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Factors associated with recent unsuppressed viral load in HIV-1-infected patients in care on first-line antiretroviral therapy in South Africa

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Abstract

Unsuppressed viral load (VL) in patients on antiretroviral therapy (ART) occurs when treatment fails to suppress a person's VL and is associated with decreased survival and increased HIV transmission. The objective of this study was to evaluate factors associated with unsuppressed VL (VL > 400 copies/ml) in patients currently in care on first-line ART for 6 months attending South African public healthcare facilities. We analysed electronic medical records of ART patients with a VL result on record who started ART between January 2004 and April 2016 from 271 public health facilities. We present descriptive and multivariable logistic regression for unsuppressed VL at last visit using a priori variables. We included 244,370 patients (69% female) on first-line ART in April 2016 for 6 months. Median age at ART start was 33 years (7% were < 15 years old). Median duration on ART was 3.7 years. Adjusting for other variables, factors associated with having an unsuppressed VL at the most recent visit among patients in care included: (1) < 15 years old at ART start (adjusted odds ratio [aOR]=2.58; 95% CI = 2.37, 2.81) versus 15–49 years at ART start, (2) male gender (aOR = 1.29; 95% CI = 1.25, 1.35), (3) 6–12 months on ART versus longer (aOR = 1.34; 95% CI = 1.29, 1.40), (4) on tuberculosis (TB) treatment (aOR = 1.78; 95% CI = 1.48, 2.13), and (5) prior ART exposure versus none (aOR = 1.20; 95% CI = 1.08, 1.32). Approximately 85% of the ART cohort who were in care had achieved viral suppression, though men, youth/adolescents, patients with prior ART exposure, those with short duration of ART, and patients on TB treatment had increased odds of not achieving viral suppression. There is a need to develop and evaluate targeted interventions for ART patients in care who are at high risk of unsuppressed VL.

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Keywords

HIV; AIDS; viral load; viral load suppression; South Africa; antiretroviral therapy; 90–90–90

Introduction

Globally, over 36.7 million people were living with HIV in 2015 (34.0–39.8 million), of which approximately 17 million people (46.3% of those infected with HIV) were on lifesaving antiretroviral therapy (ART).¹ South Africa has the world's largest HIV epidemic with approximately seven million people living with HIV in 2016. An estimated 19.2% of South Africans aged 15–49 years are HIV infected.² South Africa launched its national HIV treatment programme in 2004. By 2016, over 3.4 million people, or 49% of those infected, were being treated with ART.¹

HIV incidence has declined in South Africa from 2.2% among individuals aged 15–49 years in 2005 to 1.9% in 2012, and declined most among youth aged 15–24 from 2.8% in 2005 to 1.5% in 2012.³ Declining HIV incidence and an increased proportion of people on ART in South Africa have led to declines in HIV-related morbidity and mortality. When viral suppression is achieved and maintained, HIV transmission is substantially decreased, as is HIV-associated morbidity and mortality. However, virologic failure and acquired drug resistance may negatively affect these gains. ART failure is diagnosed clinically, immunologically, or virologically. Virologic failure occurs earliest, followed by immunological failure, then clinical failure. If virologic failure is not detected early it can lead to rapid health decline and death.^{4,5} The consequences of untimely detection of unsuppressed viral load (VL), virologic failure, and delay in switching to different ART drug regimens are increased accumulation of drug resistance mutations, limited subsequent treatment options, disease morbidity and mortality. Untimely detection of virologic failure also increases risk of HIV transmission to others.⁶

The World Health Organization (WHO) recommends VL testing as the preferred method for monitoring the clinical response of patients with HIV to ART. WHO recommends routine VL monitoring after six months on ART and then at least every 12 months to detect treatment failure earlier and more accurately.⁴ In patients with unsuppressed VL (e.g. >400 copies/ml), South African National Department of Health⁷ and WHO guidelines recommend adherence counselling and repeat testing.⁴ VL monitoring of patients on ART helps ensure early diagnosis and confirmation of ART failure and enables clinicians to take an appropriate course of action for patient management including transitioning those with drug resistance to expensive and complex second- and third-line ART regimens.

Approximately 14% of patients on first-line ART experience viral failure, defined as the inability to achieve or maintain suppression of viral replication to an HIV RNA level <400 copies/ml.^{8,9} Previous studies in South Africa and other African countries have demonstrated that predictors of first-line ART failure include gender, age, clinic attendance, prior ART exposure, prior prevention of mother-to-child transmission (PMTCT) exposure (South African PMTCT guidelines provided women with single-dose nevirapine [NVP] from 2002 to 2013¹⁰), ART adherence and general health (including baseline CD4 cell

count).^{8,5–17} However, few studies have included patients on ART for >10 years in resource-limited settings. The aim of this study is to evaluate factors associated with unsuppressed VL at a recent clinical visit in a large cohort of patients followed from 2004 in South Africa who were on first-line ART in order to inform interventions to improve adherence, and address viral failure where present, in patients on ART.

Methods

Data source and study population

We conducted a cross-sectional analysis of an observational cohort using routinely collected HIV medical records of patients in care from the BroadReach clinical HIV cohort from 271 public health facilities in five districts in South Africa (Sedibeng in Gauteng Province, Ugu and King Cetshwayo Districts in KwaZulu Natal Province, Alfred Nzo in Eastern Cape Province and Gert Sibande in Mpumalanga Province). The electronic medical record system captures basic information on:

- demographics (e.g. gender, date of birth),
- clinical information (e.g. weight, height, pregnancy status, tuberculosis (TB) symptoms, TB treatment, CD4 cell count, and VL),
- prior ART exposure (e.g. post-exposure prophylaxis, PMTCT, PMTCT and prior ART, or prior ART for >30 days),
 - For the prior ART exposure, a woman who initiated lifelong ART for PMTCT (option B+) would be counted as ‘PMTCT and prior ART’. If a woman initiated monotherapy before option B+, the prior ART exposure was classified as ‘PMTCT’.
- date of clinical and laboratory visits,
- other diagnoses (e.g. TB),
- and type of HIV treatment.

The electronic medical records did not include the date of prior ART exposure (or PMTCT) nor any adherence measures such as pill counts or on time drug pickups.

We included patients who had initiated ART between January 2004 and April 2016 and were on ART for six or more months. We excluded patients who (1) did not have VL results available in the data-set, (2) were no longer in care (defined as not visiting the clinic within six months of last clinical visit), (3) had transferred to another health facility, or (4) died. The standard first-line regimen in South Africa changed over time but as of the date of analysis (April 2016) the first-line regimen included: two nucleoside reverse transcriptase inhibitors (zidovudine or tenofovir (TDF) plus lamivudine or emtricitabine [FTC]) and one non-nucleoside reverse transcriptase inhibitor (either efavirenz [EFV] or NVP). Our analysis does not include information on those who were excluded from our cohort of patients in care (e.g. those without a VL done, those lost to follow-up, those who died). The objective of our study was to compare patients currently in ART care (on first-line ART) who were not

virally suppressed and compare them to other patients in care who were virally suppressed in order to inform interventions among patients in ART care.

Study variables

Factors associated with unsuppressed VL at last clinical visit

Variables came from clinic data at ART initiation and most recent clinic visit, including gender, age at ART start, CD4 cell count at ART start, where initiated ART (e.g. in facility or transferred in from another facility), current age, duration on ART, TB status, pregnancy status at ART start and prior ART exposure (including: >30 days prior ART exposure, ART during pregnancy or post-exposure prophylaxis).

Outcomes

Our primary outcome was an unsuppressed VL among patients currently in care on first-line ART for six or more months. Unsuppressed VL was defined using South African National Department of Health guidelines, as the most recent VL result of >400 copies/ml.⁷ We included time on ART in the multivariable regression models to control for time on ART. Therefore, a patient who previously had a VL >400 copies/ml who continued on first-line ART and was suppressed at the most recent visit would be reported as suppressed in this cross-sectional analysis.

Statistical analysis

Data analysis was carried out using STATA/SE statistical software package version 14.0 (StataCorp., College Station, TX, USA). Because the data were not normally distributed, continuous variables were described as medians and inter-quartile ranges (IQRs). Binary variables were described using frequency and percentages. Logistic regression modelling was used to analyse the contribution of the following variables, selected a priori: gender, age at ART start, current age, CD4 cell count at ART start, exposure to prior ART, method into ART programme, duration on ART and current TB status (e.g. not on treatment, on treatment, symptomatic and not on treatment), to the development of a recent unsuppressed VL.

Results

Study sample

Characteristics of patients on first-line ART for six or more months are shown in Table 1. The study sample consisted of 244,370 patients. Almost three-quarters of patients had initiated ART between 2011 and 2016 (74%) and the remaining patients initiated ART from 2004 to 2011 (26%) (Figure 1). The median age at ART start was 33 years (IQR=27–42 years), while the median current age (at date of analysis, April 2016) was 38 years (IQR = 30–46). Median duration on ART was 3.7 years (IQR = 1.9–5.8). At ART start the median CD4 cell count was 197 cells/mm³ (IQR = 108–312) and the most recent CD4 cell count was 455 cells/mm³ (IQR = 300–637).

After six or more months on ART, 15.3% (n = 37,487) of patients had a VL >400 copies/ml (e.g. unsuppressed VL) at the most recent visit (Table 2). Unsuppressed VL was more common in men than women (18.3% versus 14.0%), and in patients who started ART before 15 years old (31.8% versus 14.3% in patients who initiated between 15 and 49 years and 12.9% in patients who initiated ART when ≥ 50 years old). Approximately 21% of patients with a CD4 cell count of < 100 cells/mm³ at ART start had a recent unsuppressed VL at last VL done, compared with 14.9% of those with a CD4 cell count of ≥ 100 cells/mm³. Almost one-third (32%) of patients on TB treatment had an unsuppressed VL compared to 15.4% of patients not on TB treatment. Over 17% of patients with 30 or more days of prior ART exposure and 20% with post-exposure prophylaxis had a recent unsuppressed VL. This was higher than women who had started ART during pregnancy (12.8% of women with prior PMTCT exposure had unsuppressed VLs).

The odds of an unsuppressed VL in patients in care and on first-line treatment for six or more months are shown in Table 3. In the full multivariate model, the odds of having a recent unsuppressed VL test were greater in men compared to women (adjusted odds ratio [aOR] = 1.29, 95% CI = 1.25, 1.35), younger than 15 years old at ART being initiation (OR = 2.58, 95% CI = 2.37, 2.81) compared to initiating ART at 15–49 years, being on ART for <1 year (aOR = 1.34, 95% CI = 1.29, 1.40) or more than ten years (aOR = 1.62, 95% CI = 1.46, 1.80) compared to an ART duration of 1–5 years, having a CD4 cell count of < 100 (aOR = 1.46, 95% CI = 1.41, 1.52), prior ART exposure (>30 days prior exposure: aOR = 1.20, 95% CI = 1.08, 1.32), and being on TB treatment (aOR = 1.78, 95% CI = 1.48, 2.13) compared to not being on TB treatment. Protective factors against having a recent unsuppressed VL were older age (≥ 50 years = 0.90, 95% CI = 0.87, 0.95) and prior PMTCT exposure (0.90, 95% CI = 0.84, 0.97). Viral suppression by year of ART enrolment is in Figure 1, where 14% of patients who had initiated ART between 2013 and 2015 were not virally suppressed compared to 21% of patients who initiated in 2016 who were not virally suppressed (1527 of 5809 patients).

Discussion

This study evaluated variables associated with an unsuppressed VL in a large cohort of South African patients currently in care and on first-line ART. We found that 85% of patients in care on ART for six or more months with a VL on record were virally suppressed (VL <400 copies/ml). Our analysis demonstrated that factors associated with unsuppressed VL were male gender, initiating ART before 15 years of age, being on ART for less than one year, or more than ten years, having a CD4 cell count of less than 100 at ART start and being on TB treatment.

Of particular concern is the finding that children and adolescents who start ART have increased odds of not achieving viral suppression. This could be due to behavioural factors, like not taking medication daily and as prescribed, or structural issues, like not being able to attend the health facility during the weekday because of school.^{18–22} Other behavioural and structural factors could include alcohol use or exposure to violence. For example, a recent study among Malawian youth found almost half of all adolescents living with HIV reported non-adherence to ART in the past month, and risk factors for poor adherence included

violence in the home, recent alcohol use, and low treatment self-efficacy.²² A recent systematic review and meta-analysis in South Africa found that only 13% of HIV-infected youth (15–24 years old) were on ART and approximately 81% of youth on ART 15–24 were virally suppressed.²¹ Another key reason for poor adherence in children or failure to achieve viral suppression in children is the lack of child-friendly paediatric formulations.^{19,20} There is a need for further research to develop better paediatric formulations with improved palatability and randomised trials to test the newer drugs in adolescent populations.²⁰ Programmes tailored to address barriers to accessing and staying adherent on ART among adolescents living with HIV may help improve adherence to ART, numbers of virally suppressed adolescents with a resulting reduction in transmission.

Our study demonstrated that prior exposure to ART during pregnancy was associated with decreased odds of unsuppressed VL in patients who returned to care after a prior break in care. There were significant changes in the roll-out of HIV prophylaxis and treatment in pregnant women from 2002 to 2016 highlighted below:

- In 2002, South Africa rolled out a national PMTCT programme.
 - NVP was used as the first-line ART as per WHO guidelines.¹⁰
 - The threshold for treatment was CD4 cell count of 350 cells/mm³ or lower.
- In 2012, EFV was recommended over NVP for everyone, including pregnant women.
- In 2013, South Africa changed the guidelines to option B in which all pregnant women could initiate ART regardless of CD4 cell count using a fixed dose combination (FDC) of TDF, FTC, and EFV.¹⁰
- In January 2015, South Africa rolled out option B+ in which all pregnant and breastfeeding women were eligible to initiate lifelong ART.¹⁰

Our sample included women who had initiated ART from 2004 to 2011, when NVP was prescribed, and 2012–2016, when FDCs were given during pregnancy or for life after January 2015 (Option B+). Unfortunately, date of prior PMTCT exposure was not included in the electronic medical records so we do not know when prior ART exposure happened nor what the prior ART regimen was. Research has demonstrated that NVP drug resistance mutations are frequently detected after single-dose NVP, which remain detectable for several months and may affect future treatment of NVP-exposed women and children, especially in the case of recent exposure (6–12 months).^{23,24} The increased odds of achieving viral suppression among women in our study with prior ART exposure may be due to better treatment adherence or frequency of VL monitoring in pregnant and post-partum women.²⁵ Further, our study excluded patients who were no longer in care, had died, or were on second- or third-line ART. Another explanation is that those patients who were excluded may have had increased drug resistance and viral failure, compared to those included in our sample.

Previous studies have found that high rates of viral suppression can be achieved in routine care in South Africa, indicating the effectiveness of recommended ART regimens.²⁶ Our

study confirmed what other studies in South Africa have found, including that factors associated with unsuppressed VL include gender, age, and baseline CD4 cell count.^{8,11,12} Our study also identified that being on TB treatment at time of analysis and VL done and duration on ART (e.g. shorter [≤ 12 months] and longer [>5 years] duration) were risk factors for unsuppressed VL. The HIV Prevention Trials Network 052 trial demonstrated that 93% of participants on ART achieved viral suppression by 12 months and that the annual incidence of viral failure was 3.6%. In our study, patients who had been on ART for one year or longer (e.g. initiated ART from 2012 to 2015) had lower proportions of patients not virally suppressed (14%) compared to patients who initiated ART in 2016 and had their six-month VL test (21% not virally suppressed). Viral suppression was associated with similar factors found in our study including younger age and lower CD4 cell count at ART initiation. Their study also found that lower education level and lack of suppression by three months were also associated with longer time to viral suppression in early ART.²⁷

Risk of HIV transmission to sex partners and infants increases with increasing VL values⁶ as does risk of mortality. There is a need to develop and evaluate specific interventions for patients at high risk of unsuppressed VL including adapted adherence counselling and targeted resistance testing to ensure that patients with acquired drug resistance are on the appropriate ART regimen.

The results of our study can help in identifying risk groups for virologic failure among patients on first-line ART and catalyse the development of improved interventions to those groups. Further, identifying patients at risk of virologic failure allows for targeted adherence interventions and counselling to avoid treatment failure and the need for second- or third-line therapy and more powerful and expensive drugs.

The findings in this study are subject to limitations. First, we only included patients who had a VL on file, and patients currently in care, which may underestimate the true proportion of patients on ART with an unsuppressed VL. Second, our analysis is cross-sectional which does not enable us to evaluate time-varying covariates or confounders which may affect viral suppression over time. Third, the medical records did not include any adherence measures such as pill counts or on-time drug pickups so we cannot evaluate the impact of those subjective measures of adherence on VL suppression.

Conclusion

In our cohort of patients on ART for six or more months, almost 85% had achieved viral suppression, which is in line with South Africa's 90–90–90 targets. Our analysis identified at-risk groups who did not achieve viral suppression within six months or longer on ART, including children and adolescents, men, TB patients and those recently initiated on ART (less than one year), or on ART for ten or more years. Failure to achieve viral suppression in those high-risk patients must be addressed. Interventions such as targeted adherence counselling, differentiated care models (including community-based ART delivery), and targeted resistance testing are required to prevent virologic failure among these patients.

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Figure 1. Number and proportion of patients on ART for >6 months who were virally unsuppressed (by year of ART initiation). ART: antiretroviral therapy; FDC: fixed dose combination; PMTCT: prevention of mother-to-child transmission.

Table 1.

Characteristics of patients on first-line ART for six or more months (n = 244,370).

	Median (IQR)
Age (years)	
At ART start	33 (27–42)
Current	38 (30–46)
CD4 cell count (cells/mm ³)	
At ART start	197 (108–312)
Most recent	455 (300–637)
Viral load (copies/ml)	
On first-line treatment	124 (124–125)
Duration on ART (years)	
On first-line treatment	3.6 (1.9–5.8)

ART: antiretroviral therapy; IQR: inter-quartile range.

Table 2.

Characteristics of virally suppressed (VL < 400) and virally unsuppressed patients on ART for > 6 months (n = 244,370).

	Virally suppressed n = 206,883 (84.7%) n (%)	Virally unsuppressed n = 37,487 (15.3%) n (%)
Gender		
Men	61,793 (81.7)	13,815 (18.3)
Women	145,090 (86.0)	23,672 (14.0)
Age at ART start		
< 15 years	11,173 (68.2)	5221 (31.8)
15–49 years	179,861 (85.7)	29,017 (14.3)
> 50 years	21,849 (87.1)	3249 (12.9)
CD4 cell count at ART start		
100 cells/mm ³	10,164 (79.4)	7832 (20.6)
> 100 cells/mm ³	108,009 (85.1)	18,930 (14.9)
Exposure to prior ART		
No prior exposure	133,624 (84.2)	25,037 (15.8)
Post-exposure prophylaxis (PEP)	285 (80.5)	69 (19.5)
Prevention of mother-to-child-transmission (PMTCT)	10,896 (87.2)	1596 (12.8)
Prior ART exposure >30 days	4392 (82.4)	939 (17.6)
Method into ART programme		
Initiated at facility	98,511 (83.7)	19,191 (16.3)
Transferred from another facility	50,935 (85.7)	8498 (14.3)
Duration on ART		
6–12 months	17,509 (81.7)	3914 (18.3)
1–5 years	124,689 (85.8)	20,577 (14.2)
5–10 years	59,513 (83.3)	11,894 (16.7)
> 10 years	5172 (82.4)	1102 (17.6)
Current TB status		
No TB symptoms	181,194 (84.6)	32,983 (15.4)
With TB symptoms	944 (82.1)	206 (17.9)

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	Virally suppressed n = 206,883 (84.7%) n (%)	Virally unsuppressed n = 37,487 (15.3%) n (%)
On TB treatment	730 (68.1)	342 (31.9)

ART: antiretroviral therapy; VL: viral load.

Table 3.

Odds ratios for virologic failure in patients on first-line treatment for six or more months using logistic regression modelling.

Parameter	Univariate model		Full multivariate model	
	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Male gender (ref. women)	1.36 (1.33–1.40)	<0.001	1.29 (1.25–1.35)	<0.001
Age at ART start (Ref. 15–49 years): < 15 years	2.44 (2.35–2.54)	<0.001	2.58 (2.37–2.81)	<0.001
Age at ART start (ref. 15–49 years): 50 + years	0.77 (0.75–0.80)	<0.001	0.90 (0.87–0.95)	<0.001
Duration on ART (ref. 1–5 years): 6–12 months	1.25 (1.21–1.31)	<0.001	1.34 (1.29–1.40)	<0.001
Duration on ART (1–5 years): 5–10 years	1.15 (1.13–1.18)	<0.001	1.28 (1.23–1.34)	<0.001
Duration on ART (1–5 years): >10 years	1.19 (1.11–1.27)	0.004	1.62 (1.46–1.80)	<0.001
CD4 cell count at ART start (ref. > 100)	1.48 (1.44–1.53)	<0.001	1.46 (1.41–1.52)	<0.001
Initiated at facility (ref. transferred from another facility)	1.17 (1.14–1.20)	<0.001	1.39 (1.33–1.45)	<0.001
TB status: TB symptoms (ref. no symptoms)	1.18 (1.02–1.38)	0.031	1.03 (0.84–1.27)	0.767
TB status: On TB treatment (ref. no symptoms)	2.56 (2.25–2.92)	<0.001	1.78 (1.48–2.13)	<0.001
Prior ART: PEP (ref. no prior exposure to ART)	1.31 (1.01–1.71)	0.041	0.99 (0.64–1.54)	0.961
Prior ART: PMTCT (ref. no prior PMTCT)	0.78 (0.74–0.82)	<0.001	0.90 (0.84–0.97)	0.003
Prior ART: Prior ART >30 days (ref. no prior exposure to ART)	1.15 (1.07–1.23)	0.001	1.20 (1.08–1.32)	0.001

ART: antiretroviral therapy; CI: confidence interval; OR: odds ratio; PEP: post-exposure prophylaxis; PMTCT: prevention of mother-to-child transmission.