The use of third-line combined antiretroviral treatment and determinants of treatment outcomes among HIV/AIDS patients in Ethiopia

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APPROVAL SHEET

ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE, DEPARTMENT OF INTERNAL MEDICINE, POSTGRADUATE PROGRAM

I, Dr. Anteneh Eshetu, hereby declare that this thesis entitled "The use of third-line combined antiretroviral treatment and determinants of treatment outcomes among HIV/AIDS patients in Ethiopia: a retrospective study with longitudinal analysis" in line with the requirement of graduate studies was fully undertaken by me under the guidance of my advisor and that I have, to the best of my knowledge and effort, avoided plagiarism or duplication of materials unless and otherwise cited and/or acknowledged and that it has not been so far submitted for any form of publication or consideration before the final approval.

Principal investigator	Signature	Date

I hereby certify that I have read and evaluated this research thesis relating to "The use of third-line combined antiretroviral treatment and determinants of treatment outcomes among HIV/AIDS patients in Ethiopia: a retrospective study with longitudinal analysis" under my guidance from its inception up to in its current format and that it can be submitted for final approval in partial fulfilment to the Certificate of subspecialty in infectious disease.

Advisor	Signature	Date

As a member of the research open defence examination, I certify that I have read and evaluated the thesis prepared by Anteneh Eshetu(MD), and examined the candidate. I recommend that the thesis be accepted as fulfilling the thesis requirements for the Certificate of subspecialty in infectious disease.

Examiner	Signature	Date

Assurance of Principal Investigator

We the undersigned are the principal investigator and the advisor of this study. We declare that this thesis is our original work.

Principal investigator: Dr. Anteneh Eshetu

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Table of abbreviations

Abbreviation	
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
BMI	Body mass index
cART	Combined ART
DRV	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
ETV	Etravirine
FTC	Emtricitabine
GART	Genotypic antiretroviral resistance test
INSTI	Integrase strand transfer inhibitors
NRTI	Nucleoside(-tide) reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitors
PWHIV	People with HIV
PI	Protease inhibitor
RAL	Raltegravir
RTV	Ritonavir
TAF	Tenofovir alafenamide
TB	Tuberculosis

TDF	Tenofovir disoproxil fumarate
WHO	World health organization

Abstract

Background:

The treatment of human immunodeficiency virus (HIV) infection involves the use of combination antiretroviral therapy (cART). The use of these multidrug regimens substantially reduces the progression to AIDS, opportunistic infections, hospitalizations, and death. The standard of care in HIV management is to maximally suppress plasma HIV RNA to prevent HIV disease progression and the emergence of drug-resistant virus. Third-line regimens include drugs such as newer generation NNRTIs like etravirine (ETV), boosted PIs like ritonavir-boosted darunavir (DRV/r), as well as the integrase inhibitor like Dolutegravir (DTG) with or without previously used ARV drugs that potentially maintained residual antiviral activity, especially from the NRTI class.(1,2) Although there were few studies with newer agents, cohort data showed high mortality among people for whom second-line ART had failed. Salvage regimens were recommended with new drugs such as DRV/r, ETV and RAL.

Objectives:

General objectives:

To describe baseline, virologic and therapeutic characteristics of PWHIV on 3rd line cART

Specific objectives

To analyse the virologic suppression in PWHIV on 3rd line cART

To describe the adherence status of PWHIV on 3rd line cART

To assess the duration of protease inhibitors' exposure in PWHIV on 3rd line cART

To analyse medical comorbidities in PWHIV on 3rd line cART

Methods:

This is a retrospective study with longitudinal analysis among adults (≥ 18 years) attending Tikur Anbessa Specialized Hospital, Infectious Diseases unit, ART clinic. Then, a longitudinal analysis was conducted to determine virological suppression among patients who was initiated on third-line therapy and for whom a follow-up viral load was determined. The study is aimed to describe the population of patients on third-line therapy.

Results:

A total of 51 patients are on third line cART(both guideline and expert recommended regimens). Fifty one percent (n= 26) patients are female. Majority of the respondents claimed that they acquired the virus through unprotected sexual intercourse (66%) and 28% percent of patents acquired the virus through vertical transmission from mother to child. Majority of patients had WHO stage-III or stage-IV defining conditions (37.3% & 35.3% respectively). Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz was the first line regimen in 37.3% of patients and Tenofovir Disoproxil Fumarate, Lamivudine and Ritonavir boosted Atazanavir was a second line cART in 39.2% patients. Dolutegravir, Lamivudine, Ritonavir boosted Darunavir is the expert recommended third line regimen (94.1%). 76.5% (n= 39) have undetectable viral load on third line cART. Patients transferred due to first line treatment failure had an 11 times greater chance of having undetectable HIV RNA levels compared to those referred due to second line treatment failure.

Conclusions:

The use of expert recommended third line cART composed of DTG, 3TC, DRV and RTV is effective in our setting especially in PWHIV who are referred to our center after 1st line cART treatment failure.

Key words: HIV/AIDS, Third line cART, Virologic suppression

1. Introduction

1.1 Background

The treatment of human immunodeficiency virus (HIV) infection involves the use of combination antiretroviral therapy (cART). The use of these multidrug regimens substantially reduces the progression to AIDS, opportunistic infections, hospitalizations, and death. The standard of care in HIV management is to maximally suppress plasma HIV RNA to prevent HIV disease progression and the emergence of drug-resistant virus.

Minimizing the viral load is best achieved with the use of an ART regimen that consists of two to three fully active agents from at least two different classes of drugs. Among patients with virologic failure and drug-resistant virus, this goal can still be achieved even if fewer than two to three active agents are used; however, the likelihood of virologic suppression depends upon the drugs used and the number and types of drug-resistant mutations that are present. For patients with the drug-resistant virus who have failed multiple regimens, the treatment goal is still to decrease the viral load to below the level of detection, and if this is not attainable, to the lowest level possible.

Antiretroviral treatment began in 2003 and free ART was launched in Ethiopia in 2005. Since 2009 the World Health Organization (WHO) has recommended that third-line regimens be made available in all countries. Third-line regimens include drugs such as newer generation NNRTIs like etravirine (ETV), boosted PIs like ritonavir-boosted darunavir (DRV/r), as well as the integrase inhibitor like Dolutegravir (DTG) with or without previously used ARV drugs that potentially maintained residual antiviral activity, especially from the NRTI class.(1,2) Although there were few studies with newer agents, cohort data showed high mortality among people for whom second-line ART had failed. Salvage regimens were recommended with new drugs such as DRV/r, ETV and RAL.

1.2 Significance of the study

The result of this study will have an input regarding the treatment of ARV experienced HIV/AIDS patients, treatment outcomes, and factors related to treatment success.

1.3 Statement of the problem

Current approaches to third-line therapy require access to routine viral load monitoring and HIV resistance testing. Unlike the implementation of standardized first- and second-line

regimens currently in use in most countries, third-line regimens are generally individualized to account for treatment history, toxicities, as well as resistance patterns and therefore, require a higher cadre of health care workers.

Individuals who have first-line and second-line ART failure are a particular challenge in LMICs because they have probably been exposed to medications from the three most widely used classes of antiretrovirals: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors. A wide range of resistance patterns are associated with second-line failure in LMICs, although a substantial fraction of people with second-line ART failure might also have wild-type virus

WHO estimates that less than 1% of the people taking cART globally are using third-line regimens, but the demand for third-line regimens will increase as access to viral load monitoring and use of first- and second-line ART continue to expand.

Further research is needed to guide third-line ART strategies for resource-limited settings.

Recent data from several randomized controlled trials and observational cohorts are available for DRV/r-, ETV-, DTG- and RAL-containing regimens for treatment-experienced adults; many of these ARV drugs were effective in prospective studies among children and adolescents,
but most studies have been conducted in middle- to high-income settings. Taken together, the data support the efficacy of new agents such as INSTIs, second-generation PIs, and NNRTIs for people for whom the current second-line ART regimens have failed. However, multiple resistance to NRTI agents with reduced antiviral efficacy is common among ART-experienced people for whom first- and second-line regimens have already failed, and there
is some uncertainty about whether maintaining or recycling previously used NRTIs provides clinical benefit, through viral fitness reduction and/or in vitro susceptibility enhancement caused by some mutations, combined with some residual antiviral activity of these drugs. Further, since NRTI agents are often associated with cumulative toxicity, maintaining them in third-line ART may not be optimal and may involve increased pill burden and risk of drug-drug interactions.

Based on the knowledge of patterns of resistance, a pragmatic choice of second-line NRTIs was chosen at a programmatic level, with the sequencing of NRTIs as per WHO recommendations. Thus, a genotypic antiretroviral resistance test (GART) does not form part of the strategy when changing from first- to second-line. Resistance development after first-line failure on an NNRTI-based regimen is predictable, and PI-based second-line ART should achieve virological suppression if adherence issues can be adequately addressed.

2. Literature review

The World Health Organization (WHO) has recommended that national ART programs in resource-limited settings develop policies for access to third-line ART, containing ritonavir-boosted darunavir and integrase inhibitors. (3) In 2018, a third-line ART program was implemented in Ethiopia. Two ARV drugs were added to the national program to be used as third-line ART: ritonavir-boosted darunavir (DRV/r) and Dolutegravir (DTG). DRV/r is a PI with a high barrier to resistance. These efforts are aimed to address heavily treatment-experienced PLHIV. Although the definition of heavily treatment-experienced PLHIV is not standard, heavily treatment-experienced PLHIV can be described as having two or fewer antiretroviral (ARV) classes available for use with limited fully active ARV agents within each class. (4) Amongst patients with viral loads suggestive of treatment failure, an initial examination into adherence should be conducted. Barriers to ARV adherence may be multifactorial and may consist of a combination of medication-related adverse effects, issues related to medication procurement, pill burden, difficulty swallowing or overall treatment fatigue.

Virological failure develops frequently in adults on a second-line protease inhibitor (PI)-based antiretroviral therapy (ART) in resource-limited settings, occurring in 38% of patients by 36 months in a systemic review. A second-line ART treatment failure, which is defined as having two subsequent viral counts of or greater than 1000 copies/ml, done at least 3–6 months apart, leads to 3rd line treatment with higher pill burden and toxicities.

The numbers receiving second-line ART are expected to rise from an estimated 300 000 in 2013 to 2–4 million by 2030, comprising 12%–17% of all patients receiving ART.(5) These in turn will lead to increased demand for 3rd line ART.

The introduction of the new wave of integrase inhibitors (INSTIs) was a landmark event in the history of HIV treatment.

In a pooled subgroup analysis, DRV/r plus an optimized background regimen chosen by genotyping and phenotyping was shown to be superior to the control group (using boosted PIs) in highly treatment-experienced individuals. However, the evidences are limited in resource-limited settings. According to POWER-1 and 2 trials, Darunavir/r 600mg/100 mg twice daily showed greater efficacy than the CPI regimen at week 24, irrespective of baseline CPI viral susceptibility or number of RTV-boosted PIs used. The efficacy was also sustained at week 48.(6) The likely reason for resistance to darunavir is that people may experience prolonged virological failure while on a second-line PI-based regimen before being referred for assessment of eligibility for third-line ART.(7) studies in resource-limited settings have shown that prolonged virologic failure, even on a PI-based regimen, results in resistance mutation accumulation.

Integrase strand transfer inhibitors are a new class of ARV drugs designed to block the action of the integrase viral enzyme, which catalyses several key steps in the HIV-1 lifecycle and is responsible for insertion of the viral genome into the DNA of the host. DTG is a drug in this class that offers some novel and intriguing characteristics: it has a favourable pharmacokinetic profile with a prolonged intracellular half-life, rendering feasible a once-daily dosing without needs of pharmacokinetic boosting and without regard to meal. It also offers a favourable resistance profile showing a higher genetic barrier to resistance compared to other INSTIs. Dolutegravir had substantial activity against Raltegravir- and Elvitegravir-resistant HIV, particularly if key integrase gene mutations were not present.(8)

Even though there are limited data on the effectiveness of third-line cART and related factors, prolonged PI use, longer years on cART and younger age had been found to be important predictors of virologic failure. A South African cohort study also identified factors independently associated with virologic suppression following third-line cART to be female sex, lower darunavir resistance score and lower VL at the start of salvage ART. (9)

For patients who have failed multiple ART regimens, the construction of a new ART regimen should be done in consultation with an expert in managing treatment-experienced patients. In general, the anchor of the ART regimen, if available, should include either a fully active INST such as DTG, or a fully active boosted PI, such as DRV, paired with two NRTIs, at least one of which is fully active. If no active NRTI exists, then an INSTI plus a boosted PI regimen can be considered. (10)

In general, DRV/r and DTG-based regimens with their good tolerability and high genetic resistance barrier, are still valid options, showing excellent results in terms of virological response in both drug-naive and PI-experienced patients. (11)

3. Objectives of the study

General objectives:

To describe baseline, virologic and therapeutic characteristics of PWHIV on 3rd line cART

Specific objectives

To analyse the virologic suppression in PWHIV on 3rd line cART

To describe the adherence status of PWHIV on 3rd line cART

To assess the duration of protease inhibitors' exposure in PWHIV on 3rd line cART

To analyse medical comorbidities in PWHIV on 3rd line cART

4. Method

This is a retrospective study with longitudinal analysis among adults (≥ 18 years) attending Tikur Anbessa Specialized Hospital, Infectious Diseases unit, ART clinic. Then a longitudinal analysis was conducted to determine virological suppression among patients who are initiated on third-line therapy and for whom a follow-up viral load was determined. The study is aimed to describe the population of patients on third-line therapy.

Source Population

PLHIV on cART on follow-up at Tikur Anbessa Specialized Hospital (TASH).

Study Population

PLHIV on currently available and guide-line recommended 3rd line cART at Tikur Anbessa Specialized Hospital.

Inclusion criteria

All adult PWHIV patients age 18 years or more on 3rd line cART on follow-up at TASH.

Exclusion criteria

PWHIV on 3rd line cART for less than 12 months

Study variables

Independent variables

Age

Sex

Body mass index

Adherence status

Marital status

Duration of the disease

Types of 1st and 2nd line cART

Duration of 2nd line cART

Medical comorbidities

Duration of protease inhibitor use

HIV viral load when 3rd line cART is started

Baseline CD4 count

Dependent variable

Recent viral load (in the last 01 year)

Data collection

The primary investigator and a trained data collector will collect the research data using a well-structured questionnaire. Then the filtered data set will be entered on SPSS version 25 for further analysis. Baseline CD4 count, HIV-1 viral load at the initiation of cART, recent HIV-1 viral load (determination in the last 12 months), recent kidney function test, and recent liver function tests will be collected from patients' follow-up charts.

Sampling method and sample size

All adult PWHIV on third-line cART at Tikur Anbessa Specialized Hospital and Zewditu memorial Hospital will be included for cohort description. There are 45 patients at TASH and 25 patients at Zewditu memorial hospital who are registered and taking 3rd line cART, making the total number of the expected study participants 70.

Ethical considerations

Addis Ababa University, college of health science's Institutional review board gave ethical clearance to the study. Verbal consent was taken from the patient himself/ herself and the data was documented anonymously. Only consenting patients were enrolled in the study.

Dissemination of the result

As this study is being done for the fulfilment of the fellowship program, the result will be communicated to the stakeholders and clinicians so that it will have an impact on routine patient care. Additionally, I will send the manuscript to reviewers for publication on reputable international journals.

Operational Definitions

Virologic suppression: viral load equal to or less than 200 copies/mL after 06 months of cART.

Result

A. Socio- Demographic characteristics

The average age of the respondents was 41.1 years, with a standard deviation of 13.6. Out of the 51 respondents, 26 (51%) were female. Additionally, 48 (94.1%) of the patients were from Addis Ababa.

Table 1. Socio demographic characteristics of the participants

No	Variable	Category	Frequency	Percentage (%)
1	Sex	Male	25	49%
		Female	26	51%
2	Residence	Addis Ababa	48	94%
		Other	3	6%
3	Current Follow-Up Hospital	TASH	48	94.1%
		Other	3	5.9%
4	Marital status	Single	21	41.2%

		Married	15	29.4%
		Divorced	9	17.6%
		Widower	6	11.8%
5	Occupation	Student	9	18.4%
		Private employee	11	22.4%
		Civil servant	6	12.2%
		Housewife	6	12.2%
		Daily laborer	4	8.2%
		Other	13	26.5%

B. Past History of Patients

The study found that most patients (52.9%) underwent HIV testing due to PITC, while 66% acquired HIV through sexual transmission. Only 10.5% of female patients received ARV drugs for PMTCT reasons. A majority of patients (60.8%) were transferred from another hospital, with 56.7% of those transferred due to second line treatment failure. Additionally, 39.2% of patients had TB and were treated before ART initiation, while 25.5% acquired TB after ART initiation, with the majority (64.3%) acquiring pulmonary TB. 37.3% of patients were classified as WHO clinical stage III, and 87.2% had their baseline CD4 count determined. Finally, 37.3% of patients were treated with 1e as a first line ART regimen, while 39.2% were treated with 2h as a second line cART regimen.

The study found that the mean RNA level during second-line cART treatment failure was 134,492 ± 183,663.5. Respondents reported an average income of 6,816 ETB, while the average duration of the patients' ART treatment was 163 months. The mean baseline CD4 count was 147.3 with a standard deviation of 167.3. The average maximum number of CD4 count was 554.1 with a standard deviation of 307.8. The mean baseline viral load of the participants was 72,088.3 with a standard deviation of 170,935.1. Finally, the mean RNA level during first-line ART treatment failure was 57,727.6 with a standard deviation of 128,341.8.

Table 2. Past medical history of the participants.

No	Variable	Category	Frequency	Percentage (%)
1	Reason for testing	VCT	10	19.6
		PITC	27	52.9
		MTCT	14	27.5
2	Mode of acquisition of HIV	Sexual transmission	33	66%
		Vertical transmission	14	28%
		Unknown	3	6%
3	Transferred from another institutions	Yes	20	39.2%
		No	31	60.8%
4	Reason for transfer – out	First line treatment failure	13	43.3%
		Second line treatment failure	17	56.7%
5	Treated TB before cART initiation	Yes	31	60.8%
		No	20	39.2%
6	Develop TB after cART initiation	Yes	13	74.5%
		No	38	25.5%
7	WHO clinical stage	I	6	11.8%
		II	7	13.7%
		III	19	37.3%
		IV	18	35.3%
		Unknown	1	2%
8	First line regimen	1a	3	5.9%
		1b	2	3.9%

		1c	9	17.6%
		1d	12	23.5%
		1e	19	37.3%
		1f	2	3.9%
		Other	4	7.8%
9	Second line regimen	2a	2	3.9%
		2f	16	31.4%
		2g	2	3.9%
		2h	20	39.2%
		2i	1	2%
		Other	10	19.6%

C. Current Medical History

Among the patients, 48 (94.1%) are on DTG + 3TC+ DRV/r treatment regimen as a 3rd line regimen treatment. Out of the total, 49 (96.1%) have good adherence for third line regimen treatment. Only two patients' treatment was modified due to toxicity. A total of 35 (68.6%) participants did not disclose their HIV status to their partner. Among the 20 patients whose partners' HIV status is known, 11 (55%) of them are negative. Moreover, 31 (60.8%) of the patients did not engage in sexual intercourse with their partners. Only 10 (19.6%) of the participants' partners were taking cART treatment. Furthermore, only 2 (3.9%) patients smoke cigarettes, while 3 (5.9%) of the patients use khat. Additionally, 4 (7.8%) of the patients drink alcohol. The mean systolic blood pressure is 114 with a standard deviation of 19.8, and the mean BMI is 23.9 with a standard deviation of 4.6.

Table 3. Current medical history of participants

No	Variable	Category	Frequency	Percent (%)
1	Third line regimen	01	2	3.9%
		02	1	2%
		Other	48	94.1%
2	Medication Adherence	Fair	1	2%
		Good	49	96%
		Poor	1	2%
3	Partner Status	1	5	25%
		2	11	55%
		3	4	20%
4	Method of sex with Partner	1	1	2.1%
		2	7	14.9%
		3	8	17%
		4	31	66%
5	Smoking Cigarettes	Yes	49	96.1%
		No	2	3.9%
6	Drinking Alcohol	Yes	47	92.2%
		No	4	7.8%

D. Other medical Comorbidities

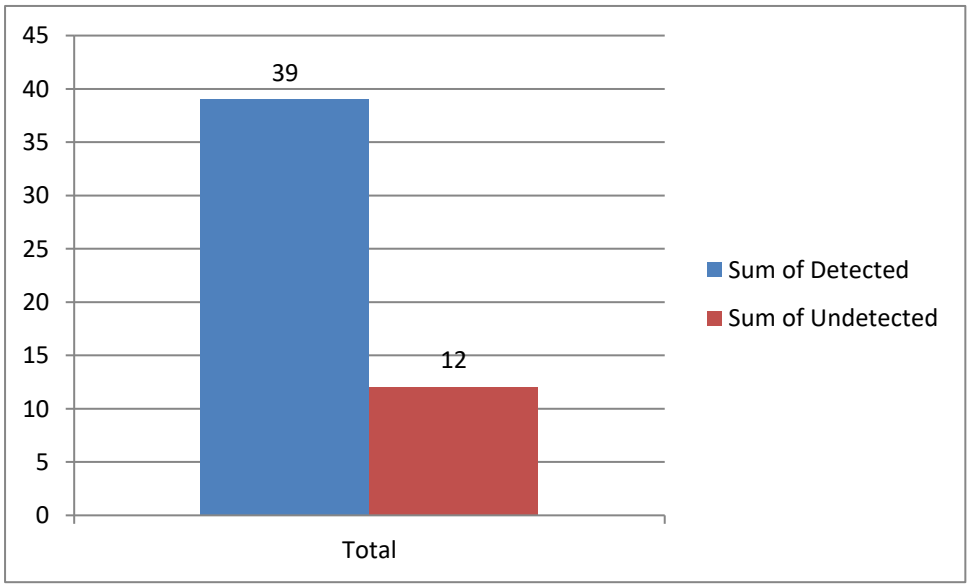
13.7% of the patients were Diabetic, while 9.8% are hypertensive. And 13.7% of the patients were diagnosed with dyslipidemia. Out of the total participants, 98% did not have any major

psychotic disorder. None of the patients underwent a genotype resistance test. Only one patient developed drug-drug interaction during the study. VDRL is positive in only 7.8% of the patients.

Table 4- Other comorbidities of the participants

No	Variable	Category	Frequency	Percent (%)
1	Diabetes mellitus	Yes	7	13.7%
		No	44	86.3%
2	Hypertensive	Yes	5	9.8%
		No	46	90.2%
3	Chronic HBV	Yes	1	2%
		No	50	98%
4	VDRL Positivity	Yes	4	7.8%
		No	47	92.2%
5	Dyslipidemia	Yes	7	14.3%
		No	42	85.7%

Figure1- the Last HIV RNA level of the patients on the third line cART



Seventy six point five percent (76.5%) of patients on expert recommended third line cART achieved virologic suppression.

A. Associated Factors

The analysis involved calculating frequency and percentage for categorical variables, and using mean and median for continuous variables. Chi-square was used for categorical independent variables with a categorical dependent variable to find associations. Two variables (Drinking alcohol and reason for transfer out) had a p value of <0.05. Bivariate correlation analysis was done for continuous variables, but no variable had a p value of <0.05. Binary logistic regression analysis was done for univariate analysis on the two variables (Drinking alcohol and reason for transfer out) after testing the fitting of the model using Hosmer Lemeshow goodness-fit test.

The two variables underwent multivariate binary logistic regression following a fitting test using Hosmer Lemeshow goodness-fit test. The test indicated a good fit for the variable analysis. The reason for patients being transferred to the current treatment center was significantly associated with the last HIV RNA viral load after the regression. Patients transferred due to first line treatment failure had an 11 times greater chance of having undetectable HIV RNA levels compared to those referred due to second line treatment failure.

Table-5 Multivariate binary logistic regression analysis of the independent variable to dependent variable.

*P-value 0.01-0.05 ** P-value 0.001-0.01 ***p-value <0.001

	Variable	Category	HIV Last viral load		Crude Odd Ratio (COR)	Adjusted Odds Ratio(AOR)
			Detected	Undetected		
1	Drinking Alcohol	Yes	1	3	12.66(1.17-136.45)*	226166(.000)
		No	38	9	1	1
2	Reason for transfer out	First line treatment failure	7	6	13.7(1.38-136.2)*	11.48(1.12-116.7)*
		Second line treatment failure	16	1	1	1

Discussion

The given result states that 56.7% of the patients transferred out for 3rd line regimens treatment were after the failure of 2nd line treatment. This indicates that a significant proportion of patients require 3rd line treatment due to the ineffectiveness of the 2ndline regimen. This finding highlights the importance of monitoring treatment response and promptly switching to more effective regimens to achieve viral suppression. Furthermore, the

result mentions that 76.5% of patients on expert recommended third-line combination antiretroviral therapy (cART) achieved virologic suppression. This suggests that the expert recommended third-line cART is effective in controlling viral replication in a majority of patients who have failed previous treatment regimens. This finding emphasizes the significance of expert guidance and treatment protocols in managing HIV infection. Additionally, the result states that patients transferred due to first-line treatment failure had an 11 times greater chance of having undetectable HIV RNA levels compared to those referred due to second-line treatment failure. This implies that patients who experience treatment failure at the first-line stage have a higher probability of achieving virologic suppression compared to those who fail at the second-line stage. This could be attributed to several factors, including the availability of more potent drugs and better treatment adherence in patients who have recently started treatment. Overall, the given result provides valuable insights into the outcomes of patients who require third-line regimens and their chances of achieving virologic suppression. It highlights the importance of regular monitoring, early detection of treatment failure and prompt switching to more effective regimens. Moreover, it underscores the significance of expert recommendations in guiding treatment decisions for patients with virologic failure.

A set of research results highlight the development of virological failure in adults on second-line ART treatment in resource-limited settings, occurring in 38% of the months according to a systemic review. The study recommends the use of darunavir/ritonavir (DRV/r) plus an optimized background regimen chosen by genotyping for these patients. The studies conducted in resource-limited settings also demonstrate that prolonged virologic failure, even on protease inhibitor (PI)-based regimens, leads to the accumulation of resistance mutations. Predictors of virologic failure include the prolonged use of second-line ART regimens, PI use, longer year's on cART, and younger age. Furthermore, a cohort study conducted in South Africa identified factors independently associated with virologic suppression following third-line cART, which include female sex, lower darunavir resistance score, and lower viral load at the start of salvage ART. The construction of new ART regimens for patients who have failed multiple regimens should be done by experts. Both DRV/r and dolutegravir (DTG) based regimens are suggested as valid options due to their good tolerability and high genetic resistance barrier. These regimens have shown excellent results in terms of virological

response in both drug-naïve and PI-experienced patients. In the context of these research findings, it can be observed that the first set of results highlights the effectiveness of expert-recommended third-line cART in achieving virologic suppression. The significantly higher chances of achieving undetectable HIV RNA levels among patients referred due to first-line treatment failure compared to second-line treatment failure suggest the importance of timely switching to more potent regimens after treatment failure. This emphasizes the need for careful monitoring and appropriate interventions to prevent further viral replication and drug resistance. The second set of results emphasizes the challenges faced in resource-limited settings, where virologic failure on second-line ART is frequent. The use of DRV/r in combination with an optimized background regimen selected through genotyping is suggested as a potential solution. The studies also highlight the accumulation of resistance mutations and predictors of virologic failure, such as prolonged use of second-line regimens, PI use, longer duration on cART, and younger age. This underscores the importance of regularly assessing treatment efficacy, considering alternative regimens, and ensuring adherence to therapy. The South Africa cohort study identifies additional factors associated with virologic suppression following third-line cART, including female sex, lower darunavir resistance score, and lower viral load at the start of salvage ART. These findings emphasize the importance of individualized treatment approaches and considering patient-specific factors when constructing new ART regimens. Overall, these research findings suggest that expert-recommended third-line cART can effectively achieve virologic suppression in HIV patients who have failed previous regimens. However, resource-limited settings face additional challenges, such as frequent virologic failure on second-line ART and the accumulation of resistance mutations. Timely switching to more potent regimens, such as DRV/r and DTG-based regimens is crucial in preventing virologic failure and further resistance development. Individualized treatment approaches, considering patient-specific factors, are essential in optimizing treatment outcomes.

In conclusion, the given result sheds light on the prevalence of treatment failure at different stages and the effectiveness of third-line regimens in achieving virologic suppression. It underscores the importance of proactive monitoring and timely interventions to optimize treatment outcomes for patients with HIV. This information has significant implications for

healthcare providers, policymakers, and researchers working towards improving HIV treatment strategies and outcomes.

Conclusion

The findings of this research provide valuable insights into the effectiveness of third-line regimens treatment for patients who fail second-line treatment. The results suggest the need for improved treatment options for patients who do not respond to second-line treatment. The high rate of virologic suppression among patients on expert recommended third-line cART is encouraging and supports the use of these regimens. The finding that early treatment transfer after first-line treatment failure is associated with better treatment outcomes raises questions about current treatment protocols and calls for further investigation. Overall, this research contributes to our understanding of HIV treatment and may inform future treatment guidelines and recommendations.

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Research Questionnaire

The patient has to give informed and agreed verbal consent.

Chart No.: ---------

Unique ART No.: ---------

Subject initials: ----------

I. Demography
1. Age (years)
2. Sex: 1.M---- 2.F----
3. Address: Region------ City------
4. Current follow-up hospital: 1. TASH----- 2. Others (specify)----
5. Marital status: 1. Single 2. Married 3. Divorced 4. Widower 5. Unknown
6. Occupation: 1. Student 2. Private employee 3. Civil servant 4. Farmer 5. Sex worker 6. Housewife 7. Daily laborer 8. Others (specify)

II. History
7. When did you become first aware of your HIV-1 infection? ------months
8. What was the reason for HIV testing?
   1. VCT 2. PITC. 3. Antenatal care. 3. MTCT. 4. Premarital. 5. Travel 6. Employment. 7. Others
9. How did you acquire HIV infection?
   1. Sexual transmission. 2. Vertical transmission 3. Blood transfusion. 4. Percutaneous. 5. Unknown
10. Have you ever received ARV drugs for PMTCT reasons? (For FEMALES only)
    1. Yes 2. No
11. If your answer for Q.10 is "Yes", what is the regimen?
    1. Nevirapine. 2. Zidovudine. 3 Triple ART. 4. unknown
12. Are you transferred in from another health institution?
    1. Yes (Specify). 2. No.
13. What was the reason for your transfer-out?
    1. First-line treatment failure (Specify the regimen)
    2. Second-line treatment failure (Specify the regimen)
    3. Patient's preference
    4. Others (specify)
14. Were you treated for TB before cART initiation?

1. Yes(when?) 2. No 3. unknown

15. Indicate the type of TB?
    1. PTB (drug-susceptible). 2. EPTB. 3. Disseminated TB 4. PTB (MDR)
16. Did you develop TB after cART initiation?
    1. Yes 2. No 3. Unknown
17. Indicate the type of TB?
    1. PTB. 2. EPTB. 3. Disseminated TB. 4. Unknown
18. Did you receive IPT?
    1. Yes. 3. No
19. Did you use steroids or other immunosuppressive agents?
    1. Yes (specify) 2. No
20. Were you diagnosed with OIs other than TB or neoplasms before cART initiation?
    1. Yes (specify). 2. No. 3. Unknown
21. WHO clinical stage when HIV was diagnosed?
    1. I. 2. II. 3. III. 4.IV 5. Unknown
22. How long have you been on cART altogether? -------months
23. Was the baseline CD4 count determined before cART initiation?
    1. Yes. 2. No
24. What was the baseline absolute CD4 count? ----- CD4%? -------
25. What was the maximum CD4 count achieved? ------- (specify the time?)
26. What was the baseline HIV viral load in copies per mL?
27. What was the first line cART regime you were given?
    1. 1a- d4T/3TC/LPV/r. 2. 1b- d4T/3TC/EFV. 3. 1c- AZT/3TC/NVP. 4. 1d- AZT/3TC/EFV. 5. 1e- TDF/3TC/EFV. 6. 1f- TDF/3TC + NVP. 7. 1g- ABC+3TC+EFV. 8. 1h- ABC+3TC+NVP 9. 1j- TDF/3TC/DTG 10. Others
28. What was the interval between the initiation of first-line cART and the diagnosis of first-line treatment failure? ------months
29. What was the HIV RNA level when first-line cART failure was diagnosed? -------- copies/mL.
30. What was the second line cART regimen?
    1. 2a- ABC+ddI+ LPV/r. 2. 2b- ABC+ddI+NFV 3. 2c- TDF+ddI+NFV. 4. 2d- TDF+ddI+NFV. 5. 2e- AZT/3TC + LPV/r. 6. 2f- AZT/3TC+ ATV/r 7. 2g- TDF/3TC + LPV/r. 8. 2h- TDF/3TC+ ATV/r 9. 2i- ABC+ 3TC+LPV/r 10. Others (Specify)
31. What was the HIV RNA level when second-line cART treatment failure was diagnosed? -----copies/mL and the time----- years.
32. What is the current third-line regimen?
    1. 3a- DRV/r + DTG + AZT + 3TC
    2. 3b- DRV/r + DTG +TDF+ 3TC
    3. 3d- DRV/r + ABC + 3TC + EFV
    4. Others (specify)
33. How is the patient's adherence described during 3rd-line cART treatment?
    1. Good. 2. Fair 3. Poor 4. Unknown
34. Was TB diagnosed during the course of 3rd line cART?
    1. Yes. 2. No

35. Were the second-line or third-line regimens modified or switched due to toxicity or inconvenience?
    1. Yes. 2. No
36. Did you disclose your HIV status to your partner?
    1. Yes. 2. No
37. What is your partner's HIV status?
    1. Positive 2. Negative. 3. Unknown
38. How do you practice sex with your partner?
    1. Without any barrier 2. With condom. 3. With and without condom. 4. No intercourse
39. If your partner is HIV positive, is he /she taking cART?
    1. Yes. 2. No
40. What is your monthly average income? ------birr
41. Are you currently smoking cigarettes?
    1. Yes. 2. No
42. Are you currently using Khat?
    1. Yes. 2. No
43. Are you currently drinking alcohol?
    1. Yes 2. No
44. Are you using other illicit drugs?
    1. Yes. 2. No

III. Other comorbidities?

45. Diabetes mellitus?
    1. Yes----duration and medications. ----------
    2. No
46. Hypertension?
    1. Yes----duration and medications. ----------
    2. No
47. Chronic HBV infection?
    1. Yes-----when was it diagnosed and HBV DNA levels in copies/mL -------
    2. No
48. Chronic HCV infection?
    1. Yes-----when was it diagnosed and HCV treatment/viral load
    2. No
49. VRDL or RPR status?
    1. Reactive
    2. Non-reactive
50. Dyslipidemia?
    1. Yes------describe the nature and medications
    2. No
51. Do you often suffer from depressive symptoms?
    1. Yes. 2. No
52. Do you usually suffer from anxiety?
    1. Yes. 2. No
53. Were you diagnosed with major psychiatric problems?
    1. Yes----specify the treatment

2. No

54. Physical exam
    1. BP (mmHg) ------
    2. BMI (Kg/m2) -----

IV. Laboratory results and others

55. Genotype resistance testing
    1. Not done. 2. Done and the result--------
56. The last HIV RNA level (in the last 12 months). --------- copies/mL.
57. Any identified drug-drug interaction?
    1. No 2. Yes (Specify)
58. List current medications of the patient. ----------