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Pre-treatment integrase inhibitor resistance is uncommon in ART-naïve individuals with HIV-1 subtype A1 and D infections in Uganda

Suzanne M. MCCLUSKEY[1,2], **Kimia KAMELIAN**[3], **Nicholas MUSINGUZI**[4], **Simone KIGOZI**[4], **Yap BOUM II**[4], **Mwebesa B. BWANA**[4], **Conrad MUZOORA**[4], **Zabrina L. BRUMME**[5,6], **Mary CARRINGTON**[7,8], **Jonathan CARLSON**[9], **Brian FOLEY**[10], **Peter W. HUNT**[11], **Jeffrey N. MARTIN**[11], **David R. BANGSBERG**[12], **P. Richard HARRIGAN**[3], **Mark J. SIEDNER**[1,2,4], **Jessica E. HABERER**[1,2], **Guinevere Q. LEE**[*,1,2,6,13]

[1]Massachusetts General Hospital, Boston, USA [2]Harvard Medical School, Boston, MA, USA [3]Division of AIDS, University of British Columbia, Vancouver, BC, Canada [4]Mbarara University of Science and Technology, Mbarara, Uganda [5]Simon Fraser University, Burnaby, BC, Canada [6]BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada [7]Basic Science Program, Frederick National Laboratory for Cancer Research in the Laboratory of Integrative Cancer Immunology, National Cancer Institute, Bethesda, MD, USA [8]Ragon Institute of MGH, MIT, and Harvard, Boston, MA, USA [9]Microsoft Research, Seattle, WA, USA [10]Los Alamos National Laboratory, Los Alamos, NM, USA [11]University of California, San Francisco, CA, USA [12]Oregon Health Sciences University, Portland, OR, USA [13]Weill Cornell Medicine, New York, NY, USA

Abstract

Objective: Dolutegravir (DTG) is now a preferred component of first-line antiretroviral therapy (ART). However, prevalence data on natural resistance to integrase inhibitors (INSTIs) in circulating non-subtype B HIV-1 in sub-Saharan Africa is scarce. Our objective is to report prevalence of pre-treatment integrase polymorphisms associated with resistance to INSTIs in an ART-naïve cohort with diverse HIV-1 subtypes.

Design: We retrospectively examined HIV-1 integrase sequences from Uganda.

Methods: Plasma samples were derived from the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort, reflecting enrollment from 2002–2010, prior to initiation of ART. HIV-1 integrase was amplified using nested-PCR and Sanger-sequenced (HXB2 4230–5093). Stanford HIVdb v8.8 was used to infer clinically significant INSTI-associated mutations. HLA typing was performed for all study participants.

[*]**Corresponding Author:** Guinevere Q. Lee, PhD, Division of Infectious Diseases, Department of Medicine, Weill Cornell Medicine, BB-524 413 East 69th Street, New York, NY 10021. gul4001@med.cornell.edu.

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Results: Plasma samples from 511 ART-naïve individuals (subtype: 48% A1, 39% D) yielded HIV-1 integrase genotyping results. Six out of 511 participants (1.2%) had any major INSTI-associated mutations. Of these, two had E138T (subtype A1), three had E138E/K (subtype D), and one had T66T/I (subtype D). No participants had mutations traditionally associated with high levels of INSTI resistance. HLA-genotypes A*02:01/05/14, B*44:15, and C*04:07 predicted the presence of L74I, a mutation recently observed in association with long-acting INSTI cabotegravir virologic failure.

Conclusion: We detected no HIV-1 polymorphisms associated with high levels of DTG resistance in Uganda in the pre-DTG era. Our results support widespread implementation of DTG, but careful monitoring of patients on INSTI with virologic failure is warranted to determine if unique mutations predict failure for non-B subtypes of HIV-1.

Keywords

HIV-1; integrase strand transfer inhibitors; dolutegravir; mutation; HIV integrase; sub-Saharan Africa; Uganda

INTRODUCTION

The World Health Organization now recommends dolutegravir (DTG) as a component of first-line antiretroviral therapy (ART),[1, 2] partially due to DTG's high genetic barrier to resistance[3, 4] and recent release of a fixed-dose combination of lamivudine, tenofovir disoproxil fumarate, and DTG, which is available for a lower cost than efavirenz-containing regimens in much of sub-Saharan Africa (SSA). In addition, the new generation INSTI cabotegravir (CAB) is being investigated as a component of long-acting therapy[5, 6] and pre-exposure prophylaxis.[7–9]

In light of the major role INSTIs are likely to play in the HIV treatment landscape in SSA, it is of great public health importance to evaluate the susceptibility of circulating HIV strains to newer generation INSTIs. Most clinical studies involving DTG have been conducted in the United States and Europe (where HIV-1 subtype B predominates), while fewer studies have been conducted in regions where diverse HIV-1 subtypes co-circulate, such as in Uganda where subtypes A1 and D predominate. Until recently, programmatic use of INSTIs in SSA has been limited to salvage regimens. Thus, population exposure to INSTIs has been low, and pre-treatment prevalence of major integrase mutations is expected to be rare, with studies from SSA reporting 0 – 2.4% prevalence.[10–12] We identified an ideally suited Ugandan cohort with diverse viral subtypes in which we aimed to examine naturally-occurring polymorphisms in non-subtype-B HIV integrase that have been associated with reduced susceptibility to INSTIs.[13]

METHODS

Ethics Statement

The study was approved by ethics committees at Mbarara University of Science and Technology (14/01–03), Uganda National Council of Science and Technology (HS 07, HS 938), Partners Healthcare (2011P000522), University of British Columbia/ Providence

Health Care (H11-01642), Weill Cornell Medical College (19-12021173), University of California San Francisco (10-03,457), and Frederick National Laboratory for Cancer Research (IRB 3314). Participants provided written consent.

Study design and study population

Data were collected from the Uganda AIDS Rural Treatment Outcomes (UARTO) study (NCT 01596322), which has been described previously.[14, 15] Eligible participants were ART-naïve, age 18 and above, and lived within 60 kilometers of the study site. Individuals who self-reported prior ART use were excluded. Participants were enrolled from Kampala (pilot study, urban setting, 2002–2004) and from Mbarara (main study, rural setting, 2005–2015). At study enrollment, pre-ART plasma specimens were obtained for HIV-1 RNA viral load and were frozen at −80°C for future testing. Pre-ART HIV integrase sequencing and HLA typing were planned for participants enrolled from 2002 – 2010, an era during which INSTIs were not part of recommended ART regimens in Uganda. Pre-ART HIV-1 reverse transcriptase sequences were also obtained for this group, which have been reported previously.[14, 15] The present analysis included participants for whom integrase sequencing was completed. HLA-genotyping was performed for all studied individuals.

Laboratory procedures

Total nucleic acid was extracted from 500 μL of plasma using NucliSENS easyMag (bioMérieux). Invitrogen SuperScript® III One-Step RT-PCR System with Platinum® Taq DNA Polymerase was used for reverse transcription and first-round PCR reactions targeting HIV-1 HXB2 coordinates 3597–6004 (forward primer 5'-AAAACAGGAAARTATGCAA-3'; reverse primer 5'-AGCTCTTCGTCGCTGTCTCCGCTT-3'). Nested second-round PCR reactions targeted HIV-1 HXB2 coordinates 3626–5980 (forward primer 5'-TGCCCACACTAATGATGTAA-3'; reverse primer 5'-CTTCCTGCCATAGGAGATGCCTA-3'). These primers are optimized to account for HIV-1 genetic diversity, and we obtained successful HIV-1 integrase genotypes for 87% of specimens. Bulk Sanger sequencing was performed on ABI 3730 DNA Sequencer using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). Chromatograms were aligned against reference sequence HXB2 (integrase 4230–5093) by an in-house automated alignment and base-calling program RECall.[16] HLA typing was performed using Roche 454/ Fluidigm HLA Typing Kits.[17] Briefly, locus-specific primers were used to amplify polymorphic exons of HLA-A, B and C genes with Fluidigm Access Array (Fluidigm Singapore PTE Ltd, Singapore). The Fluidigm PCR amplicons were pooled and were sequenced on a 454 FLX Genome Sequencer (454 Life Sciences Corpora- tion, Branford, CT). HLA alleles and genotypes were called using the Conexio ATF 454 HLA-typing software (Conexio Genomics Inc, Perth, Australia).

Subtyping, drug resistance inference, and statistical analysis

We used the Los Alamos Recombinant Identification Program 3.0 (window size 400 with a 95% confidence threshold) for subtype inference,[18] with confirmation by REGA 2.0 (BIOAFRICA).[19] All subtyping calls were re-confirmed by neighbor-joining phylogenetic analyses with relevant Los Alamos 2010 HIV-1 subtype references.[20] The Stanford HIVdb

algorithm v8.8 was used to infer major and accessory mutations associated with reduced INSTI susceptibility.[13] We also evaluated the presence of mutations outside the integrase region that have been reported to affect INSTI susceptibility.[21] We used Stata 14.0 and R for statistical and phylogenetic analyses. Statistical significance was defined as $p<0.05$.

RESULTS

Baseline characteristics

We obtained successful HIV-1 integrase genotypes for 511/590 (87%) specimens (GenBank accession numbers MH925338 – MH925677; MW341596 – MW341779). We describe the demographics of the study population in Table 1. The distribution of HIV-1 subtypes was: 48% A1, 39% D, 4% C, and 8% belonging to other subtypes. All participants were INSTI-naïve.

Prevalence of pretreatment INSTI-associated mutations

We identified major INSTI-associated mutations in 6/511 (1.2%) participants (Table 2, left panel). These included T66I (n = 1; subtype D), E138K (n = 3; subtype D), and E138T (n = 2; subtype A1). Accessory INSTI-associated mutations were more common, occurring in 28.4% of participants (n = 145/511). Mutation prevalence in this cohort was similar to that reported in the Stanford HIV Drug Resistance Database (Table 2, right panel).[13] None of the study participants had >1 INSTI-associated resistance mutation.

Level of resistance to integrase inhibitors

The Stanford HIVdb algorithm classifies degree of resistance to INSTIs into “susceptible,” “potential low-level,” “low-level,” “intermediate” and “high.” Based on this classification system, 98.6% of participants had viruses that were fully susceptible to second-generation INSTIs DTG and bictegravir (BIC). Potential low-level resistance to DTG and BIC was identified in 1.2% and 1.4% of participants, respectively. In addition, we identified low-level resistance to DTG in one participant (0.2%). Cabotegravir (CAB)-associated resistance mutations were not listed in HIVdb at the time of writing. Polymorphisms associated with partial resistance to raltegravir (RAL) and elvitegravir (EVG) were more common and included potential low-level resistance to RAL and EVG in 9.8% of participants, low-level resistance in 2.0% and 1.8% of participants respectively, and high-level resistance to EVG with T66TI in one HIV-1 subtype D-infected participant (0.2%).

Association of L74I with HLA-genotypes

Given recent reports linking integrase L74I to CAB-associated treatment failures in subtype A1[5, 6], and the knowledge that certain resistance-associated HIV polymorphisms are selected under HLA-associated immune pressures,[22] we explored the relationship between HLA-genotype and the accessory mutation L74I, which was observed in 30 individuals in our cohort. We began by exploring associations between HLA alleles observed with L74I using Fisher’s exact tests, in a subtype-specific manner. In doing so we identified six associations with p-values <0.05. In subtype A1, HLA-A*02 (inclusive of A*02:01, A*02:05, A*02:14), B*44:15 and C*04:07 (p=0.046, 0.025 and 0.017 respectively), and in subtype D, B*14:02:01, B*15 (inclusive of B*15:03, B*15:10, B*15:16) and C*03

(inclusive of C*03:02, C*03:04) were significantly associated with L74I (p=0.046, 0.013, 0.006 respectively). For each of these six HLA genotypes, we then fit multivariable logistic regression models to a dataset restricted to subtypes A1 and D infections only (L74I n=27). Each model featured L74I as the outcome of interest and presence/absence of each HLA allele as the predictor of interest. We included viral subtype and an interaction term between viral subtype and HLA-genotype as covariates. L74I remained significantly associated with HLA-A*02 (p=0.028), HLA-B*44:15 (p=0.014) and HLA-C*04:07 (p=0.0074), yielding adjusted odds ratios of 2.6, 3.7 and 4.2 respectively; all were linked to subtype A1 in the initial subtype-stratified univariable analysis.

DISCUSSION

Polymorphisms associated with resistance to INSTIs in non-subtype B HIV-1 are understudied. In this analysis, we report that 98.6%, 98.6%, 88.3% and 88.3% of 511 participants harbored viruses that were genotypically susceptible to BIC, DTG, EVG and RAL, respectively. We observed only a 1.2% population prevalence of major integrase mutations (T66I and E138K/T), which is similar to other studies,[10, 12] but a relatively high (27.6%) prevalence of accessory integrase mutations and polymorphisms, which are not known to reduce INSTI susceptibility when occurring alone.[13] Thus, our results support widespread use of INSTIs such as DTG in SSA, but presence of pre-treatment accessory mutations calls for longitudinal surveillance for resistance mutations moving forward.

Our study also identified an association between HLA-genotype and L74I in subtype A1 HIV-1-infections. L74I was not previously identified in a comprehensive HLA-association analysis in the present Ugandan cohort that employed a much more conservative statistical significance threshold [23], however HLA associations with L74X have previously been reported in subtype B (HLA B*39:01[24]) and subtype C (HLA B*15:10[25]). Notably, L74I occurred in 6% of this Ugandan cohort with 7%, 0%, and 5% prevalence among those with subtypes A1, C, and D, respectively. When occurring alone *in vivo*, L74I is not associated with reduced INSTI susceptibility according to Stanford HIVdb.[13] However, in the ATLAS and FLAIR studies,[5, 6, 26–28] which evaluated efficacy of long-acting CAB with rilpivirine, HIV-1 subtypes associated with failure in the experimental arm were A/A1 (n=2, ATLAS) and A1 (n=3, FLAIR). All five of these individuals were from Russia and harbored the L74I polymorphism.[27, 28] Four of these individuals also went on to develop additional resistance mutations in integrase, including G140R, Q148R, and N155H.[26, 27] While L74I was not found to affect viral suppression in FLAIR and ATLAS,[26] there may be subtype-specific interaction that warrants further study. Given that subtype A1 is highly prevalent in East Africa[29] and represents approximately 12% of HIV-1 infections worldwide,[30] the co-occurrence of subtype A1-specific polymorphisms and specific HLA-genotypes that may lower the genetic barrier for resistance to INSTIs are of particular public health relevance.

Results should be interpreted in light of the relatively small sample size. However, this analysis cohort included both urban (Kampala) and rural (Mbarara) groups, as well as a broad distribution of HIV-1 subtypes. Of note, few (4%) participants had HIV-1 subtype C, so results may not be generalizable to regions where subtype C predominates. We also recognize that study specimens were collected in the pre-INSTI era (2002 – 2015). Samples

collected from more recent cohorts after broader introduction of INSTIs may yield different prevalence estimates for integrase mutations and polymorphisms. In addition, we have not demonstrated experimentally that L74I is within an integrase epitope that is targeted by HLA-A*02, B*44:15 or C*04:07 in subtype A1 HIV-1. Finally, study results are also limited by use of Sanger sequencing, as opposed to next-generation sequencing that allows for reporting of minority variants.

In conclusion, we reported a low prevalence of major INSTI mutations in treatment-naïve Ugandans infected with HIV-1 subtypes A1, C and D. Importantly, none of the mutations observed would significantly impact the efficacy of DTG, supporting WHO and PEPFAR guidelines for widescale implementation of DTG-containing regimens in SSA. However, effects of L74I on INSTI-based therapy, its link to HLA-genotypes, and whether it lowers the genetic barrier to INSTI require population-level validation.

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Table 1.

Study population for assessment of pre-treatment integrase resistance

	n = 511
Female	353 (69)
Age (n=506)	34 (29 – 39)
Study site	
Kampala (urban setting)	58 (11)
Mbarara (rural setting)	453 (89)
Year of study enrollment	
2002 – 2003	50 (10)
2004 – 2005	68 (13)
2006 – 2007	271 (53)
2008 – 2010	122 (24)
Pretreatment CD4 (n=503)	127 (66 – 195)
Pretreatment log10 viral load (n=502)	5.19 (4.71 – 5.66)
HIV-1 subtype	
A1	247 (48)
C	21 (4)
D	200 (39)
Other	43 (8)

Categorical data are listed as count (%).

Continuous data are listed as median (interquartile range).

Table 2.

Pre-treatment integrase mutations in the UARTO Cohort, as compared to the Stanford Database

Legend									
0%									
>0 – 5%	UARTO Cohort*					Stanford Database**			
6 – 10%	HIV-1 Subtype					HIV-1 Subtype			
11 – 20%	A1	C	D	Other	Total	A1	B	C	D
>20%	n = 247	n = 21	n = 200	n = 43	n = 511	n = 1366	n = 7893	n = 3394	n = 494
Major Integrase Mutations									
T66A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	5 (0)	0 (0)
T66I	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)	2 (0)	0 (0)	2 (0)	1 (0)
T66K	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
E92Q	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
G118R	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
E138K	0 (0)	0 (0)	3 (2)	0 (0)	3 (1)	1 (0)	25 (0)	2 (0)	2 (0)
E138A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
E138T	2 (1)	0 (0)	0 (0)	0 (0)	2 (0)	2 (0)	0 (0)	0 (0)	0 (0)
G140S	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
G140A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
G140C	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Y143C	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Y143H	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (0)	0 (0)
Y143R	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
S147G	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	1 (0)
Q148H	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Q148K	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Q148R	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0)	0 (0)	1 (0)
N155H	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
R263K	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0)	10 (0)	0 (0)	0 (0)
Major	**2 (1)**	**0 (0)**	**4 (2)**	**0 (0)**	**6 (1)**	-----	-----	-----	-----
Other Integrase Mutations									

Legend									
0%									
>0 – 5%	UARTO Cohort*					Stanford Database**			
6 – 10%	HIV-1 Subtype					HIV-1 Subtype			
11 – 20%	A1	C	D	Other	Total	A1	B	C	D
>20%	n = 247	n = 21	n = 200	n = 43	n = 511	n = 1366	n = 7893	n = 3394	n = 494
M50I	31 (13)	11 (52)	4 (2)	4 (9)	50 (10)	257 (19)	779 (10)	1326 (41)	19 (4)
H51Y	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	2 (0)	0 (0)	0 (0)	0 (0)
V54I	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)	9 (1)	59 (1)	22 (1)	1 (0)
L68V	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)	0 (0)	110 (1)	7 (0)	2 (0)
L74F	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
L74I	17 (7)	0 (0)	10 (5)	3 (7)	30 (6)	254 (19)	312 (4)	196 (6)	16 (3)
L74M	3 (1)	0 (0)	3 (2)	0 (0)	6 (1)	28 (2)	54 (1)	26 (1)	5 (1)
Q95K	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)	13 (0)	0 (0)
T97A	30 (12)	1 (5)	11 (6)	3 (7)	45 (9)	93 (7)	52 (1)	28 (1)	26 (5)
H114Y	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
S119R	1 (0)	2 (10)	3 (2)	0 (0)	6 (1)	15 (1)	399 (5)	55 (2)	12 (2)
F121Y	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
A128T	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	4 (0)	41 (1)	21 (1)	1 (0)
P142T	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
P145S	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Q146P	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
G149A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (0)	0 (0)	0 (0)
V151A	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
V151I	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)	1 (0)	346 (4)	12 (0)	3 (1)
V151L	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
S153F	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
S153Y	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
E157Q	3 (1)	0 (0)	5 (3)	0 (0)	8 (2)	16 (1)	252 (3)	23 (1)	19 (4)
G163K	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	12 (0)	2 (0)	1 (0)
G163R	0 (0)	1 (5)	0 (0)	0 (0)	1 (0)	2 (0)	22 (0)	18 (1)	1 (0)
G193E	5 (2)	1 (5)	5 (3)	0 (0)	11 (2)	41 (3)	421 (5)	74 (2)	21 (4)

Legend									
0%									
>0 – 5%	UARTO Cohort*					Stanford Database**			
6 – 10%	HIV-1 Subtype					HIV-1 Subtype			
11 – 20%	A1	C	D	Other	Total	A1	B	C	D
>20%	n = 247	n = 21	n = 200	n = 43	n = 511	n = 1366	n = 7893	n = 3394	n = 494
S230R	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)	1 (0)	0 (0)	4 (0)	0 (0)
D232N	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16 (1)	31 (0)	5 (0)	1 (0)
Non-integrase mutations	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-----	-----	-----	-----
Any	**78 (32)**	**13 (62)**	**44 (22)**	**10 (23)**	**145 (28)**	-----	-----	-----	-----

Data expressed as count (%)

*Sixty-four percent of the UARTO sequences in this analysis are currently represented in the Stanford database, which contributes to the similar mutation prevalence seen in this study to what is documented in the Stanford database for subtypes A1, C, and D. UARTO sequences were not previously formally analyzed for pre-treatment INSTI resistance.

**Summarized from the Stanford Database (13. Liu, et al. 2006)