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Analysis of HIV Integrase Resistance in Black Men Who Have Sex with Men in the United States

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Abstract

Resistance to reverse transcriptase and protease inhibitors was frequently detected in HIV from black men who have sex with men (MSM) enrolled in the HIV prevention trials network (HPTN) 061 study. In this study, integrase strand transfer inhibitor (INSTI) resistance was analyzed in black MSM enrolled in HPTN 061 (134 infected at enrollment and 23 seroconverters) and a follow-up study, HPTN 073 (eight seroconverters). The ViroSeq HIV-1 Integrase Genotyping Kit (Abbott Molecular) was used for analysis. Major INSTI resistance mutations were not detected in any of the samples. HIV from 14 (8.4%) of the 165 men, including 4 (12.9%) of 31 seroconverters, had accessory or polymorphic INSTI-associated mutations. The most frequently detected mutation was E157Q. These findings are promising because INSTI-based regimens are now recommended for first-line antiretroviral treatment and because long-acting cabotegravir is being evaluated for pre-exposure prophylaxis.

Keywords: HIV integrase, integrase inhibitor, drug resistance, men who have sex with men

Regimens that include integrase strand transfer inhibitors (INSTIs) have excellent efficacy, safety, and tolerability profiles in both antiretroviral (ARV) treatment (ART)-naive and ART-experienced patients.[1] The first INSTI approved by the United States Food and Drug Administration (FDA) was raltegravir in 2007, followed by dolutegravir in 2013, and elvitegravir in 2014.[2] INSTI-based regimens have been recommended for first-line ART since 2009. New INSTIs are currently under development, and a long-acting injectable form of the INSTI, cabotegravir, is being evaluated for pre-exposure prophylaxis (PrEP).[3,4]

The emergence of drug-resistant HIV has important implications, both for HIV-infected persons receiving ART and for at-risk uninfected individuals who could benefit from ARV-based prevention strategies. The U.S. Department of Health and Human Services recommends HIV drug

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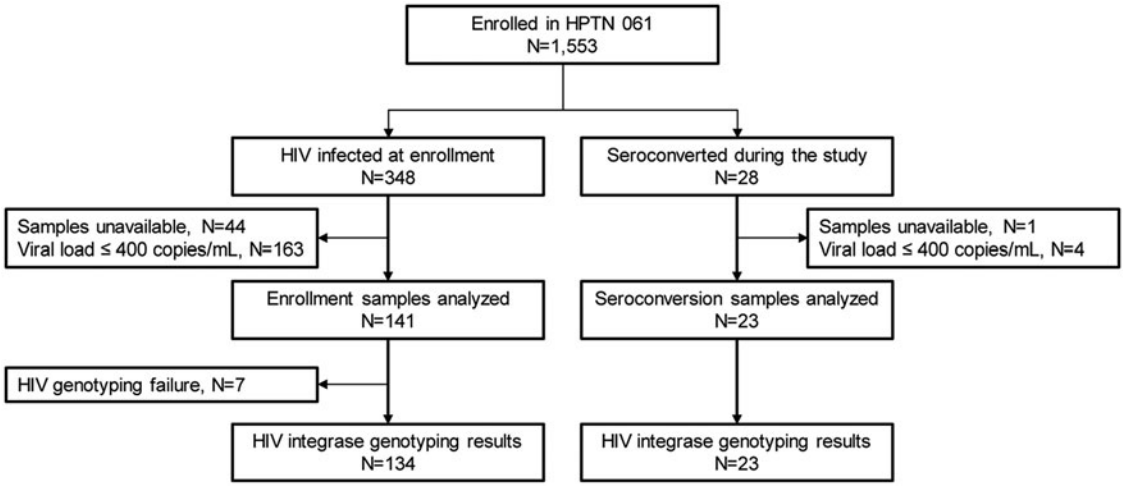

FIG. 1. HIV integrase genotyping among HIV-infected black MSM enrolled in HPTN 061. HIV integrase genotyping was performed for 141 (41%) of the 348 men who were HIV infected at enrollment and 23 (82%) of the 28 seroconverters in HPTN 061; the remaining men either had viral loads ≤400 copies/ml or no sample available for additional testing. HIV integrase genotyping was successful for 134 (95%) of the 141 enrollment samples and all 23 seroconverter samples in HPTN 061. HIV integrase genotyping was also successful for samples from eight men who seroconverted during a follow-up study, HPTN 073 (not shown). HPTN, HIV Prevention Trials Network; MSM, men who have sex with men.

resistance testing for all HIV-infected individuals entering care.[5] Standard HIV drug resistance testing assesses resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs); testing for INSTI resistance is only recommended when clinically suspected by a provider.[5] The overall prevalence of INSTI resistance in the United States, particularly among men who have sex with men (MSM), is not well characterized. One U.S. study found that 16% of individuals who received clinically indicated testing for INSTI resistance had mutations associated with resistance to raltegravir or elvitegravir.[6]

The HIV prevention trials network (HPTN) 061 study (NCT 00951249) is the largest longitudinal U.S. cohort of black MSM to date.[7,8] The HPTN 061 study was designed to assess the feasibility and acceptability of a multicomponent intervention to reduce HIV incidence in black MSM in the United States. HIV-uninfected black MSM at a high risk of HIV acquisition and men already living with HIV were enrolled between 2009 and 2010, after raltegravir was approved by the U.S. FDA but before the first reported cases of transmitted INSTI resistance.[9,10] Men were enrolled in six U.S. cities (Atlanta, Boston, Los Angeles, New York City, San Francisco, and Washington, D.C.) and followed for 1 year.[7,8]

HIV drug resistance to NRTIs, NNRTIs, and PIs was frequently detected in the HPTN 061 cohort,[11] as described previously: 28% of the HIV-infected men had drug-resistant HIV at enrollment and 22% of the HIV seroconverters had drug-resistant HIV at the first HIV-positive study visit.[11] In this report, we analyzed INSTI resistance in the HPTN 061 cohort and in HIV seroconverters in a follow-up study, HPTN 073 (NCT 01808352; 2013–2015), that evaluated PrEP uptake and adherence among black MSM in three U.S. cities (Raleigh/Durham, Los Angeles, and Washington, D.C.).[12]

HIV RNA was prepared using the ViroSeq HIV-1 Genotyping System (Abbott Molecular, Des Plaines, IL).[11] INSTI resistance testing was performed using the ViroSeq HIV-1 Integrase Genotyping Kit (research use only; Abbott Molecular); samples were analyzed from men who had viral loads >400 copies/ml. In brief, a 1.1 kb amplicon of the HIV-1 integrase gene was amplified from HIV RNA using a one-step, reverse transcription polymerase chain reaction. Samples were sequenced using two forward and two reverse primers, amplifying the entire HIV integrase gene (864 base pairs). An Applied BioSystems 3130xl Genetic Analyzer was used for sequence analysis (Thermo Fisher Scientific, Waltham, MA). INSTI resistance was predicted using the ViroSeq Algorithm Advisor included in the software package.

In HPTN 061, 348 men were HIV infected at enrollment and 28 men seroconverted during study follow-up (Fig. 1).[7,8] HIV integrase genotyping was performed for 141 (41%) of the 348 men who were HIV infected at enrollment and 23 (82%) of the 28 seroconverters; the remaining men either had viral loads ≤400 copies/ml or no sample available for additional testing. HIV integrase genotyping was successful for 134 (95%) of the 141 enrollment samples and all 23 seroconverter samples. In HPTN 073, eight men seroconverted during study follow-up; HIV integrase genotyping was successful for all eight seroconverter samples. All men included in this analysis were infected with HIV-1 subtype B.

None of the men had HIV genotypes that predicted resistance to raltegravir, dolutegravir, or elvitegravir using the ViroSeq Integrase Algorithm Advisor. Accessory or polymorphic INSTI-associated mutations were detected in 14 men (10/134 men in HPTN 061 who were HIV infected at enrollment, 2/23 seroconverters in HPTN 061, and 2/8 seroconverters in HPTN 073; Table 1). The most frequently detected mutation was E157Q (detected in eight individuals). Two of the men who were infected at enrollment in HPTN 061 and had accessory or polymorphic INSTI-associated mutations also had resistance to other drug classes (both had the NRTI mutation M184V, one also had the NNRTI mutations K101E and G90S).

Table 1. Integrase Strand Transfer Inhibitor-Associated Mutations in Black Men Who Have Sex with Men in the United States

	HPTN 061		*HPTN 073*
	Enrollment (N = 134)	*Seroconversion (N = 23)*	*Seroconversion (N = 8)*
INSTI-associated mutations	*10 (7%)*	*2 (9%)*	*2 (25%)*
T97A	1	1	—
A128T	1	—	—
E157Q	6	1	1
L74 M, E157Q	1	—	—
T97A, G163R	1	—	—
T97A, E157Q	—	—	1

HPTN, HIV Prevention Trials Network; INSTI, integrase strand transfer inhibitor.

Nonsuppressive ARV use and HIV drug resistance to NRTIs, NNRTIs, and PIs were frequently observed in HIV from men in HPTN 061; many of these men had limited treatment options.[11] The absence of major INSTI resistance mutations in this cohort and in seroconverters in the more recent HPTN 073 study is promising, because INSTI-based treatment regimens are now first-line regimens for ART, and a long-acting formulation of cabotegravir is being evaluated for use as PrEP.[3,4]

HIV from 4 (13%) of the 31 seroconverters in HPTN 061 and HPTN 073 had one or two INSTI-associated mutations detected. Although these accessory and polymorphic mutations are not sufficient to cause high-level INSTI resistance, their presence could increase the overall level of INSTI resistance if those individuals acquired subsequent major INSTI resistance mutations.[13] The most frequently detected INSTI-associated mutation in this study was E157Q, which can reduce raltegravir and elvitegravir susceptibility two- to threefold, while increasing susceptibility to dolutegravir.[14] In a case study, a patient whose virus harbored the E157Q mutation failed ART with raltegravir and then dolutegravir.[15]

This study evaluated INSTI resistance using an assay based on bulk (population) sequencing. Methods such as next-generation sequencing (NGS) can detect resistance mutations present at lower levels. NGS was performed for the eight seroconverters in HPTN 073 in a separate study. In addition to detecting E157Q in two men, a rare non-polymorphic mutation selected *in vitro*, N155S, was detected as a minority variant in one seroconverter, and accessory mutations were detected in other cases (unpublished data). Given the increasing use of INSTIs as preferred treatment options and their potential role as PrEP agents, further surveillance for INSTI resistance is clearly warranted.

Acknowledgments

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Sequence Data

The sequence data obtained in this study are available in GenBank under Accession numbers KY574889-KY575022, KY434636-KY434658, and KY369927-KY369934.

Authors' Contributions

All authors contributed to article preparation. I.C. performed HIV integrase genotyping for HPTN 061, contributed to study design, analyzed laboratory data, and drafted the article; Y.Z. performed HIV integrase genotyping for HPTN 073 and analyzed laboratory data; V.C., HPTN Laboratory Center Quality Assurance/Quality Control Representative for HPTN 061, assisted with sample and data management; G.A.C. provided support for HIV integrase testing; M.C., data analyst for HPTN 061; G.B., data analyst for HPTN 073; S.G., project coordinator for HPTN 061; S.R., project coordinator for HPTN 073; J.G. provided expertise on HIV integrase resistance; H.M.S., coinvestigator for the HPTN 061 site in San Francisco; S.S., principal investigator for the HPTN 061/073 site in Los Angeles; C.D.R., principal investigator for the HPTN 061 site in Atlanta; I.K., costudy leader for the HPTN 061/073 site in Washington, D.C.; S.M., principal investigator for the HPTN 061 site in New York City; H.V.T., coinvestigator for the HPTN 061 site in New York City; C.B.H., principal investigator for the HPTN 073 site in Raleigh/Durham; S.D.F., chair of the HPTN 061 black Caucus, assisted with cultural data interpretations; D.P.W., protocol cochair for HPTN 061; K.H.M., protocol cochair for HPTN 061, principal investigator for the HPTN 061 site in Boston; B.A.K., protocol chair for HPTN 061, principal investigator for one HPTN 061 site in New York City; S.H.E., protocol virologist, responsible for study design, analyzed data, and drafted the article.

Author Disclosure Statement

None of the authors has a conflict of interest or potential conflict of interest, with the following exceptions: G.A.C. is an employee and shareholder of Abbott Laboratories. S.H.E. has collaborated on research studies with investigators from Abbott Laboratories (distributor of the ViroSeq HIV-1 Genotyping System). Abbott Laboratories provided reagents for integrase genotyping. J.G. has received consulting income from Bristol-Myers Squibb, Gilead Sciences, Merck & Co., Theratechnologies, and ViiV Healthcare/GlaxoSmithKline. His institution has received research support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen Therapeutics, Merck & Co., Sangamo BioSciences, and ViiV Healthcare/GlaxoSmithKline. I.C. contributed to this article in her personal capacity. The views expressed are her own and do not represent the views of the Health Resources and Services Administration or the United States Government.

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