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# 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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# 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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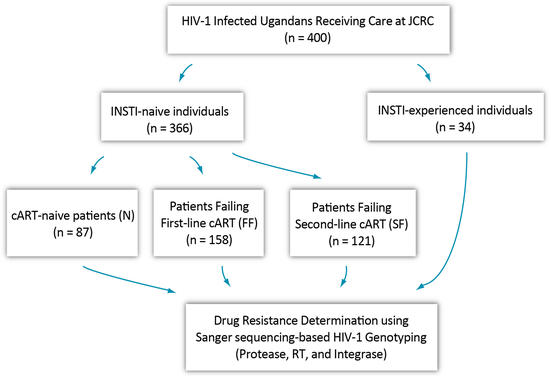
## Introduction

- 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



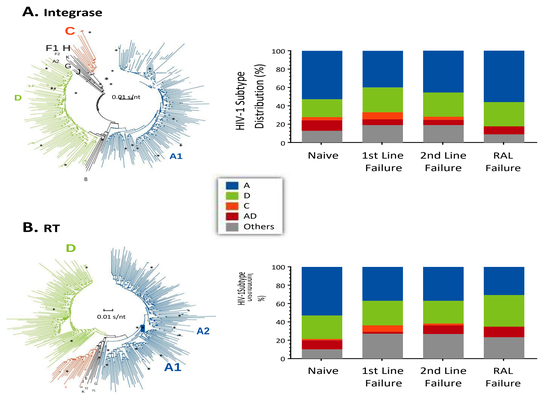

## Results

### Clinical and virological characteristics of the patients

| Group of patients [a] | cART regimen (No. patients)[b] | Mean 1 RNA log10 c/ml [c] | HIV-1 Subtype No. (%) A | D | C | A/D | Other [d] |
|---|---|---|---|---|---|---|---|
| cART naive (n = 87) | None | 4.64 | 42(47.1) | 17(19.5) | 3(3.4) | 9(10.3) | 17(19.5) |
| Failing First-line cART (n = 158) | AZT, 3TC, NVP (38) | 0.54 | 14(36.9) | 11(28.9) | 4(10.5) | 2(5.3) | 7(18.4) |
| | TDF, 3TC, EFV (34) | 1.21 | 14(41.2) | 10(29.4) | 2(5.9) | 1(2.9) | 7(20.6) |
| | AZT, 3TC, EFV (18) | 1.31 | 18(44.4) | 6(33.3) | 1(5.6) | 1(5.6) | 2(11.1) |
| | TDF, 3TC, FTC (15) | 0.43 | 1(20) | 1(20) | 1(20) | 0(0.0) | 2(40) |
| | Other (14) | 7.5 | 5(35.7) | 5(35.7) | 2(14.3) | 2(14.3) | 0(0.0) |
| | 3TC, D4T, NVP (13) | 2.2 | 8(61.5) | 1(7.7) | 0(0.0) | 1(7.7) | 3(23.1) |
| | ABC, 3TC, NVP (10) | 2.56 | 4(40) | 1(10) | 1(10) | 1(10) | 3(30) |
| | ABC, 3TC, EFV (7) | 0.64 | 7(100) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| | TDF, 3TC, NVP (6) | 0.97 | 0(0.0) | 3(50) | 0(0.0) | 1(16.7) | 2(33.3) |
| | 3TC, AZT, NVP (4) | 2.22 | 0(0.0) | 1(25) | 1(25) | 1(25) | 1(25) |
| | d4T, 3TC, NVP (3) | 0.97 | 0(0.0) | 3(100) | 0(0.0) | 0(0.0) | 0(0.0) |
| | AZT, 3TC, ABC (2) | ND | 0(0.0) | 1(50) | 0(0.0) | 0(0.0) | 1(50) |
| | FTC, TDF, EFV (2) | 0.7 | 1(50) | 0(0.0) | 0(0.0) | 0(0.0) | 1(50) |
| | TDF, ABC, AZT (n = 2) | ND | 1(50) | 0(0.0) | 0(0.0) | 0(0.0) | 1(50) |
| Failing Second-line cART (n = 121) | TDF, 3TC, LPVr (30) | 1.22 | 13(43.3) | 4(13.3) | 2(6.7) | 2(6.7) | 9(30) |
| | TDF, 3TC, ATVr (30) | 2.2 | 14(46.7) | 7(23.3) | 1(3.3) | 2(6.7) | 6(20) |
| | ABC, 3TC, LPVr (25) | 2.13 | 12(48) | 8(32) | 1(4) | 0(0.0) | 4(16) |
| | ABC, 3TC, ATVr (25) | 3.64 | 3(60) | 0(0.0) | 0(0.0) | 0(0.0) | 2(40) |
| | AZT, 3TC, LPVr (13) | 7.82 | 4(30.7) | 3(23.1) | 0(0.0) | 3(23.1) | 3(23.1) |
| | LPVr (7) | 0.05 | 3(42.9) | 4(57.1) | 0(0.0) | 0(0.0) | 0(0.0) |
| | AZT, 3TC, ATVr (6) | 2.53 | 4(66.7) | 2(33.3) | 0(0.0) | 0(0.0) | 0(0.0) |
| | Other (5) | 0.7 | 1(20) | 1(20) | 0(0.0) | 1(20) | 2(40) |
| Failing RAL-based cART (n =34) | RAL, LPVr (16) | 2.2 | 7(43.75) | 4(25) | 0(0.0) | 3(18.75) | 2(12.5) |
| | Other (6) | 0.3 | 4(66.6) | 1(16.7) | 0(0.0) | 0(0.0) | 1(16.7) |
| | RAL, DRVr (5) | 9.5 | 4(80) | 1(20) | 0(0.0) | 0(0.0) | 0(0.0) |
| | RAL, ATVr (2) | 8.5 | 1(50) | 1(50) | 0(0.0) | 0(0.0) | 0(0.0) |
| | RAL, TDF, 3TC, LPVr (2) | 2.7 | 2(100) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| | TDF, 3TC, RAL, DRVr (2) | 0.03 | 1(50) | 1(50) | 0(0.0) | 0(0.0) | 0(0.0) |
| | RAL, ETR, DRVr (2) | 1.1 | 2(100) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |

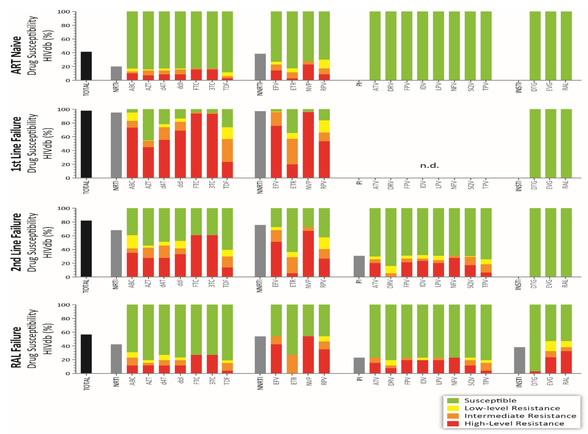
The HIV subtype was predicted using SCUEAL subtype classification algorithm. Viral loads were assayed using Abbott m2000sp/rt or Roche COBAS Amplicor Monitor ultrasensitive tests, v1.5.

### 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



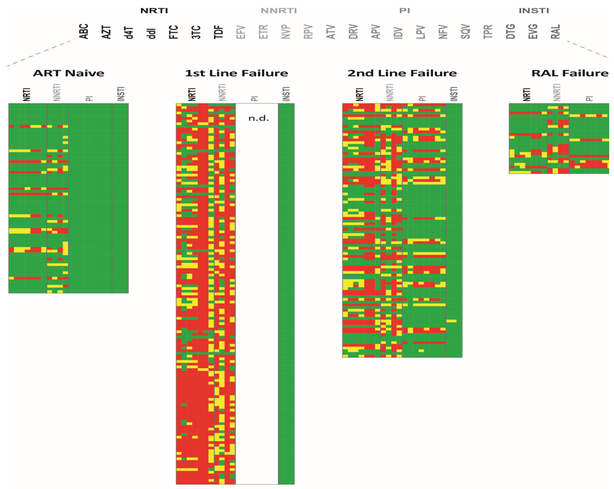

- Resistance to at least one ART, 97.8%, 81.9% and 56.6% in FF, SF and RF. Any NNRTI resistance, 38.5%, 96.4%, 75.5%, and 53.8% in N, FF, SF, and RF. Any PI resistance, 30.8% and 23% in second line and RAL failures respectively. Any INSTIs resistant mutation in 38.2% RF.

### 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 integrase major resistance mutations.

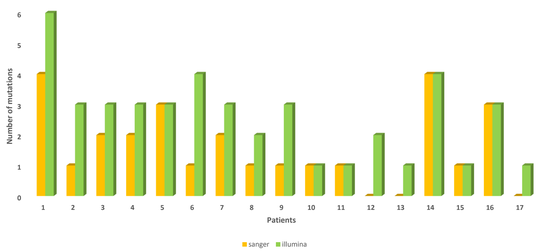
### HIV-1 genotypic resistance interpretation based on Sanger sequencing



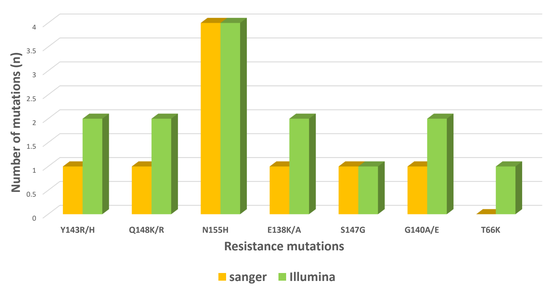

HIVdb program Genotypic resistance interpretation algorithm from Stanford university HIV drug resistance database was used to predict the levels of susceptibility. A susceptible genotype is shown in green, intermediate and high level resistance is shown in yellow and red respectively.

### INSTIs DRMs detected by Population and Illumina in RAL failures

| Illumina | Sanger |
|---|---|
| S147G, G140A, E138K, Q148K, S230N, M50L | S147G, G140A, E138K, Q148K |
| N155H, Y143H, M50I | N155H |
| Y143R, T97A, G163R | Y143R, T97A, |
| T97A, L74M, M50I | T97A, L74LM |
| T97A, N155H, L74I | T97A, N155H, L74I |
| T97A, L74M, V151I, G163R | T97A |
| T97A, M50I, N155H | T97AT, N155H |
| N155H, V151I | N155H |
| E157K, R263G, M50I | M50I |
| M50L | M50L |
| M50L | M50L |
| G118V, M50I | NONE |
| T66K | NONE |
| T97A, L74M, V151I, G163R | G163R, T97A, L74LM, V151I |
| M50L | M50L |
| M50L, L74M, T97A, V151I, G163R | L74M, T97A, V151I, G163R |
| M50I | NONE |

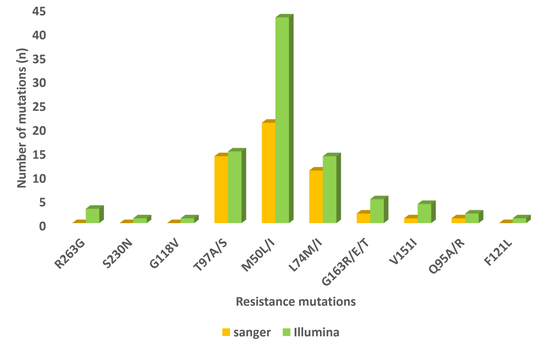



### Comparison of INSTIs major DRMs detected by Sanger and Illumina



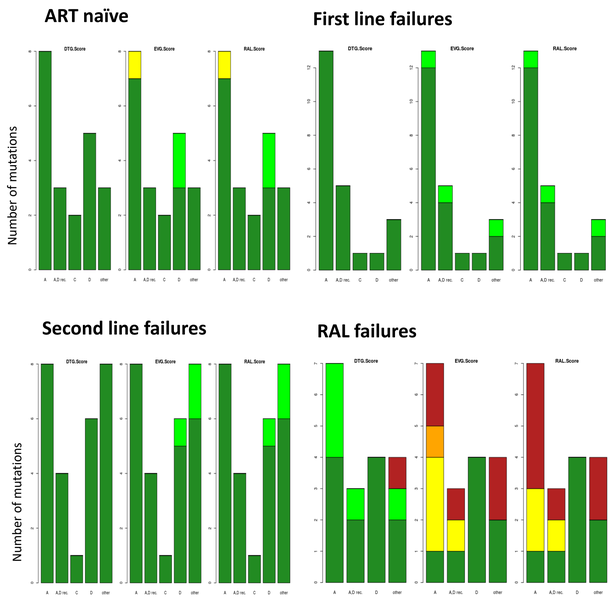

Y143R/H, Q148K/R, G140A/E, 1.47%, 3.0%, S147G, 1.47%, 1.47% , T66K, 0.0%, 1.47% Sanger and Illumina respectively.

### 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 from 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

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