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Evaluation of the real-world incidence of integrase inhibitor resistance since adoption as guideline preferred therapy

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Introduction

- Current Department of Health and Human Services guidelines recommend second-generation integrase inhibitors (INSTIs), bictegravir (BIC) and dolutegravir (DTG) as the anchor antiretroviral of choice for most treatment-naïve patients living with HIV (PLWH).[1]
- Second generation INSTIs have a higher barrier to resistance when compared to earlier INSTIs.[1] In clinical trials, BIC and DTG resistance was almost nonexistent.[2,3,4,5,6]
- In the United States, transmitted INSTI-resistance (INSTI-R) is estimated to be approximately 0.8% and prevalence of overall INSTI-R is 6.3%.[8] Prevalence of HIV and rates of virologic suppression are not uniform across the country.[7] Therefore, prevalence of drug-resistance mutations is not likely to be consistent throughout the United States.
- The purpose of this project is to describe the real-world incidence of both transmitted and treatment emergent INSTI-R in patients taking an INSTI single tablet regimen (STR) in a major metropolitan area and identify risk factors for developing INSTI-R.

Study Design

- Retrospective, observational study
- Chart review utilizing Epic electronic medical records (EMR) for patients of the University of Illinois Chicago Hospital and Health Sciences System Community Clinic Network (UCCN) between 2017 and 2020

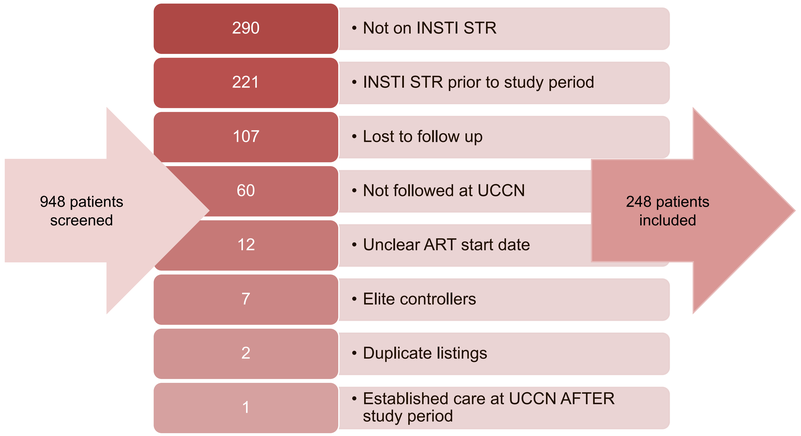
Table 1. Patient eligibility

Inclusion criteria	Exclusion criteria
• ≥ 18 years of age • Prescribed elvitegravir, DTG, or BIC for at least 12 months • Followed at UIH for at least 12 months post-initiation of an INSTI-based regimen • At least one viral load collected >12 months after initiation of an INSTI STR	• Patients without a viral load collected after INSTI-based regimen initiation • Elite controllers, defined as people living with HIV who maintain suppressed HIV-1 RNA viral loads without antiretroviral therapy (ART)

- Endpoints were analyzed using chi-square and fisher's exact tests.

Results

Figure 1. Patient selection



Results

Table 2. Baseline characteristics, n (%)

Baseline characteristic	All participants (n=248)	Participants who developed VF (n=17)
Male gender	159 (64.1)	10 (58.8)
Black race	168 (67.7)	13 (76.5)
Undetectable VL (< 50 copies/mL)	180 (72.6)	4 (23.5)
CD4 T-cell count > 200 cells/mm^3	222 (89.5)	12 (70.5)
Previous ART regimen		
INSTI-based	106 (42.7)	6 (35.3)
NNRTI-based	69 (27.8)	4 (23.5)
PI-based	29 (11.7)	3 (17.6)
Naïve	30 (12.1)	3 (17.6)
Combination	10 (4.0)	1 (5.9)
Other*	1 (0.4)	0 (0.0)
INSTI in STR		
Bictegravir	163 (65.7)	9 (52.9)
Dolutegravir	40 (16.1)	4 (23.5)
Elvitegravir	45 (18.1)	4 (23.5)
Baseline INSTI-R testing	2 (0.01)	0 (0.0)

NNRTI: non-nucleoside reverse transcriptase inhibitor, PI: protease inhibitor; VF: virologic failure - ≥ 2 consecutive viral loads > 200 copies/mL collected at least 24 weeks after initiation of regimen.* 1 participant had a regimen consisting of entry inhibitors and nucleoside reverse transcriptase inhibitors (NRTI)

Primary Endpoints: Development of virologic failure (VF) and documented INSTI-R at baseline or at the time of VF

- Of the 38.7% of subjects with baseline genotypes available, none had baseline INSTI mutations.
- A total of 17 (6.8%) subjects developed VF.
- Two of the 17 (11.8%) received subsequent INSTI-R testing and 10 eventually achieved viral suppression without regimen changes (58.8%).
- No subjects developed INSTI-R, which was significantly less than the prevalence reported nationally of 6.3% (p = 0.0029).

Table 3. Average number of follow-up visits and time to VF

Duration of follow-up	Mean number of clinic visits (SD)	Number of subjects with VF, n (%)
12 months (n = 248)	3 (2.5)	7 (2.8)
24 months (n = 225)	6 (4.1)	13 (5.2)
36 months (n = 119)	9 (5.0)	17 (6.8)

Table 4. Baseline drug resistance, N = 36

Drug Class	Mutation (n)*	Interpretation
NRTI	D67N (4)	With other TAMs can reduce susceptibility to ABC + tenofovir
	K70R (1)	Low-level resistance to ABC + tenofovir
	L74V (1)	Intermediate resistance to ABC
	M184V (17)	High-level resistance to 3TC and FTC + low-level resistance to ABC; increased susceptibility to tenofovir
	M41L (1)	In combination with T215Y, reduced susceptibility to ABC and tenofovir
	T215Y (5)	Low-level resistance to ABC + tenofovir
NNRTI	E138A/G(3) , G190A(2), K101E(2) Y181C(5) , Y188L(1), V106I(6)	Confer varying levels of resistance to RPV
INSTI	No transmitted INSTI resistance isolated	

ABC: abacavir, 3TC: lamivudine, FTC: emtricitabine, RPV: rilpivirine, TAMS: thymidine analog mutations
*of 96 subjects with baseline genotyping available

Table 5. Acquired drug resistance, N = 1

Drug Class	Mutation (n)*	Interpretation
NRTI	L74I (1), K219E (1)	Intermediate level resistance to abacavir
NNRTI	N348I (1)	No effect on rilpivirine susceptibility = no effect on currently available INSTI STR
INSTI		No acquired INSTI resistance isolated.

Results

Secondary endpoint: Difference in patient specific factors leading to medication nonadherence

Table 6. Predictors for nonadherence

Risk factor	n (%)	VF, n (%)
Comorbidities		
Diabetes	30 (12.1)	0 (0.0)
Psychiatric comorbidities	73 (29.4)	4 (23.5)
Substance use disorders	24 (9.7)	1 (5.9)
Hepatitis B	10 (4.0)	0 (0.0)
Hepatitis C	20 (8.1)	0 (0.0)
Other	19 (7.7)	2 (11.8)
Social history (current use)		
Alcohol	39 (15.7)	4 (23.5)
Tobacco	53 (21.4)	5 (29.4)
Drug	60 (24.2)	2 (11.8)
Number of concomitant medications, median (Q1, Q3)	3 (1,7)	2 (0,6)
Interacting medications		
Cations	48 (19.4)	0 (0.0)
Rifamycins	1 (0.4)	1 (5.9)
Anticonvulsants	2 (0.8)	0 (0.0)
Betamethasone, budesonide, or dexamethasone	1 (0.4)	0 (0.0)

Figure 2. Predictors for the development of DRM in patients with VF compared to study population[10,11]

High VL at baseline*,+	Female gender*	Non-white race
n= 10 (58.8%) **p< 0.001**	n= 7 (41.2%) p = 0.61	n= 15 (88.2%) p =0.60

* Associated with the development of drug resistance mutations + defined as > 1000 copies/mL

Table 7. Reasons for nonadherence reported in EMR notes

Risk Factor	Subject with VF, n (%)
Substance use	11 (52.9)
Adverse effects	5 (29.4)
Medication access issues	5 (29.4)
Psychiatric comorbidities	4 (23.5)

Conclusions

The true rate of INSTI-R in UCCN patients is still unknown and factors associated with developing INSTI-R were unable to be assessed. Among patients at UCCN on INSTI-based STRs, INSTI-R rates were lower than the national average. A planned future analyses will include patients on INSTI-based non-STR regimens as increased pill burden is a known risk factor for nonadherence leading to VF and drug resistance.

Conflict of Interest Disclosure

Neither the presenting author nor any of the co-authors have any known or potential conflicts of interest to disclose.

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