70)	.32
Number care visits in prior 3 months, median (IQR)	2 (1–2)	.34	2 (1–3)	.93
Year of diagnosis		.28		.92
2003–2004, n (%)	7 (35)		1 (14)	
2005–2006, n (%)	38 (46)		8 (21)	
2007–2009, n (%)	91 (52)		18 (20)	
Lifetime HIV tests, median (IQR)	3 (2–5)	.71	2.5 (2–4)	.50
Most recent CD4, median (IQR)	392 (285–571)	.31	442 (297–648)	.29
Most recent logVL, mean (SD)	4.2 (.9)	.01	4.1 (1.0)	.51

* Row percents are displayed.
[a] p-values are based on Pearson's X^2 test or Fisher's exact test for nominal and categorical variables, and the Wilcoxon rank sum test, or Student's t test for continuous variables, depending on the normality of their distribution. Diagnoses over time were assessed with the Cochran-Armitage test for trend.
SD = standard deviation; IQR = interquartile range.

guidelines [35] began recommending baseline genotypes for *all* patients before initiation of therapy, regardless of duration of infection or need for treatment. A difference in the availability of genotypes by site suggests that site or provider characteristics – including perception of resistance rates within their community – may influence which clients receive a test. Variation in terms of reimbursement rates for resistance testing in different states may affect ordering practices. The lack of predictors for having TDR as well as its high prevalence underscores the need for universal uptake of baseline resistance testing for all newly diagnosed YMSM of color.

Table 3
Specific resistance mutations, HIV-infected young men of color who have sex with men

Frequency	Class	Specific mutation(s)
5	PI	L90 M
1	PI	I47V
1	NRTI	D67N
1	NRTI	M41L
1	NRTI	T215E
10	NNRTI	K103N
2	NNRTI	Y188L
2	NNRTI	G190A
2	NNRTI	Y181C
1	NRTI	D67N and K219Q
1	NRTI and NNRTI	G190A and K219Q
1	NRTI and NNRTI	K65R, Y181C and G190S

We were surprised to observe that both having a genotype and TDR were associated with lower risk alcohol use behaviors. The median time to entry into care was 2 weeks, which corresponds to the period over which alcohol use was assessed. Thus, those individuals whose providers ordered genotypes may have also received intensive prevention counseling which resulted in lower risk behaviors for that period. Thus, this finding may be an artifact. Although not statistically significant, only 15% of the sample with TDR had ≥3 or more partners in the 3 months before enrollment, as compared with 28% of the sample without TDR. We can hypothesize that perhaps some of these black and Hispanic YMSM in primary relationships (i.e., those with low numbers of partners) may engage in risk behaviors with either undiagnosed partners or those with incompletely suppressed viral loads [36,37]. A recent modeling study found that 68% of HIV transmissions were from main partners, attributable in large part to a higher number of unprotected and receptive anal sex acts [38]. Among a sample of acutely HIV-infected persons, more than 50% thought a steady partner infected them [39]. Relation-

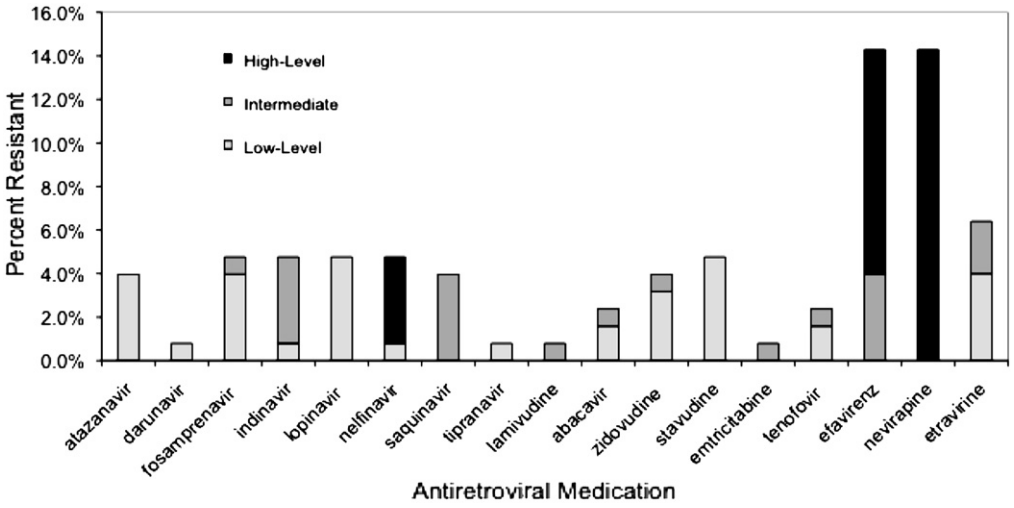

Figure 1. Antiretroviral susceptibility, HIV-infected young men of color who have sex with men. Levels of antiretroviral drug resistance in the cohort. These are interpretations from the Stanford Database based on genotypic mutations.

ships with main partners are an important source of influence on risk behaviors, and interventions targeting these dyads may help to reduce both HIV transmission risks and TDR.

Our findings are subject to limitations. We relied on self-report of all risk behaviors from participants and we cannot be certain that all interviewers elicited truthful responses, although all interviewers underwent extensive training using a standard protocol. Some clients who were re-engaging in care may not have had a baseline genotype available. Although we cannot rule this out as a source of bias, the median number of months between diagnosis and entry into care for participants was .5 for those with genotypes and .4 for those without genotypes (p = .96), or about 2 weeks for both groups, indicating most of the participants were newly diagnosed. Furthermore, although enrollment into the cohort study began in June 2006, approval for enrollment into the resistance sub-study was acquired starting in April 2008 and sites may have had difficulty retrospectively acquiring genotypes. The fact that universal baseline genotypes were not available on all participants from all sites limits the generalizability of our results. The strength of this study was its use of SDRMs, selected especially for surveillance of TDR, in contrast to the broader International AIDS Society-USA list that includes mutations that are not as clinically relevant [26].

The high prevalence of TDR underscores critical roles of both early case identification and secondary prevention. YMSM of color have the highest incidence of undiagnosed HIV infection as compared with any other group, and increasing the proportion of those who know their status is critical [40]. Engagement in care, reinforcement of risk-reduction messages, and provision of both adherence and psychosocial support are needed to assist YMSM in maintaining preventative behaviors over time.

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