Retrospective study of the prevalence of acquired drug resistance after failed antiretroviral therapy in Libya

Nader Shalaka[1]

[1]Department of Infectious Diseases, Tripoli University Hospital, University Road, Ain Zara, Tripoli, Libya (Correspondence to Nader Shalaka: nadershalaka@yahoo.com; n.shalaka@uot.edu.ly).

Abstract

Background: The increasing rate of drug-resistant HIV mutations in Libya and other African countries threatens the efficacy of antiretroviral therapy (ART), thus necessitating urgent regional strategies to combat resistance and improve treatment outcomes.

Aim: To characterize the frequency and pattern of acquired HIV drug resistance mutations in patients showing ART failure while using non-nucleoside reverse transcriptase inhibitors (NNRTI) prescribed by the Department of Infectious Diseases at Tripoli University Hospital, Libya.

Methods: We collated retrospective data on 128 people living with HIV, aged 18 years or above, who experienced first-line treatment failure at Tripoli University Hospital, Libya, from 2014 to 2017. We analysed the extant HIV amino acid sequences to identify resistance mutations using algorithms from the Stanford University HIV drug resistance database.

Findings: All included cases had at least one resistance mutation (n = 128; 100%) and 119 (93%) had both nucleoside reverse transcriptase inhibitors (NRTI) and NNRTI mutations. M184V/I was the most common NRTI mutation (n = 119; 93%) while K103N was the most common NNRTI mutation (n = 100; 78%). Thymidine analog mutations were detected in 51 cases (40%); featuring T215Y, D67N and M41L. Predicted full susceptibility was highest for Tenofovir (66.4%), followed by Etravirine (60%).

Conclusion: We detected high level drug resistance and associated mutations among people living with HIV. Implementing drug regimens with high genetic barriers to resistance, coupled with rigorous monitoring and surveillance of HIV resistance development, could help mitigate such resistance in the future.

Keywords: HIV/AIDS, anti-retroviral therapy, treatment failure, drug resistance, Libya

Citation: Shalaka N. Retrospective study of the prevalence of acquired drug resistance after failed antiretroviral therapy in Libya. East Mediterr Health J. 2024;30(7):470–480. https://doi.org/10.26719/2024.30.7.470.

Received: 23/10/2023; Accepted: 23/05/2024

Background

By the end of 2022, approximately 39 million people globally were living with HIV, with 29.8 million receiving antiretroviral therapy (ART) (*1*). This represents a significant increase from the 7.7 million accessing treatment in 2010; however, the long-term success of ART is increasingly threatened by the emergence of drug-resistant mutations, potentially leading to treatment failure (*2*).

In developing countries, lack of laboratory monitoring, including quantification of HIV viral load, delays recognition of ART failure with the consequence of large accumulations of resistance mutations, limiting options for second-line treatment and increasing the rates of morbidity and mortality (*3,4*). National shortages of ARTs further complicate (*5*) and limit access to first-line ARTs with high genetic barrier to resistance, resulting in delayed treatment success (*6*).

In Libya, the national HIV programme, established in the late 1990s, recommended a first-line ART regimen comprising a non-nucleoside reverse transcriptase inhibitor (NNRTI) (Efavirenz or Nevirapine) combined with a nucleoside reverse transcriptase inhibitor (NRTI) backbone of Lamivudine and Zidovudine or Abacavir. Despite more than 20 years of national data on the types of HIV services provided in Libya, there are virtually no data on resistance mutations of HIV isolates from patients who failed a first-line ART (*7*). Also, little is known about circulating HIV genotypes among people living with HIV in Libya.

Given the current political instability and healthcare infrastructure limitations in Libya, conducting prospective research on HIV drug resistance presents significant challenges. In this context, retrospective analysis of electronically stored data offers valuable insights into the characteristics and extent of drug resistance among people living with HIV in Libya. Studying local data on HIV drug resistance prevalence and specific mutations in Libya can inform the development of national, evidence-based treatment guidelines tailored to the Libyan context. This could improve patient outcomes and maximize the effectiveness of available medications. Understanding HIV drug resistance in Libya can contribute to broader public health initiatives in the Middle East and North Africa, allowing for more effective regional responses to

the HIV epidemic and the potential cross-border spread of resistant strains.

This study aimed to describe the pattern of acquired HIV drug resistance mutations found in patients exhibiting treatment failure while on NNRTI-based therapies from 2014 through 2017. It describes the potential effects of drug resistant mutation on second-line antiretroviral therapy

Methods

Study design and population

This study was designed as a retrospective, descriptive analysis of electronically stored patient data on HIV drug resistance for persons living with HIV after documented failure of NNRTI-based ART, who were treated at the hospital from January 2014 to December 2017.

Tripoli University Hospital is a tertiary referral hospital that provides specialist medical services to patients from Tripoli and other cities in the western and central regions of Libya. The Department of Infectious Diseases provides specialist HIV management as an ambulatory care as well as a 14-bed capacity ward dedicated to the management of inpatients with HIV/AIDS.

We collated data on HIV-positive adults who attended HIV care at our department and experienced first-line ART failure between 2014 and 2017, ensuring the data remained anonymous and retrospective to protect participant confidentiality and comply with ethical standards.

Case data was selected from the electronic record database using the following inclusion criteria: (i) 18 years or older at the time of ART failure; (ii) virological failure, which was defined as a viral load of more than 1000 copies per millilitre on 2 consecutive measurements (*8*); and (iii) patient was regularly on NNRTI-based ART for at least 6 months prior to HIV resistance testing. We excluded patient data for: (i) patients receiving protease inhibitors as antiretroviral therapy; (ii) irregular use of antiretroviral therapy; and (iii) patients with HIV viral loads of less than 1000 copies per millilitre.

Data collation and preparation for analysis

We collated anonymous study data from electronic patient files using a standard data collection form. For patients diagnosed with first-line ART failure between 2014 and 2017, we anonymously collected variables such as age, gender, and HIV risk factors. We gathered data on ART regimen, duration on ART, HIV viral load, CD4 counts at the time of ART failure, and targeted HIV amino acid sequences and drug resistance mutations for each case.

Immunologically advanced HIV infection was defined as CD4 counts of less than 200 cells per microliter (*8*). Analysis of HIV sequences to identify drug resistance mutations and determine HIV subtypes was performed using algorithms from the Stanford University HIV Drug Resistance Database (v8; https://hivdb.stanford.edu/).

Ethics

The study was approved by the ethics review board of Tripoli University Hospital (Approval no. IDD-2018-07). The review board waived written informed consent because the study involved collecting anonymous retrospective data, ensuring no direct harm to participants and no public availability of individually identifiable information.

Data analysis

We performed all statistical analysis using R version 4.0.2 (*9*). We chose to use median and interquartile range (IQR) to summarize our quantitative variables and used the Mann–Whitney U-test for bivariate analysis. We represented categorical variables (grouped quantitative and qualitative variables) using frequency tables and percentages of the total. For these variables, we used either Chi-squared or Fisher's exact tests for low sample sizes (Tables 1,2,3). All analyses were 2-sided and *P*-values of < 0.05 were considered statistically significant.

Results

Patient characteristics

Table 1 summarizes the demographics and basic disease data. A total of 128 cases were included in this study (men=87; 68%). The median age at the time of HIV diagnosis was 33 years with a median of 30.6 months of ART use before treatment failure. Compared to men, women tended to be younger at the time of HIV diagnosis (29.3 vs. 33.2; *P*= 0.02).

HIV and ART characteristics

All sequenced HIV isolates were group M and circulating recombinant form 02 subtype (CRF02). At the time of ART failure, 109 (85%) of cases were on an Efavirenz-based regimen and 71 (55.5%) had Zidovudine as the NRTI backbone. Seventy-four (57.8%) cases had advanced HIV with CD4 counts of less than 200 (median=136; IQR=39-280), and 100 (78%) had HIV viral loads of more than 10 000 copies per ml.

Prevalence and pattern of HIV drug resistance mutations

All study participants (n=128; 100%) had at least one resistance mutation, with a median of 5 drug resistant mutations per case. One hundred and twenty-seven (99%) had at least one NNRTI resistance mutation while 119 (93%) had both NRTI and NNRTI resistance mutations, with a median of 2 NRTI and 2 NNRTI mutations per case. M184V/I was the most frequently detected NRTI mutation (n=119; 93%) followed by T215Y/F/S (n=40; 31.3%) and L74V/I (n=30; 23.4%), while only one case had a Q151M mutation. The most frequently detected NNRTI mutations were K103N (n= 100; 78%), G190A (n=17; 13.3%), Y181C (n=15; 11.7%), K101E (n=14; 11%), and V108I (n=32; 25%). Thymidine analog mutations (TAMs) were detected in 51 cases (40%). The most frequently detected TAMs

Table 1. Demography, HIV history and antiretroviral therapy data from 128 confirmed cases at Tripoli University Hospital, Libya, 2014–2017

Characteristics	Male	Female	Total	*P*
Currently pregnant	87 (68)	41 (32)	128 (100)	NA
Not currently pregnant	33.2 (28.5–39)	29.3 (25–35)	32.7 (27.3–37)	0.02
Age range at time of HIV diagnosis (n; %)[b]				0.3
15-30	30 (34.5)	21 (51.2)	51 (39.8)	
30-45	54 (62.1)	20 (48.8)	74 (57.8)	
>45	3 (3.4)	0 (0)	3 (2.4)	
Median duration since confirmatory diagnosis (years; IQR)[a]	7.9 (5.2–10.6)	6.3 (4.2–8.3)	7.7 (4.8–9.8)	0.05
Duration on ART (months; IQR)[a]	36 (11.4–70.8)	16.8 (6–61.2)	30.6 (9.6–69.6)	0.08
Route of HIV acquisition (n;%)[b]				0.001
Heterosexual	10 (11.5)	27 (65.9)	37 (28.9)	
People who inject drugs	51 (58.6)	0 (0)	51 (39.8)	
Blood transfusion or contact with infected blood products	4 (4.5)	2 (4.8)	6 (4.7)	
Unknown	22 (25.3)	12 (29.3)	34 (26.6)	
Median CD4 count (n; IQR)[a]	135 (41.5–278.5)	142 (37–318)	136 (39–280)	0.9
CD4 count (n; %)[b]				0.8
<50	23 (26.4)	12 (29.3)	35 (27.3)	
50-200	26 (29.9)	13 (31.7)	39 (30.5)	
200-350	16 (18.4)	4 (9.8)	20 (15.6)	
>350	15 (17.2)	8 (19.5)	23 (18)	
Missing	7 (8)	4 (9.8)	11 (8.6)	
HIV viral load (n; %)[b]				0.8
<10 000	20 (23)	8 (19.5)	28 (21.9)	
>10 000	67 (77)	33 (80.5)	100 (78.1)	
Median number of drug resistant mutations per case (n; IQR)[a]	6 (3–7)	5 (3–6)	5 (3–7)	0.2
NNRTI regimen, (n; %)[b]				0.5
EFV-based	76 (87.4)	33 (80.5)	109 (85.2)	
NVP-based	11 (12.6)	8 (19.5)	19 (14.8)	
NRTI backbone, (n; %)[b]				0.8
Thymidine analogues (AZT)	47 (54)	24 (58.5)	71 (55.5)	
Others (non-AZT)	40 (46)	17 (41.5)	57 (44.5)	

[a]*Mann–Whitney U-test for continuous variables;* [b]*Chi-square test for categorical variables. IQR: Interquartile range; ART: Antiretroviral therapy; IDU: Injection drug use; DRM: Drug resistance mutations; NNRTI: Non-nucleoside reverse transcriptase inhibitors; EFV: Efavirenz; NVP: Nevirapine; NRTI: Nucleoside reverse transcriptase inhibitors; AZT: Zidovudine.*

were T215Y (n=28; 55%), D67N (n=22; 43%) and M41L (n=20; 39%). Twenty-two cases (43%) had 3 or more TAMs.

Prevalence of drug resistance mutations by drug exposure

Figures 1 and 2 present resistance mutation profiles according to prescribed ART regimen. At the time of treatment failure, cases who were on Zidovudine were more likely to have M41L (χ^2=4.6; p =0.03), D67N (χ^2=8.8; *P* =0.002), T215F/Y (χ^2=21; P <0.005) mutations; and those on Abacavir to have L74V (χ^2=24; *P* <0.005) and Y115F (χ^2=14; *P* <0.005) mutations. There were no statistically significant differences in selected mutations between Efavirenz and Nevirapine.

The potential impact of resistance mutations on predicted drug susceptibility

The predicted susceptibility to all NNRTIs and NRTIs at the time of ART failure is presented in Figure 3. The predicted full NRTI susceptibility was highest for Tenofovir (n=85; 66.4%) and Zidovudine (n=79; 61.7%). Participants who received non-zidovudine-based ART retained better susceptibility to other NRTIs than those failing zidovudine-based ART (n=50; 87.7% vs. n=29; 40.8% retained susceptibility to Zidovudine (*P* <0.001), and n=46; 80.7% vs. n=39; 54.9% retained susceptibility to Tenofovir *P*= 0.004]). The predicted full NNRTI susceptibility was highest for Etravirine (n=77; 60%) and Rilpivirine (n=41; 32%) with no statistically significant

Table 2. Detected NRTI-resistance mutations and their effect on NRTI drug susceptibility in 128 cases, Libya, 2014–2017

Mutations	ABC	AZT	D4T	DDI	FTC	3TC	TDF
M41L	5	15	15	10	0	0	5
M41L + E44D + L210W + T215FSY	5	5	5	5	0	0	5
M41L + D67EN + T215FSY	5	5	5	5	0	0	5
M41L + M184IV + T215FSY	10	0	0	0	0	0	0
M41L + L210W	10	10	10	10	0	0	10
M41L + L210W + T215FSY	10	0	0	0	15	15	10
M41L + T215FSY	10	10	10	10	5	5	10
A62V	5	5	5	5	0	0	5
K65R	45	-10	60	60	30	30	50
K65R + Q151M	10	10	0	0	10	10	10
D67EN	5	15	15	5	0	0	5
D67EN + K70ER + M184IV + K219EQ	10	0	0	0	0	0	0
D67EN + K70ER + K219EQ	10	15	10	10	10	10	10
D67EN + T215FSY + K219EQ	5	5	5	5	0	0	5
K70ER	15	30	15	15	10	10	15
L74IV	30	0	0	60	0	0	5
L74IV + M184IV	15	0	0	0	0	0	0
V75AIM	5	10	30	15	5	5	5
F77L	5	10	10	10	5	5	5
F77L + F116Y + Q151M	15	10	10	10	15	15	15
Y115F	30	0	0	0	0	0	15
Y115F + M184IV	15	0	0	0	0	0	5
F116Y	5	10	10	10	5	5	5
Q151M	60	60	60	60	15	15	15
Q151M + M184IV	10	10	10	0	0	0	15
M184IV	15	-10	-10	10	60	60	-10
L210W	5	15	15	10	0	0	5
L210W + T215FSY	10	10	10	10	0	0	10
T215FSY	10	60	40	15	0	0	10
K219EQ	5	10	10	5	0	0	5
K70ER + M184IV	0	0	10	0	0	0	10
K70ER + T215FSY	0	0	5	5	0	0	0
A62V + K65R	0	0	0	0	0	0	5

Note: These numbers represent the effect or weighting of each mutation or combination of mutations on individual drug susceptibility. Positive numbers mean reduced susceptibility whereas negative numbers mean increased sensitivity. The larger the number, the greater the effect on drug susceptibility when a particular mutation/combination is present.

NRTIs: Nucleoside reverse transcriptase inhibitors; 3TC: Lamivudine; ABC: Abacavir; AZT: Zidovudine; D4T: Stavudine; DDI: Didanosine; FTC: Emtricitabine; TDF: Tenofo-vir.

Table 3. Detected NNRTI-resistance mutations, combinations and their impact on NNRTI drugs susceptibility in 128 cases, Libya, 2014–2017

Mutations	EFV	NVP	ETR	RPV	DOR
A98G	15	30	10	15	15
A98G + Y181C	5	5	5	5	5
A98G + F227L	15	15	15	15	15
L100I	60	60	30	60	15
L100I + K103HNSV	0	0	0	0	15
L100I + K103HNSV + P225H	0	0	0	0	-10
K101EHP	60	60	60	60	15
K101EHP + G190AES	0	0	5	0	5
K103HNSV + Y181C	0	0	0	0	5
K103HNSV + P225H	0	0	0	0	10
V106M	60	60	0	0	30
V108I	10	15	0	0	10
V108I + Y181C	0	0	0	0	5
E138AGKQ	10	10	10	45	5
Y181C	30	60	30	45	10
Y181C + G190AES	0	0	10	10	10
Y181C + H221Y	0	0	0	10	10
Y188FHL	60	60	10	60	60
G190AES	60	60	45	60	60
H221Y	10	15	10	15	10
P225H	45	45	0	0	20
F227L	15	30	0	0	60
M230IL	45	60	30	60	60
Y318F	10	30	0	0	60
K101EHP + Y181C	5	5	5	0	0
K103HNSV	60	60	0	0	0
V179ET	10	10	10	10	0
K238NT	30	30	0	0	0
K101EHP + Y188FHL	0	0	5	0	0
V179ET + Y181C	0	0	10	10	0
K101EHP + M184IV	0	0	0	15	0
E138AGKQ + M184IV	0	0	0	15	0

Note: These numbers represent the effect or weighting of each mutation or combination of mutations on individual drug susceptibility. Positive numbers mean reduced susceptibility whereas negative numbers mean increased sensitivity. The larger the number, the more the effect on drug susceptibility when a particular mutation/combination is present.

NNRTIs: Non-nucleoside reverse transcriptase inhibitors; EFV: Efavirenz; NVP: Nevi-rapine; ETR: Etravirine: RPV: Rilpivirine; DOR: Doravirine.

difference between Efavirenz or Nevirapinebased first-line ART.

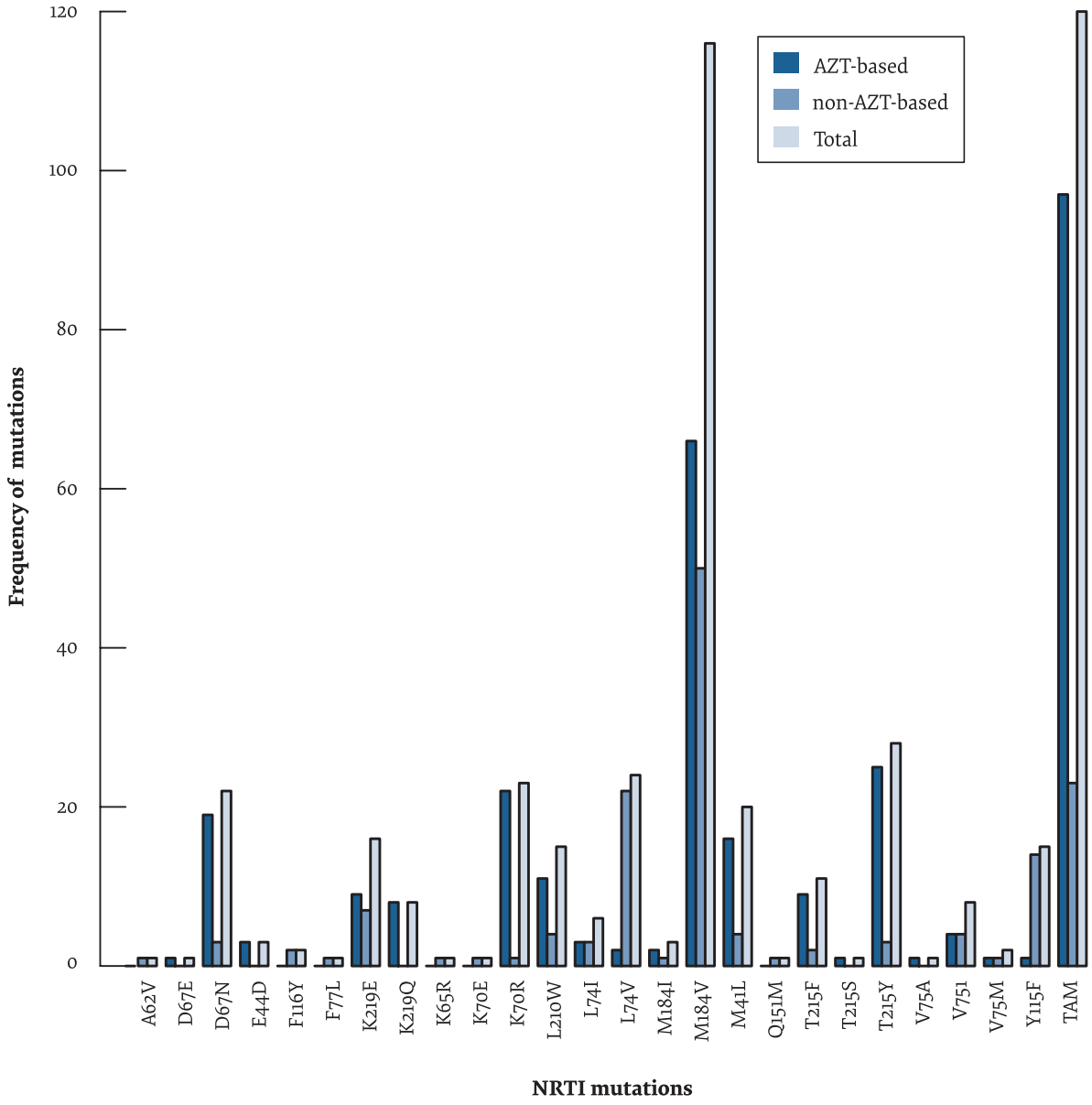
The proportion of cases with resistance to all 3 NRTIs (Zidovudine, Abacavir, and Tenofovir), including second-line regimens, was 3% (n=4) and 6% in NNRTIs (including second-generation) (n=8). Tables 2 and 3 summarize detected NRTI and NNRTI-resistance mutations and their effects on both NRTI and NNRTI drug susceptibility in 128 cases from 2014 to 2017.

Discussion

This study provides the first insights into HIV subtypes and drug resistance mutations among patients with first-line ART failure in Libya. All HIV isolates were group M, subtype CRF02, aligning with findings from West and Central Africa (*10*) but differing from the diverse subtypes in the Middle East and North Africa (*11*). Subtype B predominates in Morocco (*12*), while Algeria (*13*), Tunisia (*14*) and Egypt (*15*) show various subtypes and CRFs. Understanding HIV genetic diversity is crucial for local epidemic tracking, ART response and resistance surveillance (*16,17,10*).

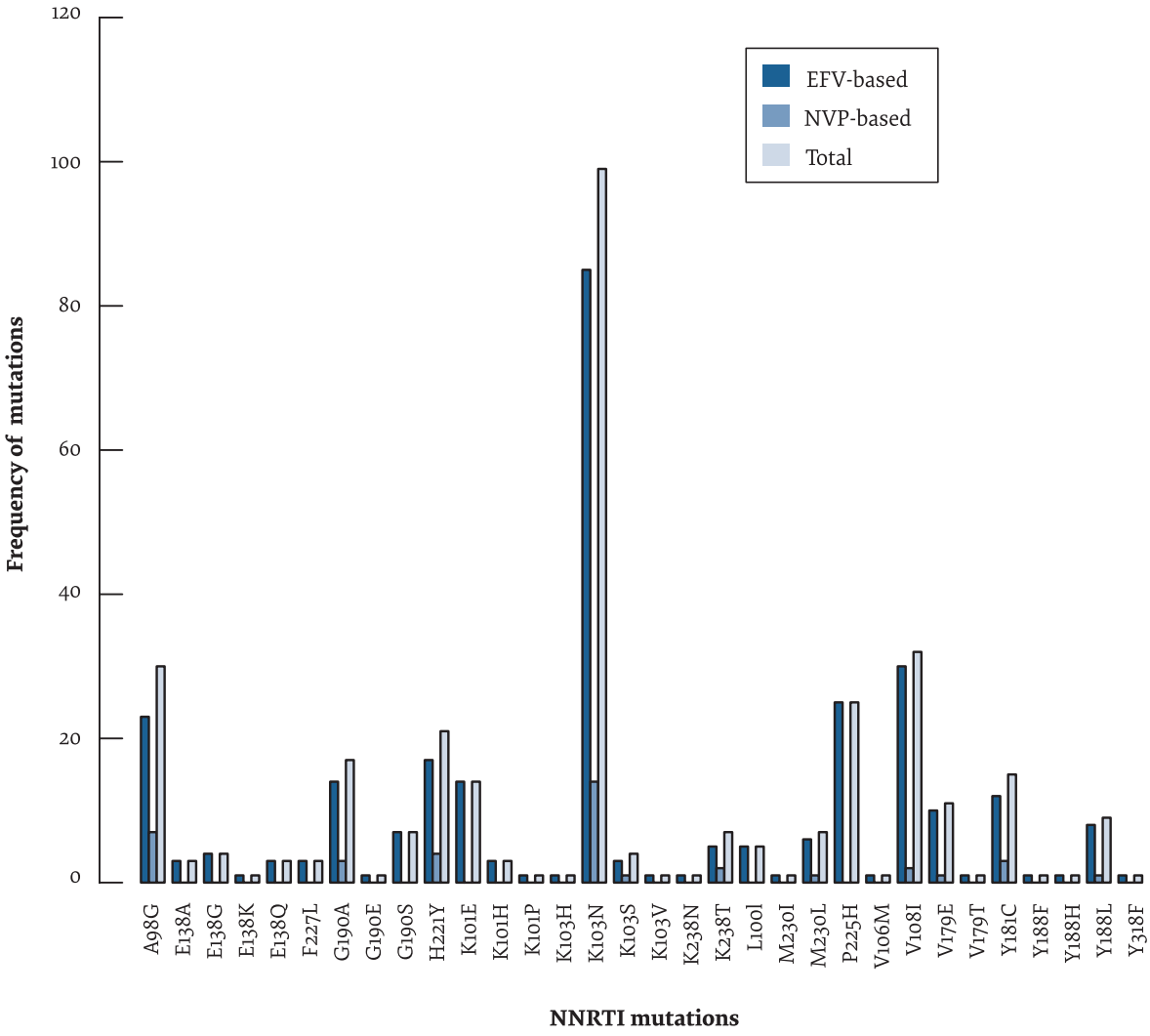
We found that 100% of HIV sequences had at least one drug resistance mutation at first-line ART failure. This high drug resistance mutation prevalence is similar to reports from Tunisia (83%) (*18*), Kenya (82%) (*19*), South Africa (85-90%) (*20-21*) and sub-Saharan Africa (70%) (*22*).

Figure 1. Pattern and frequency of NRTI resistance mutations in AZT vs. non-AZT based anti-retroviral therapy in 128 cases, Libya, 2014–2017



NRTI: Nucleoside reverse transcriptase inhibitors: Zidovudine; TAM: Thymidine analogue mutations

Figure 2. Pattern and frequency of NNRTI resistance mutations per ART regimen in 128 cases, Libya, 2014–2017



NNRTI: Non-nucleoside reverse transcriptase inhibitors; ART: Antiretroviral therapy;EFV: Efavirenz: Nevirapine

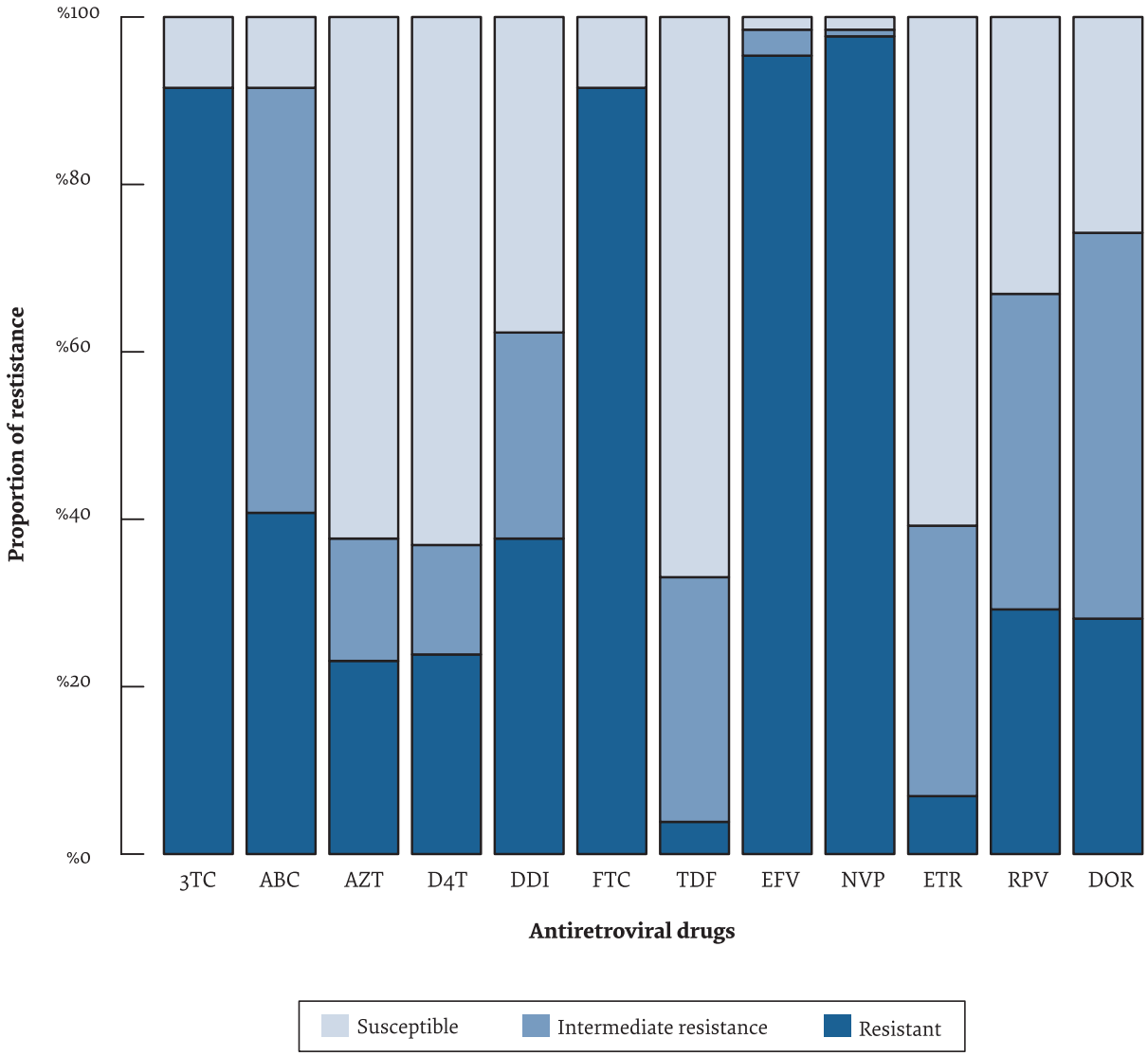
High drug resistance mutation rates can diminish ART efficacy, limit therapeutic options, increase transmitted resistance risks, complicate management and reduce control over AIDS-related outcomes (*23–24,3–4*). Low CD4 counts and high viral loads suggest prolonged treatment failure before diagnosis (*26*).

The M184V mutation was prevalent (93%), similar to other settings (*19,20*), likely due to widespread Lamivudine use, which is still used despite resistance (*27*). Zidovudine regimens were more likely to select TAMs at ART failure (53.8% vs. 22.8%; *P* <0.005), consistent with African and European studies (*21,28*). TAMs accumulate with prolonged Zidovudine use in non-suppressive regimens, leading to late ART failure diagnoses and prolonged failed regimens, which worsen outcomes and limit NRTI use (*29–30,3,22,24*).

NRTI cross-resistance variations were noted; non-Zidovudine ART retained better susceptibility to other NRTIs than Zidovudine-based ART [87.7% vs 40.8% to Zidovudine (*P* <0.001), 80.7% vs 54.9% to Tenofovir (*P*= 0.004)], suggesting non-Zidovudine regimens may better preserve NRTIs for second-line ART (*31, 32*). The K103N mutation prevalence (78%) was consistent with settings using NNRTIs as first-line ART (*12,21,33*), likely due to Efavirenz use and its common selection for this mutation (*34*). K103N confers high-level resistance to first-generation NNRTIs (*35*).

For second-generation NNRTIs, 38 (29.7%), 9 (7%), and 36 (28%) of our cases had high-level resistance to Rilpivirine, Etravirine, and Doravirine, respectively. Only 41 (32%), 77 (60.2%), and 33 (25.8%) cases would benefit from these drugs as fully active in salvage regimens,

Figure 3. Predicted susceptibility to various NRTIs and NNRTIs during ART failure in 128 cases, Libya, 2014–2017



NRTIs: Nucleoside reverse transcriptase inhibitors;NNRTIs: Non-nucleoside reverse transcriptase inhibitors;ART: Antiretroviral therapy;3TC: Lamivudine; ABC: Abacavir; AZT: Zidovudine; D4T: Stavudine; DDI: Didanosine; FTC: Emtricitabine; TDF: Tenofovir; EFV: Efavirenz; NVP: Nevirapine; ETR: Etravirine: RPV: Rilpivirine; DOR: Doravirine

respectively. Resistance levels to second-generation NNRTIs were similar to findings in Thailand (*33*) and South Africa (*32,36*), making them less viable options for inclusion in second-line regimens under Libyan guidelines.

Our study has limitations. Firstly, the study was retrospective, and some parts of the data were missing for some of the cases. Secondly, the study included only patients on ART who completed resistance testing, and this may have underestimated the prevalence of drug resistant mutations among patients who were lost to follow-up, stopped ART or died. Thirdly, it is possible that drug resistant mutations were underestimated among patients with HIV viral loads below 1000 copies/ml. As there was no pre-existing baseline data on the prevalence of resistance before initiating first-line ART, all detected drug resistant mutations were assumed to be acquired after initial treatment failure.

Conclusion

This study documents a high prevalence of HIV drug resistance after failing an NNRTI-based ART at Tripoli University Hospital in Libya. We highlight the need to

improve first-line treatment outcomes and to reduce the risk of developing HIV drug resistance via inaccurate or ineffective service delivery. The Libyan national HIV programme needs to address drug resistance by including drugs with a high genetic barrier to resistance (such as Dolutegravir-based ART) in first-line ART regimens. It also needs to improve HIV treatment adherence strategies and closely monitor for increases in treatment failures due to drug resistance. Libya also needs structured HIV virologic monitoring programmes. Timely virologic monitoring and prompt switch to second-line ART could limit the accumulation of drug resistance and enable successful future virologic suppression. In addition, Libyan national HIV service delivery requires assistance in capacity-building, including improving diagnostic laboratory infrastructure, training and recruitment of qualified laboratory personnel and training physicians in the latest evidenced-based HIV medical care and management.

Acknowledgments

The author would like to thank our colleagues for their insightful comments and suggestions.

Funding: None.

Conflicting interest: None declared.

Étude rétrospective de la prévalence de la pharmacorésistance acquise après l'échec d'un traitement antirétroviral en Libye

Résumé

Contexte : Le taux croissant de mutations du VIH pharmacorésistantes en Libye et dans d'autres pays d'Afrique menace l'efficacité du traitement antirétroviral (TAR), d'où le besoin urgent de mettre en place des stratégies régionales pour combattre la résistance et améliorer les résultats thérapeutiques.

Objectif : Caractériser la fréquence et le schéma des mutations du VIH pharmacorésistantes acquises chez les patients présentant un échec du TAR tout en utilisant des inhibiteurs non nucléosidiques de la transcriptase inverse (INNTI) prescrits par le Département des maladies infectieuses de l'hôpital universitaire de Tripoli, en Libye.

Méthodes : Nous avons rassemblé des données rétrospectives sur 128 personnes vivant avec le VIH, âgées de 18 ans ou plus, qui avaient connu un échec de traitement de première intention à l'hôpital universitaire de Tripoli (Libye), de 2014 à 2017. Nous avons analysé les séquences existantes d'acides aminés du VIH afin d'identifier les mutations de résistance à l'aide d'algorithmes issus de la base de données sur la pharmacorésistance du VIH de l'Université de Stanford.

Résultats : Tous les cas inclus présentaient au moins une mutation de résistance (n = 128 ; 100 %) et 119 (93 %) montraient à la fois des mutations aux inhibiteurs nucléosidiques de la transcriptase inverse (INTI) et aux INNTI. La M184V/I était la mutation la plus fréquente pour les INTI (n = 119 ; 93 %) tandis que pour les INNTI (n = 100; 78 %), la K103N était la plus fréquente. Des mutations des analogues de la thymidine ont été détectées dans 51 cas (40 %), représentées par les mutations T215Y, D67N and M41L. La sensibilité totale prédite était la plus élevée pour le ténofovir (66,4 %), suivi de l'étravirine (60 %).

Conclusion : Nous avons détecté des niveaux élevés de pharmacorésistance et de mutations associées chez les personnes vivant avec le VIH. La mise en œuvre de schémas thérapeutiques présentant de fortes barrières génétiques à la résistance, associée à un suivi et à une surveillance rigoureux du développement de la résistance du VIH, pourrait contribuer à atténuer cette résistance à l'avenir.

دراسة استرجاعية لمعدل انتشار المقاومة المكتسبة للأدوية بعد فشل العلاج بمضادات الفيروسات القهقرية في ليبيا

نادر شلاكه

الخلاصة

الخلفية: هناك زيادة في معدل طفرات فيروس العوز المناعي البشري المقاومة للأدوية في ليبيا وغيرها من البلدان الأفريقية، وهذه الزيادة تهدد فاعلية العلاج بمضادات الفيروسات القهقرية، ما يعني الحاجة الملحة إلى استراتيجيات إقليمية لمكافحة المقاومة وتحسين حصائل العلاج.

الأهداف: هدفت هذه الدراسة الى توصيف تواتر ونمط طفرات مقاومة فيروس العوز المناعي البشري المكتسبة للأدوية لدى المرضى الذين تظهر عليهم علامات فشل العلاج بمضادات الفيروسات القهقرية، وذلك أثناء استخدام المثبطات المنتسخة العكسية اللانوكليوزيدية التي وصفها لهم قسم الأمراض المعدية في مستشفى طرابلس الجامعي بليبيا.

طرق البحث: جمعنا بيانات استرجاعية عن 128 مصابًا بفيروس العوز المناعي البشري، لا يقل سن الواحد منهم عن 18 عامًا، ممن عانوا من فشل علاج الخط الأول في مستشفى طرابلس الجامعي بليبيا، من عام 2014 إلى عام 2017. وقد حللنا تسلسلات الأحماض الأمينية لفيروسات العوز

المناعي البشري الموجودة لتحديد طفرات المقاومة باستخدام خوارزميات من قاعدة بيانات جامعة ستانفورد لمقاومة فيروس العوز المناعي البشري للأدوية.

النتائج: كان لدى جميع الحالات المُدرَجة طفرة مقاومة واحدة على الأقل (بعدد 128؛ 100٪) ولدى 119 حالة (93٪) طفرة في مقاومة كلٍّ من المثبطات المنتسخة العكسية النوكليوزيدية والمثبطات المنتسخة العكسية اللانوكليوزيدية. وكانت طفرة M184V/I أكثر طفرات المثبطات المنتسخة العكسية النوكليوزيدية شيوعًا (بعدد 119؛ 93٪) في حين كانت طفرة K103N أكثر طفرات المثبطات المنتسخة العكسية اللانوكليوزيدية شيوعًا (بعدد 100؛ 78٪). وقد اكتُشفت طفرات نظائر الثيميدين في 51 حالة (40٪)؛ تضمنت T215Y وD67N وM41L. وكان توقُّع الحساسية التامة أعلى ما يكون في حالة تينوفوفير (66.4٪)، يليه إيترافيرين (60٪).

الاستنتاجات: رصدنا ارتفاع مستوى مقاومة الأدوية، وما يرتبط بها من طفرات بين المتعايشين مع فيروس العوز المناعي البشري. ويمكن أن يساعد تنفيذ أنظمة دوائية ذات حواجز جينية عالية تحول دون المقاومة، إلى جانب الرصد والمراقبة الدقيقين لتطور مقاومة فيروس العوز المناعي البشري، على التخفيف من حدة هذه المقاومة في المستقبل.

References

1. The Joint United Nations Programme on HIV/AIDS (UNAIDS). Global HIV & AIDS statistics - Fact sheet. 2023 [Internet]. Geneva: UNAIDS; [cited 2024 Jun 13]. Available from: https://www.unaids.org/en/resources/fact-sheet
2. World Health Organization. Access to antiretroviral drugs in low- and middle-income countries: technical report. Geneva: World Health Organization; 2014 [Internet]. [cited 2024 Jun 13]. Available from: https://apps.who.int/iris/handle/10665/128937
3. Boender TS, Kityo CM, Boerma RS, Hamers RL, Ondoa P, Wellington M, et al. Accumulation of HIV-1 drug resistance after continued virological failure on first-line ART in adults and children in sub-Saharan Africa. J Antimicrob Chemother. 2016 Oct;71(10):2918-27. doi: 10.1093/jac/dkw218. PMID: 27272749.
4. Bell Gorrod H, Court R, Schomaker M, Maartens G, Murphy RA. Increased Mortality with Delayed and Missed Switch to Second-Line Antiretroviral Therapy in South Africa. J Acquir Immune Defic Syndr. 2020 May 1;84(1):107-13. doi: 10.1097/QAI.0000000000002313. PMID: 32053563.
5. Meloni ST, Chaplin B, Idoko J, Agbaji O, Akanmu S, Imade G, et al. Drug resistance patterns following pharmacy stock shortage in Nigerian Antiretroviral Treatment Program. AIDS Res Ther. 2017 Oct 13;14(1):58. doi: 10.1186/s12981-017-0184-5. PMID: 29025333.
6. Boffito M, Waters L, Cahn P, Paredes R, Koteff J, Van Wyk J, et al. Perspectives on the Barrier to Resistance for Dolutegravir + Lamivudine, a Two-Drug Antiretroviral Therapy for HIV-1 Infection. AIDS Res Hum Retroviruses. 2020 Jan 1;36(1):13-8. doi: 10.1089/AID.2019.0171. PMID: 31825526.
7. World Health Organization. HIV drug resistance report 2021. Geneva: World Health Organization; 2021 [Internet]. [cited 2024 Jun 13]. Available from: https://www.who.int/publications/i/item/9789240038608
8. World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery, and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021 [Internet]. [cited 2024 Jun 13]. Available from: https://www.who.int/publications/i/item/9789240039469
9. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2020 [Internet]. [cited 2024 Jun 13]. Available from: https://www.r-project.org/
10. Giovanetti M, Ciccozzi M, Parolin C, Borsetti A. Molecular Epidemiology of HIV-1 in African Countries: A Comprehensive Overview. Pathogens. 2020 Dec 21;9(12):1072. doi: 10.3390/pathogens9121072. PMID: 33352668.
11. Sallam M, Şahin GÖ, Ingman M, Widell A, Esbjörnsson J, Medstrand P. Genetic characterization of human immunodeficiency virus type 1 transmission in the Middle East and North Africa. Heliyon. 2017 Jul 1;3(7). doi: 10.1016/j.heliyon. 2017.e00352. PMID: 28781953.
12. El Annaz H, Recordon-Pinson P, Tagajdid R, Doblali T, Belefquih B, Oumakhir S, et al. Drug Resistance Mutations in HIV Type 1 Isolates from Patients Failing Antiretroviral Therapy in Morocco. AIDS Res Hum Retroviruses. 2012 Aug 1;28(8):944-8. doi: 10.1089/AID.2011.0278. PMID: 22225652.
13. Bouzeghoub S, Jauvin V, Recordon-Pinson P, Garrigue I, Amrane A, Belabbes EH, et al. High diversity of HIV type 1 in Algeria. AIDS Res Hum Retroviruses. 2006 Apr 19;22(4):367-72. doi: 10.1089/aid.2006.22.367. PMID: 16623618.
14. El Moussi A, Thomson MM, Delgado E, Cuevas MT, Nasr M, Abid S, et al. Genetic Diversity of HIV-1 in Tunisia. AIDS Res Hum Retroviruses. 2017 Jan 1;33(1):77-81. doi: 10.1089/AID.2016.0164. PMID: 27653041.
15. Amer AN, Gaballah A, Emad R, Ghazal A, Attia N. Molecular Epidemiology of HIV-1 Virus in Egypt: A Major Change in the Circulating Subtypes. Curr HIV Res. 2021 Aug 6;19(5):448-56. doi: 10.2174/1570162X19666210805091742. PMID: 34387697.
16. Mumtaz G, Hilmi N, Akala FA, Semini I, Riedner G, Wilson D, et al. HIV-1 molecular epidemiology evidence and transmission patterns in the Middle East and North Africa. Sex Transm Infect. 2011 Mar 1;87(2):101-6. doi: 10.1136/sti.2010.043711. PMID: 21097808.

17. Amornkul PN, Karita E, Kamali A, Rida WN, Sanders EJ, Lakhi S, et al. Disease progression by infecting HIV-1 subtype in a seroconverted cohort in sub-Saharan Africa. AIDS. 2013 Nov 13;27(17):2775-86. doi: 10.1097/QAD.0000000000000012. PMID: 23842127.

18. Jlizi A, Ben Ammar El Gaaied A, Slim A, Tebourski F, Ben Mamou M, Ben Chaabane T, et al. Profile of drug resistance mutations among HIV-1-infected Tunisian subjects failing antiretroviral therapy. Arch Virol. 2008;153(6):1103-8. doi: 10.1007/S00705-008-0104-Z. PMID: 18431606.

19. Scriven YA, Mulinge MM, Saleri N, Luvai EA, Nyachieo A, Maina EN, et al. Prevalence and factors associated with HIV-1 drug resistance mutations in treatment-experienced patients in Nairobi, Kenya. Medicine. 2021 Oct 8;100(40). doi: 10.1097/MD.0000000000027460. PMID: 34614178.

20. Rossouw TM, Nieuwoudt M, Manasa J, Malherbe G, Lessells RJ, Pillay S, et al. HIV drug resistance levels in adults failing first-line antiretroviral therapy in an urban and a rural setting in South Africa. HIV Med. 2017 Feb 1;18(2):104-14. doi: 10.1111/HIV.12400. PMID: 27134275.

21. Manasa J, Lessells RJ, Skingsley A, Naidu KK, Newell ML, McGrath N, et al. High-levels of acquired drug resistance in adult patients failing first-line antiretroviral therapy in a rural HIV treatment programme in KwaZulu-Natal, South Africa. PLoS One. 2013 Aug 21;8(8). doi: 10.1371/journal.pone.0072152. PMID: 23991186.

22. Hamers RL, Sigaloff KC, Wensing AM, Wallis CL, Kityo C, Siwale M, et al. Patterns of HIV-1 drug resistance after first-line antiretroviral therapy (ART) failure in 6 sub-Saharan African countries: implications for second-line ART strategies. Clin Infect Dis. 2012 Jun 1;54(11):1660-9. doi: 10.1093/cid/cis254. PMID: 22431801.

23. Machouf N, Thomas R, Nguyen VK, Trottier B, Boulassel MR, Wainberg MA, et al. Effects of drug resistance on viral load in patients failing antiretroviral therapy. J Med Virol. 2006 May;78(5):608-13. doi: 10.1002/jmv.20582. PMID: 16555289.

24. Sigaloff KC, Ramatsebe T, Viana R, de Wit TF, Wallis CL, Stevens WS. Accumulation of HIV drug resistance mutations in patients failing first-line antiretroviral treatment in South Africa. AIDS Res Hum Retroviruses. 2012 Feb 10;28(2):171-5. doi: 10.1089/aid.2011.0136. PMID: 21767172.

25. Guo C, Wu Y, Zhang Y, Liu X, Li A, Gao M, et al. Transmitted Drug Resistance in Antiretroviral Therapy-Naive Persons with Acute/Early/Primary HIV Infection: A Systematic Review and Meta-Analysis. Front Pharmacol. 2021 Nov 24; 12:718763. doi: 10.3389/fphar.2021.718763. PMID: 34880988.

26. Bernabé KJ, Siedner M, Tsai AC, Marconi VC, Murphy RA. Detection of HIV Virologic Failure and Switch to Second-Line Therapy: A Systematic Review and Meta-analysis of Data from Sub-Saharan Africa. Open Forum Infect Dis. 2022 May 1;9(5). doi: 10.1093/ofid/ofac121. PMID: 35631582.

27. Wainberg MA. The impact of the M184V substitution on drug resistance and viral fitness. Expert Rev Anti Infect Ther. 2004 Feb;2(1):147-51. doi: 10.1586/14787210.2.1.147. PMID: 15482197.

28. De Luca A, Dunn D, Zazzi M, Camacho R, Torti C, Fanti I, et al. Declining prevalence of HIV-1 drug resistance in antiretroviral treatment-exposed individuals in Western Europe. J Infect Dis. 2013 Apr 15;207(8):1216-20. doi: 10.1093/infdis/jit017. PMID: 23315315.

29. Goodall RL, Dunn DT, Nkurunziza P, Mugarura L, Pattery T, Munderi P, et al. Rapid accumulation of HIV-1 thymidine analogue mutations and phenotypic impact following prolonged viral failure on zidovudine-based first-line ART in sub-Saharan Africa. J Antimicrob Chemother. 2017 May 1;72(5):1450-5. doi: 10.1093/jac/dkw583. PMID: 28119419.

30. Cozzi-Lepri A, Phillips AN, Martinez-Picado J, Monforte ADA, Katlama C,Hansen A-B, et al. Rate of accumulation of thymidine analogue mutations in patients continuing to receive virologically failing regimens containing zidovudine or stavudine: implications for antiretroviral therapy programs in resource-limited settings. J Infect Dis. 2009 Sep 1;200(5):687-97. doi: 10.1086/604731. PMID: 19659429.

31. Whitcomb JM, Parkin NT, Chappey C, Hellmann NS, Petropoulos CJ. Broad nucleoside reverse-transcriptase inhibitor cross-resistance in human immunodeficiency virus type 1 clinical isolates. J Infect Dis. 2003 Oct 1;188(7):992-1000. doi: 10.1086/378281. PMID: 14513422.

32. Steegen K, Bronze M, Papathanasopoulos MA, van Zyl G, Goedhals D, Variava E, et al. HIV-1 antiretroviral drug resistance patterns in patients failing NNRTI-based treatment: results from a national survey in South Africa. J Antimicrob Chemother. 2017 Jan 1;72(1):210-9. doi: 10.1093/jac/dkw358. PMID: 27659757.

33. Teeranaipong P, Sirivichayakul S, Mekprasan S, Ohata PJ, Avihingsanon A, Ruxrungtham K, et al. Role of Rilpivirine and Etravirine in Efavirenz and Nevirapine-Based Regimens Failure in a Resource-Limited Country: A Cross-Sectional Study. PLoS One. 2016 Apr 1;11(4). doi: 10.1371/journal.pone.0154221. PMID: 27116234.

34. Bacheler LT, Anton ED, Kudish P, Baker D, Bunville J, Krakowski K, et al. Human immunodeficiency virus type 1 mutations selected in patients failing efavirenz combination therapy. Antimicrob Agents Chemother. 2000 Sep;44(9):2475-84. doi: 10.1128/AAC.44.9.2475-2484.2000. PMID: 10952584.

35. Delaugerre C, Rohban R, Simon A, Mouroux M, Tricot C, Agher R, et al. Resistance profile and cross-resistance of HIV-1 among patients failing a non-nucleoside reverse transcriptase inhibitor-containing regimen. J Med Virol. 2001 Nov 8;65(3):445-8. doi: 10.1002/jmv.2055. PMID: 11745936.

36. Steegen K, Moorhouse M, Wensing AM, Venter WDF, Hans L. Is there a role for doravirine in African HIV treatment programmes? A large observational resistance study in South Africa. J Int AIDS Soc. 2021 May 1;24(5). doi: 10.1002/jia2.25706. PMID: 33951258.