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HIV Drug resistance associated with second line antiretroviral regimens failure and virological outcomes of third line regimens in Arua Regional Referral Hospital, Uganda

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Background and objectives

- The number of patients on 2nd line antiretroviral therapy is growing, but data on HIV drug resistance patterns associated to 2nd-line failure in resource constrained settings are scarce. Access to drug resistance test (DRT) and to third-line drugs is an issue in many countries.
- We aimed to i) describe HIV drug resistance patterns, ii) investigate the factors associated with extensive resistance to nucleoside reverse transcriptase inhibitors (NRTI), iii) describe the virological outcomes of 3rd line regimens, in patients failing 2nd line in HIV clinic at Arua Regional Hospital, Uganda.

Methods

Study setting:

HIV outpatient clinic in the Regional Hospital of Arua, northern Uganda, supported by MSF for access to:

- viral load monitoring, using HIV point-of-care viral load (POC VL) test SAMBA-I, which detects specimen as “detectable” or “undetectable” around the cut-off of 1000 copies/mL
- genotypic drug resistance test (DRT)
- third-line ART

Clinical procedure:

- Patient diagnosed with 2nd-line failure (2 consecutive detectable viral loads 6 months apart despite enhanced adherence counselling) receive a DRT performed at the Uganda Virus Research Institute (UVRI) in Entebbe
- Regimen is adapted according to DRT result and definition of 3rd-line is: one integrase inhibitor combined with one PI boosted with ritonavir, +/- etravirine and NRTI’s.

Study design:

Retrospective analysis of virological and clinical parameters of patients on second-line ART who were diagnosed with virological failure and received a DRT between September 2014 and March 2017.

Genotypic sensitivity score (GSS):

- GSS to HIV drugs was calculated by assigning a value to each ARV of interest, based on the 5 resistance levels: susceptible (=1), potential low-level resistance (=0,75), low-level resistance (=0,5), intermediate-level resistance (=0,25), high-level resistance (=0)
- The NRTI GSS was a combined score for 3TC, ABC, DDI, D4T, TDF and AZT; maximum possible score was 6 and extensive resistance to NRTI was defined as NRTI GSS ≤1

Statistical analysis:

- Logistic regression was used to investigate factors associated with extensive resistance to NRTI (NRTI GSS ≤1).
- Analysis were done using R software

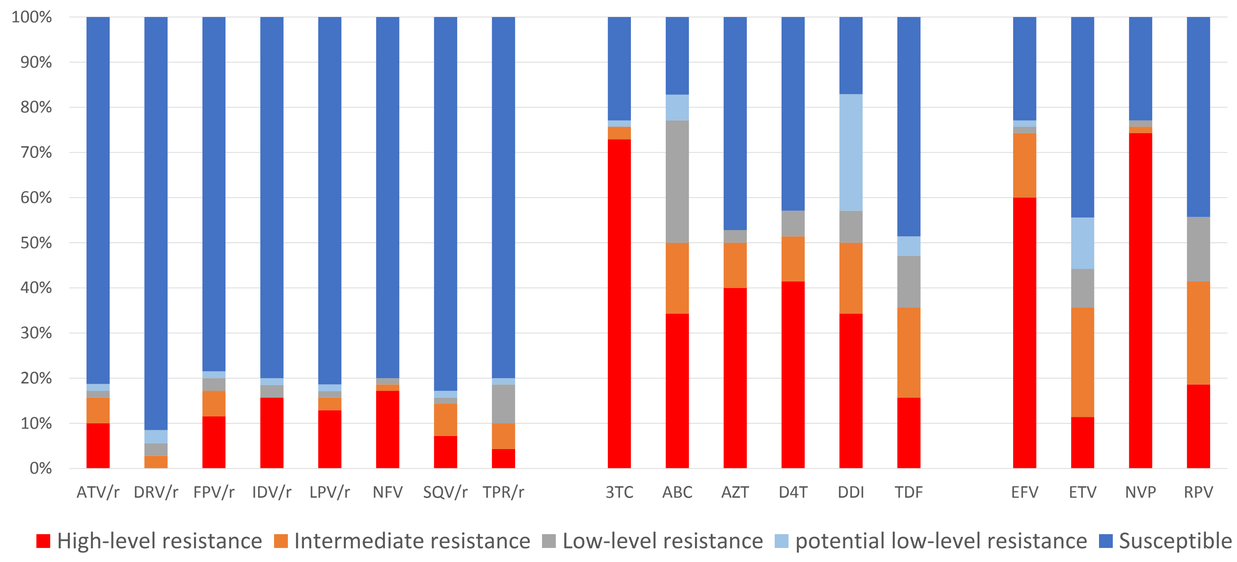
Results

Table 1: Demographic and clinical characteristics of patients at second line failure (N=78)

Characteristic	n (%)
Age (years, median [IQR])	31,5 [15-47,2]
Gender female	33 (42,3)
Country of residence	
Democratic Republic of Congo	11 (14,4)
Uganda	65 (85,6)
WHO clinical stage (n=73)	
1	54 (74,0)
2	14 (19,1)
3	5 (6,8)
Time on ART (years)	8,1 [6,8-10]
Time on second line ART (months)	29 [17,7-52,9]
Second-line regimen (n=76)	
TDF+3TC+LPV/r	30 (39,4)
ABC+3TC+LPV/r	20 (26,3)
TDF+3TC+ATV/r	14 (18,4)
AZT+3TC+LPV/r	7 (9,2)
other	5 (6,5)
CD4 count /mm^3 (n=43,median [QR])	271 [113-523]

- 78 participants included, sex ratio 1,3
- Most frequent NRTI combination were TDF+3TC (58%) and ABC+3TC (29%)
- Most frequent PI were lopinavir/r (79%) and atazanavir/r (21%)

Graph 1: Level of resistance according to HIV drug at second line failure (N=70)



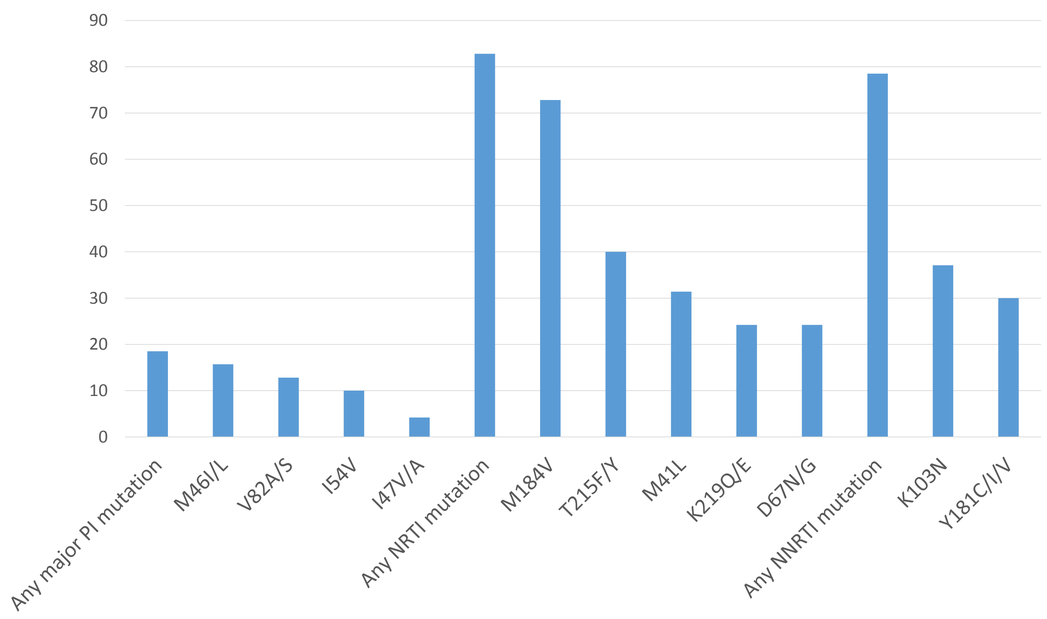
N=70 genotyping reactions were available (8 amplifications failed):

- Most frequent HIV subtype were A (47%), D (40%) and recombinants (11%)
- 13 (18,5%) had a decreased susceptibility to LPV/r and ATV/r (any level of resistance), associated with extensive resistance to NRTI in all cases but one
- (38,5%) had extensive NRTI resistance (NRTI GSS ≤1)

Factor associated with extensive resistance to NRTI:

- a nadir CD4 count<100/mm^3 was significantly associated with NRTI GSS<1 after adjustment on age and time on second line (OR=3,97, 95%CI [1,2-14,6]).

Graph 2: Frequency of main HIV resistance mutations at second-line failure (%, N= 70)



- 18,5% had at least one major PI mutation
- 82,8% had at least one NRTI mutation and median number of mutation was 2 IQR [1-5]. TAMs* were present in 52,8% and K65R in only one case.

* Thymidine analogue mutations

Table 2: Drug resistance test-informed regimen (n=70)

	n (%)
First line	3 (4,2)
Second line	37 (52,8)
Continued same regimen	7 (10,0)
Simplified second line	28 (40)
Darunavir/r + 2 NRTI	2 (2,8)
Third line	30 (42,8)
Darunavir/r + integrase inhibitor + etravirine +/- NRTI	7 (10)
Darunavir/r + integrase inhibitor +/- NRTI	11 (15,7)
Atazanavir/r + integrase inhibitor +/- NRTI	12 (17,1)

- After DRT result, 52,8 % of patients were maintained on 2nd-line, which could be frequently simplified, mostly by replacing lopinavir/r with atazanavir/r
- 42,8% were switched to 3rd-line (38,4% of all patients included), with ATV/r as PI in 40%
- Among the 30 patients switched to third line,
  - 10 had a follow-up viral load test at around 6 months : 80% were undetectable
  - 7 had a follow-up viral load at around 12 months: 85% were undetectable

Summary & Discussion

- This study highlights the critical need of DRT access in order to differentiate failure potentially due to HIV drug resistance from failure due to poor adherence, and therefore to avoid unnecessary switch to third-line.
- In another hand, extensive resistance to NRTI was found in 38,5% of cases of second line failure and access to third line drugs (darunavir/r and mostly integrase inhibitor) is also crucial.
- Low nadir CD4 count (≤ 100/mm3) was associated in our study with extensive resistance to NRTI and might be an indicator of 3rd line requirement at second line failure.
- This study provides data on drug resistance and associated mutations at second line failure in infection with uncommon subtypes; A and D represent less than 15% of worldwide HIV subtypes.
- Our data also report on “real-life” use of routine POC VL and DRT, which are not commonly available in many resources-constrained countries, for the management of second-line failure
- The retrospective design is the main limit of our study, which did not allow adherence assessment

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