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Full Length Research Paper

Human immunodeficiency virus (HIV) in Washington, D.C.: Prevalence of antiretroviral resistance in treatment naïve patients from 2007 to 2010

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HIV treatment has been greatly impacted by transmitted resistance to antiretrovirals (ARV). Several studies have documented resistance in naïve individuals and estimates of transmitted drug resistance mutations range from <5% to as high as 25%. Washington, D.C. has one of the highest human immunodeficiency virus (HIV) prevalence rates in the United States (3.2% in 2009), but local data regarding the frequency of major mutations and antiretroviral (ARV) resistance has been limited. Medical records of HIV positive, ARV-naïve adults at two facilities in Washington, D.C., The George Washington University Medical Center and the Veterans Affairs Medical Center, were retrospectively analyzed in subjects who had genotypic resistance testing from 2007 to 2010. Of 407 ARV-naïve patients, at least one transmitted drug resistance mutation was detected in 17% of our patients, with non-nucleoside reverse transcriptase (NNRTI) mutations observed in 15%. Among patients with at least one reverse transcriptase (RT) or major protease region (Pr) resistance mutation, 85% had resistance against a single ARV class. Dual and triple class resistance mutations were seen in 8 patients (2%) and 3 patients (0.7%), respectively. Most of the multiple class resistance was seen in 2010. A gradual increase in NNRTI resistance was noted during 2008 to 2010. Our prevalence of transmitted RT, major Pr mutations (17.4%) and ARV resistance (8.6%) were high but similar to rates reported by others within the United States. Given the high HIV prevalence in the District of Columbia, this has important implications for treatment of these ARV-naïve patients.

Key words: HIV, Washington D.C., naïve to antiretrovirals, transmitted drug resistance, transmitted drug resistance mutations, antiretroviral mutations.

INTRODUCTION

Human immunodeficiency virus (HIV) treatment has been greatly impacted by transmitted drug resistance (TDR) mutations to antiretroviral (ARV) agents. Based on United States Department of Health and Human Services

(DHHS) guidelines, genotypic antiretroviral resistance testing (GART) was initially given CIII and DIII recommendations in 2000 for acutely-infected and chronically-infected treatment-naïve patients,

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respectively, and then an AIII recommendation for all treatment-naïve patients entering care in 2007 (DHHS, 2007). For ARV treatment naïve individuals in the U.S., TDR mutation rates have ranged from about 5% to as high as 25% (Castor et al., 2012; Huaman et al., 2011; Hurt et al., 2009; Little et al., 1999; Little et al., 2002; MacVeigh et al., 2013; Readhead et al., 2012; Ross et al., 2007; Taniguchi et al., 2012; Truong et al., 2011; Weinstock et al., 2000; Weinstock et al., 2004; Wheeler et al., 2010; Yanik et al., 2012; Youmans et al., 2011). TDR has several important implications. TDR has been demonstrated to increase the risk of poor outcomes, including an increase in time to achieve virologic suppression, risk of virologic failure, and a more rapid decline in CD4 counts in the first year after diagnosis. (Grant et al., 2002; Little et al., 2002; Pillay et al., 2006; Taniguchi et al., 2012; Wittkop et al., 2011).

Knowledge about TDR is particularly important in Washington, D.C., which has one of the highest HIV prevalence rates in the United States (DC HAHSTA, 2010; CDC Surveillance, 2011). In 2009, the HIV seropositivity rate in residents of Washington, D.C. aged 13 or older was 3.2% (DC HAHSTA, 2010). The rate of HIV infection in African Americans was 4.7%, including 7.1% in African American males (DC HAHSTA, 2010). Among all individuals from Washington, D.C. aged 40 to 49 and 50 to 59 in 2009, 7.4 and 6.1% were infected with HIV, respectively (DC HAHSTA, 2010). The rate in Washington, D.C. exceeds the rate of a general epidemic as defined by World Health Organization and the rate of HIV in some countries who received the United States President's Emergency Plan for AIDS Relief (Nybo and Barrere, 2012). TDR in several communities has been studied but data regarding the frequency of major mutations and ARV resistance in Washington, D.C. is limited. In the retrospective review by (Boyd et al., 2008) of 42 treatment-naïve patients in Washington, D.C. who entered medical care in 2005, 7% of patients were classified as having International AIDS Society (IAS) recognized mutations detected in the reverse transcriptase (RT) region; no major mutations were detected in the protease (Pr) region. Major nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations were detected in 2.4% and 4.8% of patients, respectively (Boyd et al. 2008). Gajjala et al. (2008) identified 41 patients newly diagnosed with HIV in Washington, D.C. from 2005 to 2007; no major NRTI or Pr mutations were detected; 3 patients had major NNRTI mutations (2.4%) (Gajjala et al. 2008). In this study, the authors sought to further assess the frequency of TDR mutations and ARV resistance among treatment-naïve patients in Washington, D.C.

METHODOLOGY

After approval by the Institutional Review Boards of two facilities in

Washington, D.C., The George Washington University Medical Center (GWUMC) and the Veterans Affairs Medical Center (VAMC), as well as the Research & Development Committee at the VAMC, a retrospective review at GWUMC and the VAMC was performed for all patients age 18 or older, who had a GART from 1 January, 2007 to 31 December, 2010. Medical record review was completed to verify that the GART was performed when the patient was ARV-naïve. Data for age, gender, race/ethnicity, CD4 count and percentage, and HIV RNA copies were collected. GART results for patients at the VAMC used the TRUGENE® HIV-1 Genotyping Assay, versions 11-15 (Siemens HealthCare Diagnostics, Inc., Tarrytown, NY). Genotypes for patients at GWUMC were done either by GenoSURE® (LabCorp, Burlington, NC), Quest HIV-1 Genotype (Quest Diagnostics, Madison, NY), ViroSeq™ v. 2.6, 2.8 (Celera, Alameda, CA), or vircoTYPE™ HIV-1 VPT 4.1.01, 4.2.01, and 4.3.01 (Janssen Diagnostics, Mechelen, Belgium). RT and Pr mutations, as identified in the 2010 IAS-USA mutation list, and interpreted ARV resistance were recorded for each patient based on the genotype results provided by the test report. Genotypic resistance to integrase inhibitors was not determined.

RESULTS

A total of 1944 genotypes were ordered from 2007 to 2010 at the two institutions in this study. A total of 407 individuals naïve to ARVs based on chart review were identified. Of 407 ARV-naïve patients who had GART during 2007 to 2010, 277 were in care at GWUMC and 130 at the VAMC. The median age was 43. Men comprised the majority (81%) of the patients; no women from the VAMC cohort met our inclusion criteria. The majority (79%) of our patients were African American. The median CD4 count was 287 (interquartile range 107 to 439) cells/mm³; 144 patients (36%) had a CD4 count <200 cells/mm³. HIV RNA in copies/mL was distributed as follows: >100,000: 129 patients (32%); 10,000-100,000: 173 patients (43%); and <10,000: 96 patients (25%).

For our cohort during 2007 to 2010, 72 patients (17%) demonstrated at least one mutation for any RT or major Pr mutation. Among all study patients, 70 (17%) had at least one RT mutation, where 16 patients (3.9%) had at least one NRTI mutation, and 62 (15%) had at least one NNRTI mutation. Eight patients (2.0%) had a major Pr mutation. The majority of patients (85%) with at least one RT or major Pr mutation had resistance to a single ARV class. Eight patients had dual class resistance mutations, 5 with NRTI and NNRTI mutations and 3 with NNRTI and Pr mutations. Three patients had triple class resistance mutations. Of the 11 patients with resistance mutations to more than one class of ARVs, 8 had a GART performed in 2010. In 2010, 6.6% of patients who had a GART had multiple class resistance mutations, as summarized in Table 1.

Table 2 summarizes the frequency of RT and major Pr mutations seen in our cohort. The most common RT mutations were K103N (5.2%), V90I and V179D (both 2.5%), and M41L (1.7%). Eight patients (1.96%) had E138A/G/K. Major Pr mutations were rare and accounted for rates of <1%. However, there was

Table 1. Summary of mutations and mutations by drug class, where the percent of nucleoside/nucleotide reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease gene (Pr) mutations and multiclass resistance mutations were given by year.

Year	N	Any RT or major Pr mutation (%)	NRTI class mutation (%)	NNRTI class Mutation (%)	Major Pr mutation (%)	2 or more ARV class mutations (%)
2007	74	9.5	4.1	6.8	0	1.4
2008	99	16	1	15	0	0
2009	113	15	2.7	12.4	2	1.8
2010	121	26	7.4	23	4	6.6

Table 2. Summary of reverse transcriptase (RT) and major protease (Pr) gene mutations, where numbers and percent of total of treatment-naïve patients are given.

RT mutation	Frequency (%)	Pr mutation	Frequency (%)
K103N	22 (5.2)	V82A	3 (<1)
V90I	10 (2.5)	L90M	3 (<1)
V179D	10 (2.5)	M46L	2 (<1)
M41L	7 (1.7)	I47V	2 (<1)
E138A/G/K	8 (1.7)	I54M	2 (<1)
G190A	5 (1.2)	M46I	1 (<1)
V108I	5 (1.2)	D30N	1 (<1)

an increasing trend from 2007 to 2010 for any detected RT or major Pr mutation. This increase was primarily due to NNRTI mutations, as summarized in Table 1.

Among those with any interpreted ARV resistance, 35 (8.6%) patients demonstrated resistance to at least 1 ARV drug, such that 3 (0.7%) patients had resistance to ≥ 1 NRTI, 28 (6.9%) had resistance to ≥ 1 NNRTI, and 10 (2.5%) had resistance to ≥ 1 protease inhibitor (PI). While the majority of patients with any interpreted ARV resistance had resistance to a single class of ARVs (86%), 4 patients (0.98%) had dual class resistance (one with NRTI and NNRTI and three with NNRTI and PI), and a single patient had triple class resistance. There was a gradual increase in resistance to NNRTIs during 2007 to 2010.

DISCUSSION

We detected at least one TDR mutation in 17% of our patients during 2007 to 2010, with mutations of 15% for NNRTI, 3.9% for NRTI, and 2.0% for PI classes. Our overall TDR and resistance for specific ARV classes were higher than what was previously reported for Washington, D.C. by Boyd et al. (2005) and Gajjala et al. (2005-2007). (Boyd et al., 2008; Gajjala et al., 2008). Our patient population is similar to the HIV population in Washington, D.C. Data in 2009 from the Washington, D.C.

Department of Health revealed of individuals infected with HIV in our city, 72% were men and 75% African American, which are similar to the demographics of the population in our study (DC HAHSTA, 2010). There are other similarities in demographic and clinical data from the Department of Health and our population, including sex, ethnicity, age, and CD4 count at the time of diagnosis (DC HAHSTA, 2010).

The differences in TDR within our region with similar patient demographics may be related to many complicated factors such as provider preferences for ARVs during the study periods, adherence patterns, engagement in care, patient comorbidities and non-medical issues. We did not gather additional demographic information about our subjects or look into the effect of transmission clusters, which could also lead to different results from Boyd et al. (2008).

We also did not assess acute versus chronic infection among our treatment-naïve cohort. However, our overall TDR data mirror the mutation rates reported in other studies within the United States (Castor et al., 2012; Huaman et al., 2011; Hurt et al., 2009; Little et al., 1999; Little et al., 2002; MacVeigh et al., 2013; Readhead et al., 2012; Ross et al., 2007; Truong et al., 2011; Weinstock et al., 2000; Weinstock et al., 2004; Wheeler et al., 2010; Yanik et al., 2012; Youmans et al., 2011).

In addition, our rate of 15% NNRTI mutations contributing to NNRTI resistance was higher than what

was typically reported for this drug class (Castor et al., 2012; Huaman et al., 2011; Hurt et al., 2009; Little et al., 2002; MacVeigh et al., 2013; Readhead et al., 2012; Ross et al., 2007; Taniguchi et al., 2012; Truong et al., 2011; Weinstock et al., 2000; Weinstock et al., 2004; Wheeler et al., 2010; Yanik et al., 2012; Youmans et al., 2011). The increase in TDR was primarily due to NNRTI mutations and occurred during the 4-year study period in a trend similar to other studies in the United States (Grant et al., 2002; Ross et al., 2008; Shet et al., 2006; Simon et al., 2002). This is most likely due to provider preference for single daily pill regimens and the low barrier to resistance for the NNRTI class.

The most commonly detected RT mutations in our study were M41L for NRTIs and K103N for NNRTIs, which are among the most frequently reported in many studies (Castor et al., 2012; Huaman et al., 2011; Hurt et al., 2009; Little et al., 2002; MacVeigh et al., 2013; Readhead et al., 2012; Ross et al., 2007; Taniguchi et al., 2012; Truong et al., 2011; Weinstock et al., 2004; Wheeler et al., 2010; Yanik et al., 2012; Youmans et al., 2011). We observed low rates of individual major Pr mutations, all below 1%; our overall rate of 2% major Pr mutations is slightly less than many other studies in the United States (Castor et al., 2012; Huaman et al., 2011; Hurt et al., 2009; Little et al., 2002; MacVeigh et al., 2013; Readhead et al., 2012; Ross et al., 2007; Taniguchi et al., 2012; Truong et al., 2011; Weinstock et al., 2000; Weinstock et al., 2004; Wheeler et al., 2010; Yanik et al., 2012; Youmans et al., 2011). Although in the minority, persons with dual and triple class ARV resistance mutations were seen in 2% (8 patients) and 0.7% (3 patients), respectively.

Baseline GART results before initiating ARV therapy has been sensible for our patient care. Approximately 7% of our study population had interpreted baseline resistance to NNRTIs, an ARV class included as components of preferred and alternative regimens for patients naïve to ARVs by the DHHS guidelines (DHHS, 2013). Resistance testing has been shown to be cost-effective in the United States unless the local resistance is $\leq 1\%$ (Sax et al., 2005). Due to the relatively low levels of Pr mutations, our findings also support the use of a boosted PI regimen when empiric ARV therapy must be initiated before GART results are available. Knowledge of local resistance data will likely prove to be important for post-exposure prophylaxis regimens, as well as pre-exposure prophylaxis for which the Centers for Disease Control has issued interim guidelines for men who have sex with men (MSM), heterosexual couples at high risk for HIV acquisition, and injection drug users (CDC PrEP MSM 2011; CDC PrEP Hetero 2012; CDC PrEP IV 2013).

This study has several limitations. We believe the majority of our patients were chronically infected based on medical record review with only a few with acute/recent HIV infection. In some studies, patients with

acute/recent infections had a higher rate of detected TDR compared to patients who were chronically infected (Weinstock et al., 2004; Yanik et al., 2012). TDR mutations may have been underestimated as low prevalence mutations are not detected by most standard sequencing techniques unless the mutation is present in $>10\text{-}30\%$ of the population (Bellecave et al., 2013; Johnson et al., 2008). In some cases, the wild-type virus may become the dominant virus and certain TDR mutations may not be detected in the absence of selective drug pressure, though this may occur only after several years (Gandhi et al., 2003; Little et al., 2008; Yerly et al., 2008). It is possible the TDR rate in Washington, D.C. may be higher than the observed rate of 17%.

We observed an increasing trend of TDR mutations, especially for NNRTI mutations since 2007, which was the first year that GART received an AIII recommendation for all treatment-naïve patients by DHHS. The NNRTI mutation increase contributed to the overall TDR trend over the 4-year period. It is noteworthy that approximately 2% of our patients had E138A/G/K mutations during 2007 to 2010, as these mutations are associated with rilprivirine resistance. Rilprivirine, a NNRTI approved in 2011, has been included as a component of alternative regimens recommended by DHHS (DHHS, 2013). The rates of E138A/G/K mutations within our community may have an impact on successful virologic suppression of patients initiating therapy.

The most common mode of HIV transmission in Washington, D.C. is MSM (38.8%), followed by heterosexual contact (27.2%), and intravenous drug use (16.2%) (DC HAHSTA, 2010). MSM has been associated with higher rates of TDR (Banez et al., 2014; Little et al., 2002; Shet et al., 2006; Weinstock et al., 2004) although this has not been observed in all studies (Readhead et al., 2012). We did not collect data regarding risk factor(s) for HIV acquisition, but this warrants further investigation to determine the rate of TDR for this population compared to other risk groups in our city. Our data spanned the period from 2007 to 2010. Continued surveillance is important to follow the rising trend of TDR in Washington, D.C. and to compare this trend with other high HIV prevalence areas. This will be addressed in an ongoing registry called "The DC Cohort," a city-wide database of HIV infected patients at the major academic and community clinics in Washington, D.C. (DC Cohort, 2013).

CONCLUSION

In summary, 17% of ARV-naïve HIV-infected patients had ≥ 1 genotypic mutation, and 8.6% had resistance to ≥ 1 ARV drug from 2007 to 2010. NNRTI mutations were seen in 15% patients, followed by 3.9% for NRTI and 2% for major Pr mutations. We had an increasing trend of

NNRTI mutations during the study period. Our study found higher local rates of overall TDR and NNRTI-associated mutations than what was previously reported in Washington, D.C. Our mutation and resistance findings have important implications in treatment initiation and pre and post-exposure prophylaxis in an urban area with one of the highest prevalence rate of HIV within the United States.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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