Monitoring trends of HIV-1 drug resistance in KwaZulu-Natal amid dolutegravir rollout in South Africa

As part of a CAPRISA EDCTP-funded career development fellowship project, we describe preliminary study findings on HIV-1 drug resistance (HIVDR) amid dolutegravir (DTG) rollout in KwaZulu-Natal (KZN) province, South Africa. The main objectives of our study were:

1. To develop a database for monitoring HIVDR using routine HIV genotypic testing data of ART-experienced patients with virological failure (i.e., VLs ≥1,000 copies/mL) receiving HIV-care at public-sector facilities in KZN
2. To determine HIVDR hotspots and populations requiring priority interventions in HIV treatment care

We developed an HIV drug resistance database and conducted analysis of routine HIVDR genotypic results obtained from specimens collected in public-sector healthcare facilities across 11 districts in KZN. We obtained and curated 2148 de-identified HIVDR genotypic results with linked data (collection date, age, sex, healthcare facility) processed at the National Health Laboratory Service (NHLS) Department of Virology, UKZN, Inkosi Albert Luthuli Central Hospital, for the period January 2018 to August 2020. Permission to access de-identified data was granted by the National Health Laboratory Service (NHLS) Central Data Warehouse (CDW).

HIV drug resistance was defined as the presence of any mutation to the protease inhibitor (PI), nucleoside reverse-transcriptase inhibitor (NRTI), non-nucleoside reverse-transcriptase inhibitor (NNRTI), or integrase strand transfer inhibitor (INSTI) antiretroviral drug classes. We developed the HIVDR database further by incorporating geospatial data linked to locations of healthcare facilities requesting genotypic testing. Using the HIVDR database, we created a dashboard for data visualization, with interactive heat maps to assess hotspots of HIVDR across the 11 districts in KZN.

Of 2148 patient genotypes obtained from 151 KZN facilities, 1846 (85.9%) had ≥1 HIVDR mutation, with only 5 (0.2%) having INSTI-associated resistance. Genotypes with drug resistance (n=1846) were categorized according to age and sex (Table 1). The proportion of HIVDR mutations was significantly higher among adult females aged ≥20 years, p=0.04.

Table 1 Proportion of patient genotypes included in final analysis

Variable	Number of genotypes			% Resistance
	2018 (n=800)	2019 (n=853)	2020 (n=495)	
Sex[a]				
Female	467 (58%)	493 (58%)	312 (63%)	50% (1076/2148)
Male	324 (41%)	350 (41%)	178 (36%)	35% (747/2148)
Age[b]**, *median age in years (range)***	34 (0-73)	35 (0-70)	33 (0-70)	-
0-9 years, *median (IQR)*	5 (3-7)	4 (2-7)	5 (2-7)	6% (126/2148)
10-19 years, *median (IQR)*	16 (13-17)	15 (13-17)	15 (13-17)	18% (379/2148)
>19 years, *median (IQR)*	40 (33-46)	40 (34-46)	39 (31-45)	62% (1339/2148)
Drug regimen backbone[c, d]				
PI-based ART	756 (95%)	808 (95%)	456 (92%)	81% (1735/2148)
NNRTI-based ART	16 (2%)	18 (2%)	8 (2%)	2% (37/2148)
INSTI-based ART	4 (1%)	4 (1%)	5 (1%)	1% (12/2148)
Degree of urbanization[e]				
Urban districts (Number of requesting facilities, n=32)				
Amajuba (3)	40 (5%)	27 (3%)	15 (3%)	76% (62/82)
King Cetshwayo (19)	39 (5%)	79 (9%)	58 (12%)	88% (154/176)
Ugu (10)	66 (8%)	58 (7%)	73 (15%)	87% (172/197)
Peri-urban districts (Number of requesting facilities, n=78)				
eThekwini (66)	384 (48%)	395 (46%)	178 (36%)	85% (813/957)
iLembe (1)	43 (5%)	33 (4%)	14 (3%)	84% (76/90)
uMgungundlovu (8)	101 (13%)	85 (10%)	32 (7%)	84% (184/218)
uThukela (3)	31 (4%)	50 (6%)	41 (8%)	88% (107/122)
Rural districts (Number of requesting facilities, n=41)				
Harry Gwala (13)	6 (1%)	23 (3%)	16 (3%)	80% (36/45)
uMkhanyakude (16)	54 (7%)	53 (6%)	27 (6%)	96% (129/134)
uMzinyathi (5)	24 (3%)	18 (2%)	28 (6%)	89% (62/70)
Zululand (7)	12 (2%)	32 (4%)	13 (3%)	90% (51/57)

ART, antiretroviral treatment; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor

[a] 24 genotypes had missing sex data, of which 23 had resistance and 1 did not have resistance

[b] 3 genotypes had missing age data, of which 2 had resistance and 1 did not have resistance

[c] 65 genotypes had missing drug regimen data

[d] 8 genotypes had patients on nucleoside reverse-transcriptase inhibitors only

[e] https://doi.org/10.1186/s12913-022-07707-x Khumalo et al. BMC HSR (2022) 22:326

Approximately six in every seven genotypes had HIVDR mutations with minimal DTG-associated resistance, supporting use of DTG-based ART. The most common NNRTI mutation was K103N observed in 45% (838/1846) of genotypes with HIVDR, despite most patients (94%) being on PI-based ART. The most common major PI mutation was V82A observed in 27% (495/1846), and K65R NRTI mutation was observed in 5% (99/1846) of genotypes with HIVDR. Figure 1 summarizes the proportion of genotypes with HIVDR by drug class and year.

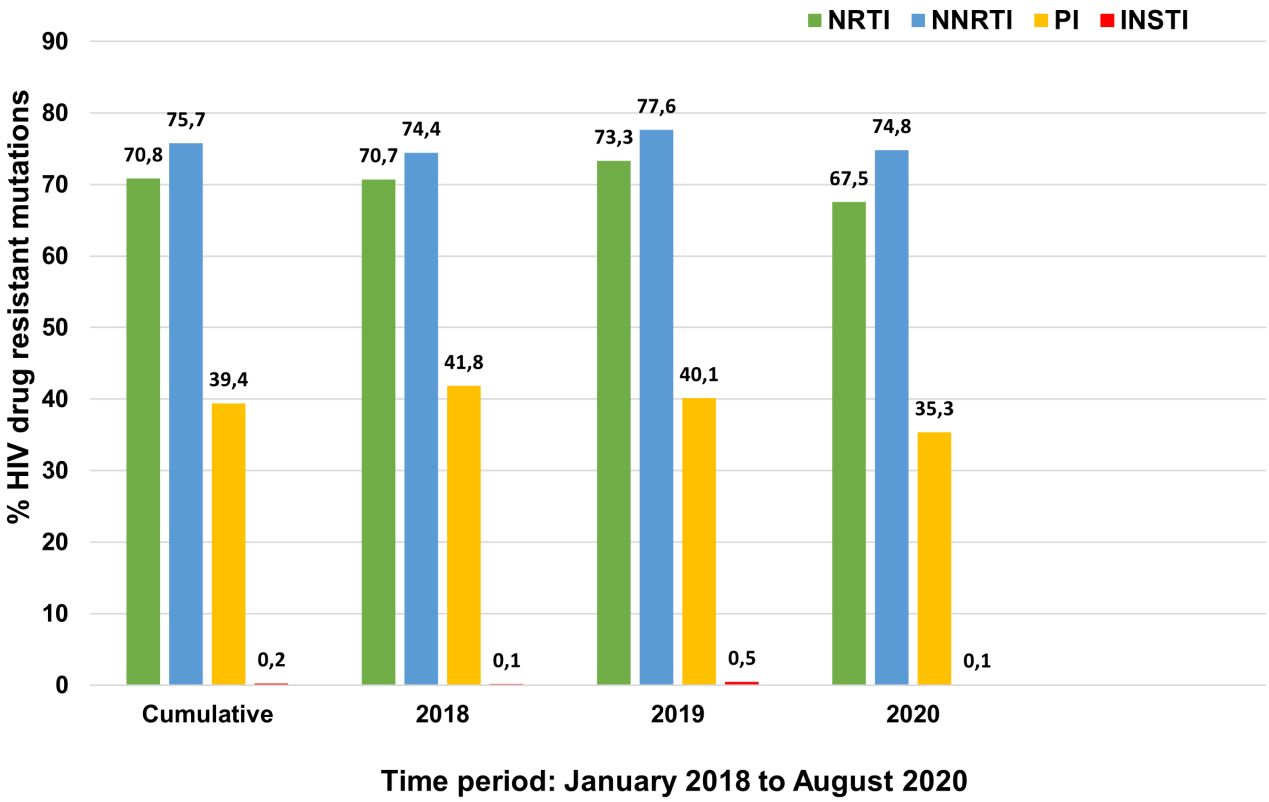

Figure 1 Genotypes with HIV drug resistance according to drug class and year

The largest proportion of genotype requests with HIVDR were from densely populated urban and peri-urban districts as shown in Figure 2. However, despite the lower number of genotype requests from rural district facilities, there were higher levels of HIVDR detected (Table 1). This highlights the need to strengthen HIV treatment monitoring and timely switching of suboptimal regimens in rural districts. Findings from the ADReSS study comparing HIV treatment outcomes between peri-urban and rural clinics in KZN, indicated that virological failure and drug resistance did not differ between sites, however viral suppression was noted earlier in peri-urban sites, which likely reflected greater attention to monitoring patients on ART [Brijkumar J. et al., HIV Medicine, 2022].

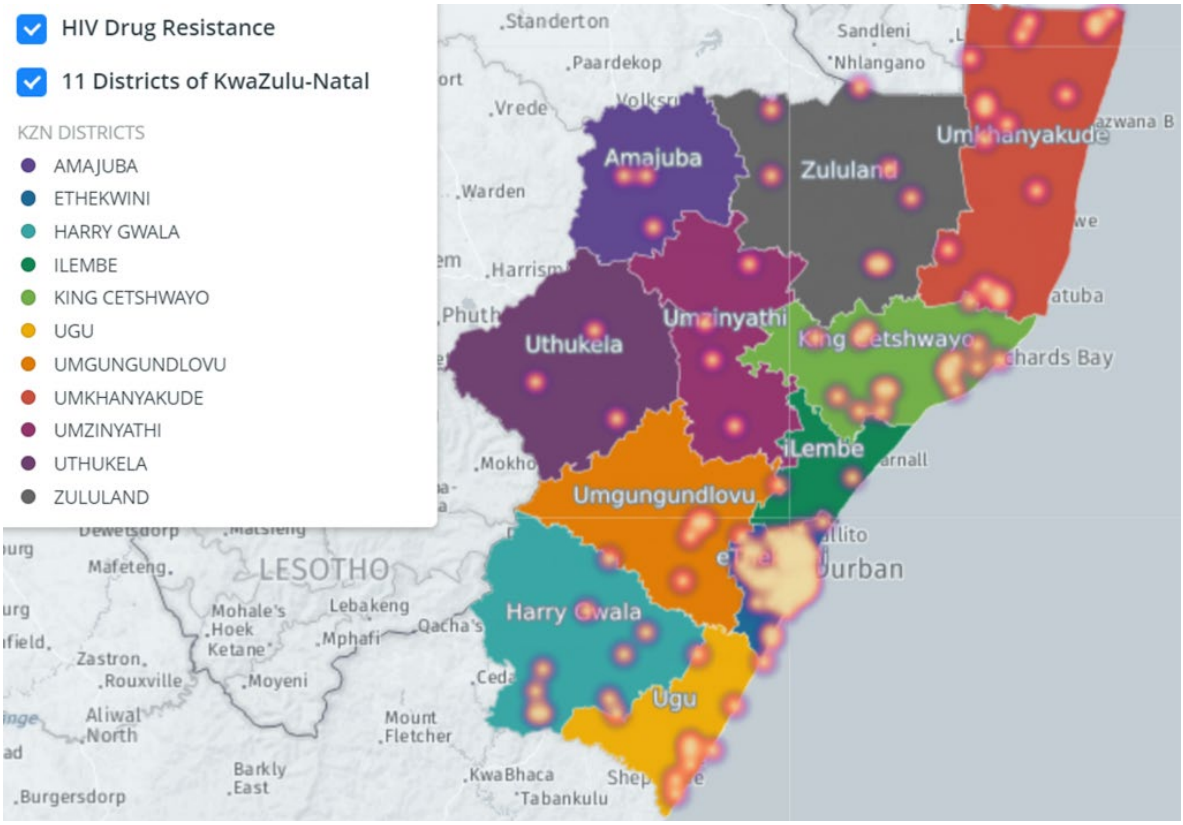

Figure 2 Heatmap of genotypes with HIV drug resistance across KwaZulu-Natal

In summary, using our database, we were able to identify facilities with high proportions of HIVDR, which is relevant to clinicians and policymakers. By incorporating geospatial analyses into our dashboard, we identified proportions of HIVDR in urban, peri-urban and rural districts. Moreover, we observed higher proportions of HIVDR among adult women, highlighting individuals needing priority HIV care. Ultimately, as DTG-use becomes more common, a trend towards decreased HIVDR prevalence is expected. However, near-real time HIVDR monitoring is required for optimization of HIV-1 treatment at public-health level, and for sustainable DTG use in first-line and subsequent ART regimens.

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