Time to consider Dolutegravir for treatment in Uganda: HIV drug resistance profiles of virologic failures on first-,second-, or third line/Raltegravir containing combined antiretroviral treatments

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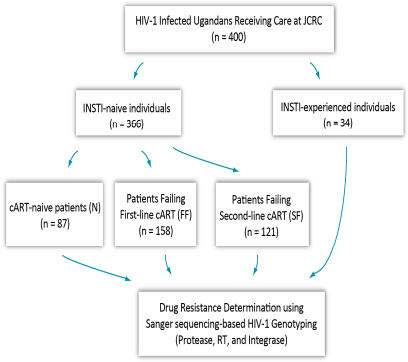
Introduction

- Uganda is among the countries with the highest burden of HIV-1 infections, with approximately 1.4 million (6.5%) people living with HIV/AIDS and 67% of them receiving combined antiretroviral therapy.
- Like other Low income countries (LICs), it is facing dilemma of increasing rates of HIV transmitted drug resistance and acquired drug resistance (DR).
- Despite increasing access to generic Dolutegravir (DTG) in LICs, data on DTG associated DR in this setting is lacking.
- We evaluated DTG associated DR in (n=400) patients who are ART naïve (N), and those failing on first line(FF), second line (SF) and RAL based third line (RF) treatments in Uganda.
- Deep sequencing using Illumina (Miseq) was done in (n=68) of these patients.

Methods

- Patients with virological failure (viral load of ≥ 1000 copies/ml) were selected for the study
- HIV-1 integrase enzyme was amplified from extracted RNA and sequenced using Sanger and Miseq platforms.
- Drug susceptibility was interpreted using HIV-1 genotyping resistance interpretation of Stanford HIV database (https://hivdb.stanford.edu) and Scueal program was used for HIV-1 subtype classifications.

The work flow chart of the patient numbers and their respective groups



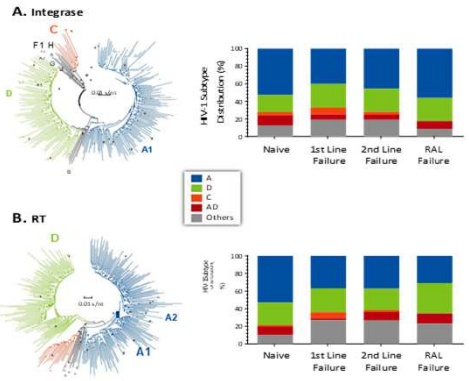
Results

HIV-1 infected patients failing on RAL-based regimen with primary and/or secondary (compensatory) INSTI mutations

Primary/secondary mutations	n (%)	DTG	RAL	EVG
M50I/L/MR	1(3.0)	S	S	S
M50I,L74I	1(3.0)	S	S	S
T97A	1(3.0)	S	P	P
T97A,G163R,L74M	3(8.8)	S	L	L
N155H	2(6.0)	P	H	H
N155H,T97A	1(3.0)	P	H	H
N155H,T97AT	1(3.0)	P	H	H
N155H,T97A,E157Q,L74I	1(3.0)	P	H	H
N155H,E157Q,G163R,M50L,L74I	1(3.0)	P	H	H
Y143R,T97A	2(6.0)	S	H	L
Y143R,T97AT,G163R	1(3.0)	P	H	I
Y143R,T97A,M50I,L74LM	1(3.0)	P	H	I
E138A,T97A,V151A	1(3.0)	P	I	I
E138K,G140A,S147G,Q148K	1(3.0)	H	H	H
T66A,T97A,G163R,L74M	1(3.0)	S	I	H

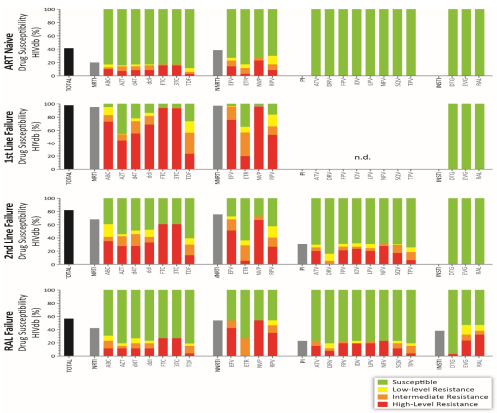
In all 400 patients; Y143R (0.75%), Q148K (0.25%), N155H (1.5%), E138A/K (0.5%), G140A (0.25%), S147G (0.25%). Accessory mutations; T97A (8.75%), M50I 6.5%), L74M/I (3%), E157Q (1.25%), V151I/A (2%), G163R (1.5%). In bold are major DRMs.

HIV subtype distribution in study patients



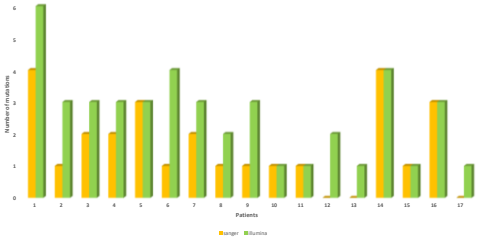
On average, subtype A, 45.7%, subtype D, 25.2%, subtype C, 4.75% and recombinant AD, 7.5%.

HIVdb drug susceptibility for all patient groups

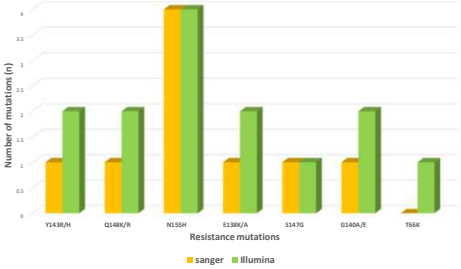


A susceptible genotype is shown in green, intermediate and high level resistance is shown in yellow and red respectively.
Resistance to at least one ART, 97.8%, 81.9% and 56.6% in FF, SF and RF. Any NNRTI resistance, 38.5%, 96.4%, 75.5%, and 53.8% in N, FF, SF, and RF. Any PI resistance, 30.8% and 23% in second line and RAL failures respectively. Any INSTIs resistant mutation in 38.2% RF.

INSTIs DRMs detected by Population and Illumina in RAL failures

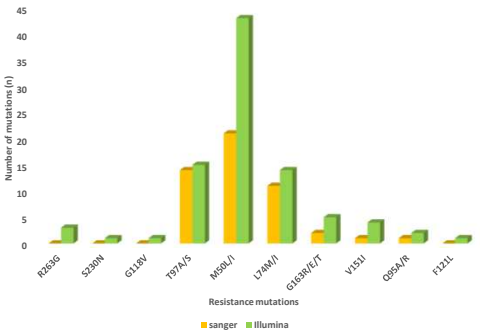


INSTIs major DRMs detected by Sanger and Illumina



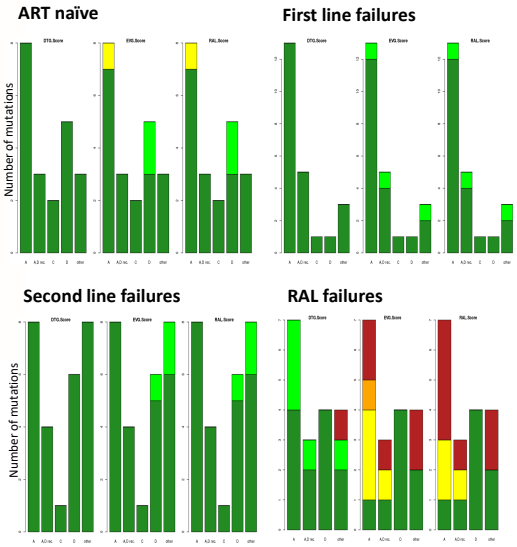
Y143R/H, Q148K/R, G140A/E, E138A/K, 1.47%, 2.94%; N155H, 5.88%, 5.88%; S147G, 1.47%, 1.47%; T66K, 0.0%, 1.47%; Sanger and Illumina respectively.

Comparison of INSTIs accessory DRMs detected by Sanger and Illumina



R263G, 0.0%, 4.4%, S230N, 0.0%, 1.47%, G118V, 0.0%, 1.47%, T97A/S, 20.5%, 22.0%, M50I/L, 30.8%, 63.2%, L74M/I, 16.17%, 20.5%, G163R/E/T, 2.94%, 7.35%, V151I, 1.47%, 5.88%, Q95A/R, 1.47%, 3.0%, F121L, 0.0%, 1.47% by sanger and Illumina respectively.

Genotypic resistance interpretation and scueal HIV subtype classifications using deep sequencing data



A='A', A1='A', A2='A', A3='A', 'A,A1 recombinant'='A', 'A1,A2 recombinant'='A', D='D', 'A,D recombinant'='A,D rec.', 'A3,D recombinant'='A,D rec.', 'A1,D recombinant'='A,D rec.', 'A2,D recombinant'='A,D rec.', C='C'
Dark green =susceptible [0-10); light green = potential low-level resistance [10,15); yellow = low-level resistance [15,30); orange = intermediate resistance [30,60); red = high-level resistance [60, inf).

Conclusion

- No primary DTG DRMs were found in 366 INSTIs naïve patients, and only one patient was found to have DTG resistance genotype in RAL failures.
- The very high NNRTIs resistance across all patient groups call for introduction of DTG or Bictegravir in treatment naïve patients in Uganda.
- DTG predicted to be effective in patients failing RAL-based salvage therapy in absence of Q148K combined with other mutations

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