Outcomes of patients failing first-line antiretroviral treatment in a decentralised programme led by nurses in the Democratic Republic of Congo

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SECTION 0:

Preamble

Declaration

I, Tinne Gils (GLSTIN002) hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and has not, in whole or in part, been submitted towards another degree, at this university or elsewhere. I empower the university to reproduce for the purpose of research, either the whole or any of portion, of the contents of this dissertation in any manner whatsoever.

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Date: October 17, 2019

Dissertation abstract

Background

Task-shifting of care and first-line treatment for people living with HIV (PLHIV) from doctors to nurses is feasible, effective and acceptable in sub-Saharan Africa. Since first-line resistance to antiretroviral therapy (ART) is increasing, comprehensive HIV care should be informed by viral load (VL) monitoring to ensure timely detection of treatment failure and switch to second-line ART if appropriate. Patients identified with a first elevated VL (FEVL) enter a cycle with extra counselling sessions, VL re-testing, and potential regimen switch, putting additional strain on scarce human resources. However, identification of treatment failure and its management remains largely doctor-led and there are limited results from programmes with nurse-led management of treatment failure.

Health service-delivery in the Democratic Republic of Congo (DRC) is challenging in a weak health system, pressured by epidemics and political unrest. Despite low HIV prevalence in the capital Kinshasa (1.6%), many PLHIV present with advanced disease and early mortality is high. HIV care and treatment, VL testing and second-line switch in decentralised facilities in Kinshasa is exclusively managed by nurses, but results have so far not been documented.

Methods

Patient outcome data in three primary care facilities in Kinshasa, were routinely collected since ART introduction in 2002 and entered in the national Tier.net database. A protocol (Section A: Study protocol) was developed with detailed methods and procedures for a retrospective analysis of patient outcomes after having had a FEVL (≥1000 copies/ml). The protocol includes analysis of predictors for favourable outcomes (i.e. retained and with VL re-suppressed at 12 months after first high VL or administratively censored or transferred with suppressed VL), and analysis of compliance to existing protocols. The protocol received approval by ethics boards of the Ministry of Health of the DRC and the University of Cape Town.

A structured literature review was conducted (Section B: Literature review), critically appraising peer-reviewed publications describing outcomes of PLHIV on ART after first-line

failure in sub-Saharan Africa under programmatic conditions. The review included studies where treatment failure and switch were managed by medical doctors, due to paucity of data of nurse-led management of treatment failure. Predictors for outcomes after failure and switch to second-line were also extracted from available literature.

A journal-ready manuscript (Section C: Manuscript) presents the findings of the analysis conducted on patients with a FEVL in three decentralised nurse-led facilities in Kinshasa, and predictors for favourable outcomes.

Results

Of 294 adults with FEVL who did not switch to second-line before confirmatory VL, 82% had a second VL (VL2) done within 24 months of FEVL at a median (interquartile range [IQR]) of 4.0 (3.1-5.6) months) after FEVL. Among patients with VL2 done, 69% had VL2 ≥1000copies/ml, of whom 75% switched to second-line a median of 1.1 (IQR, 0.7-2.0) months after VL2. Among the 85% of patients who were not deceased, LTFU or transferred out by 6 months after second-line switch, 82% had VL<1000 copies/ml. Results were similar for children. After routine VL implementation, losses in the VL-cascade steps were slightly higher, but timelines for VL2 and switch and correct switch were mostly respected. Undergoing VL2 >6 versus ≤3 months after FEVL and switching 1-3 versus ≤1 month after VL2 ≥ 1000copies/ml were independently associated with lower odds of a favourable outcome.

Conclusion

Exclusively nurse-managed detection of virologic failure and switch to second-line ART in decentralised health facilities yielded acceptable outcomes in our cohort in urban Kinshasa. Early detection and fast switch can help improve retention and viral suppression following virologic failure. Task-shifting along the viral load cascade is a feasible and safe strategy in settings with limited human resources and growing viral resistance.

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Most importantly, I want to thank the nurses who made this study possible, the real heroes of the Congolese health system, and the patients of the Kinshasa clinics, who are too often left behind.

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List of abbreviations

Antiretroviral medicines

3TC	Lamivudine
ABC	Abacavir
AZT	Zidovudine
d4T	Stavudine
ddI	Didanosine
EFV	Efavirenz
LPV/r	Lopinavir/ritonavir
NFV	Nelfinavir
NVP	Nevirapine
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Nonnucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor
RAL	Raltegravir
TDF	Tenofovir

Other abbreviations

a or ^{a}	adjusted
ARV	Anti-Retroviral
ART	Anti-Retroviral Treatment
BMI	Body-mass Index
CF	Clinical Failure
CD4	Cluster of Differentiation 4
CHK	Centre Hospitalier Kabinda
CI	Confidence Interval
DRC	Democratic Republic of Congo
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
EAC	Enhanced Adherence Counselling
FEVL	First Elevated Viral Load
FU	Follow-Up
IF	Immunological failure
IQR	Inter-Quartile Range
IRR	Incidence Rate Ratio
ITT	Intention-To-Treat
LTFU	Loss-To-Follow-Up or Lost-To-Follow-Up
med	median
mo	month/s
MSF	Médecins Sans Frontières

ml	millilitre
mm	millimeter
MeSH	Medical Subject Headings
OI	Opportunistic Infection
OR	Odds Ratio
OT	On Treatment
PLHIV	People Living with HIV
PODI	Community Dispensing Point
Prob	Probability
pyr	person years
re-sup	re-suppressed
RR	Risk Ratio
RIC	Retention In Care
SEVL	Second Elevated Viral Load
SD	Standard Deviation
TB	Tuberculosis
TO	Transferred Out
TAM	Thymidine Analogue Mutation
UNAIDS	Joint United Nations Programme on HIV/AIDS
VF	Virologic Failure
VL	Viral Load
VL1	First Viral Load after ART initiation
VL2	First Viral load after VL1
VS	Viral Suppression
WHO	World Health Organization
wk	week/s
yrs	year/s

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SECTION A:

Protocol

Study Protocol: Nurse-led management of antiretroviral treatment failure: Patient outcomes from Kinshasa, Democratic Republic of Congo.

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Background and justification

Significant progress has been made by many countries to reach the 90-90-90 targets of the Joint United Nations Programme on HIV and AIDS (UNAIDS) (1). The latest estimates of the global so-called 'care cascade', show that 70% of people living with HIV/AIDS (PLWHA) know their status, 77% of them are on antiretroviral treatment (ART) (53% of all PLWHA) and 82% of those on ART (44% of all PLWHA) are virally suppressed (2). Uptake of the 2015 recommendations of the World Health Organisation (WHO) to treat all HIV-positive patients has contributed to the progress, including in sub-Saharan Africa (3). Task-shifting of ART initiation and follow-up to nurses is a strategy that has proven to work for those patients deemed 'stable', i.e. with a suppressed viral load. Not only does it improve access by decentralising care and decongesting facilities, task-shifting has also resulted in non-inferior patient outcomes when compared to doctor-led care of ART patients (4). Nurse managed-care is cost-effective for ART patients and acceptable to patients and doctors (4,5).

Many patients, however, follow a dynamic, non-linear path through this 'cascade of care' and many get lost at every step. In Sub-Sahara Africa, were the burden of HIV is high and many health systems weak, these losses are particularly important, with patients cycling in and out of the different steps throughout their lifetimes (6). Also, while the global focus has been on its first three steps, the 'cascade' fails to account for patients who do not suppress their viral load (VL) (7). In 2013, these were estimated to represent 15% of HIV patients in low-and middle income countries (LMIC) (8). First-line resistance is on the rise in sub-Saharan Africa, and care informed by VL monitoring improves early detection of high VL and appropriate switch to second-line ART (9–11).

Patients identified with a first high VL, who often already face barriers to treatment adherence, enter an even more complex cycle. Additional steps include enhanced adherence counselling (EAC), VL re-testing 3 to 6 months later and switch to second-line treatment depending on the results. Those who re-supress on second-line treatment can re-enter the original cascade (3). Again, patients drop out at every step. Not surprisingly, the complex care for these patients adds an additional burden to the already overstretched health systems with limited medical staff. Still, task-shifting of identification of treatment failure and its management, including initiation of second-line ART, has hardly been documented. A recent study from Lesotho is the first to have described outcomes from a

nurse-led second line cascade, called the 'failure cascade' (7). In this high burden country, nurse-driven decentralised HIV care is the backbone of the HIV programme (12). While patient follow-up was completely nurse-led, the decision to switch and the choice of the second-line regimen were made with support of a medical doctor and needed approval of a national central committee.[1]

The study showed poor results; out of all patients in the Lesotho cohort who had an initial high viral load, only 41% had a suppressed VL at 18 months. Re-suppression after EAC, and timely switch to second-line for those eligible, were associated with better outcomes (7). The poor outcomes are not necessarily nurse-related, as delays in second-line switch by general practitioners were also reported in a large study in South Africa (13). Review data from LMIC showed high rates of virologic failure on second-line treatment even if doctors led care; cumulative proportions were 23% at one year and 38% at three 3 years, but low mortality (14). A multi-centre randomised trial in three West-African cities, reported that 31% of patients did not re-suppress after 1 year on the WHO recommended second-line regimen. VL above 100,000 copies/ml at baseline was associated with more virologic failure (15). In South Africa, Rohr et al. described that only 37% of patients identified with virologic failure switched to second line, and 14% of those experienced virologic failure. In patients with low peak CD4 on first line, delays of switch were associated with higher mortality and more second-line failure (16,17).

In the Democratic Republic of Congo (DRC), despite a low HIV prevalence of 1.2%, nearly 22,000 people died of HIV in 2015 (2). Less than 20% of facilities in the capital city of Kinshasa offer HIV treatment services, and those that do are overcrowded, suffer from medicines stockouts, lack of diagnostic tests and insufficient medical staff (18,19). In the DRC, only 42% of PLWHA are on treatment and 31% of all PLWHA are estimated to suppress their VL (2). HIV care is largely nurse-managed, including ART initiation and second line switch in primary care facilities. In Kinshasa, to further decongest facilities and reduce stigma, patients with supressed VL are referred to patient-managed ART pick-up points in the community with excellent retention in care (20). In 2016, the Ministry of Health adopted a plan to fast-track the HIV response and reach 90-90-90 by 2020, including through immediate treatment for all PLWHA, further decentralisation and task-shifting and improved

[1] Personal correspondence with the author

access to VL testing (21). This will lead to detection of larger numbers of patients being identified with virologic failure, needing decentralised care. So far, exclusive nurse-led second-line initiation and management has not been described.

Increasing cases found with virologic failure, on top of test and treat all policies, increase the need for decentralisation and task shifting, including of second-line care. Research is needed to explore possible benefits and disadvantages of nurse-led management of patients who do not suppress their VL. This study will describe patient outcomes after nurse-led identification and management of treatment failure in urban primary care clinics in Kinshasa.

Aim

The aim of the study is to describe the outcomes throughout the cascade of care of ART patients identified with virologic failure and whose care was led by nurses in public sector MSF supported health care facilities in Kinshasa, DRC, as well as compliance with treatment protocols and outcome predictors.

Objectives

Primary Objective

The primary objective of this study is to describe for patients identified with virologic failure, i.e. at least one viral load ≥1000 copies/ml, between January 2007 and December 2017 and on ART for a minimum of 6 months, proportions at each step of the "failure cascade", i.e. from virologic failure on, as well as treatment outcomes (viral load, retained in care, transferred out, lost-to-follow up (LTFU) and death) at 6, 12, and 24 months (if appropriate) since virologic failure in public sector health care facilities supported by Médecins Sans Frontières (MSF) in Kinshasa.

Secondary Objectives

The secondary objectives are;

i. To describe existing protocols and the implementation of decentralization of care to primary care clinics, nurse led HIV care, and viral load monitoring between 2007 and 2017 in these facilities.
ii. To describe compliance to protocols existing (first viral load (VL1) done, timing of first viral load, second viral load done, timing of second viral load (VL2), timing between detecting virologic failure criteria and second line switch, and correct regimen change) for all patients receiving care in these facilities between 2015 and 2017.
iii. To analyse predictors of favourable treatment outcomes in those patients with at least one viral load of ≥1000 copies/ml.

Methods

Study Design

This is a retrospective cohort analysis, through examination of routinely collected clinical information from patients who have received care at three public health care facilities supported by MSF in the city of Kinshasa.

Study Setting

The study data will be collected from three urban primary care facilities supported by MSF in the capital city of the DRC, Kinshasa. All HIV-care in these facilities is exclusively provided by nurses. The HIV prevalence of 1.6% in the capital is higher than the national average (1.2%) (21).

MSF has been providing HIV services in Kinshasa since 1996 and ART since 2002. Initiation and follow-up of ART patients has been decentralised to nurse-led primary care facilities since 2008 and follow-up to community pick-up points since 2010 (20). Routine VL monitoring was implemented in 2015 in MSF supported primary care facilities.

Before 2015, identification of treatment failure was based on clinical and/or immunological criteria confirmed with targeted viral load testing. Routine monitoring was done exclusively with CD4-count and clinical assessment. A viral load platform, installed at the MSF referral hospital, has been functional since mid-2015. The initial routine viral load protocol prescribed that all newly initiated patients on ART receive a VL test at six months in care (or when coming for a routine clinical visit if on ART for longer), and yearly afterwards. Patients with a first VL ≥1000 copies/ml (VL1) should receive EAC. EAC consists of two meetings with a counsellor; one at return of VL1 results, and one a month later at ART pick-up. In the first session, particular attention is given to exploration of the patients' barriers to adherence and potential solutions, while in the second session the solutions are evaluated and emotional barriers are further explored. The patients then get re-tested (VL2) three months after VL1. If the second VL is not below 1000 copies/ml, patients are switched to second line ART as soon as possible. Patients with a viral load of <1000 copies/ml were referred to a facility fast-track circuit or a community pick-up point for medicines pick-up between VL tests. Since January 2017 the protocol was adapted to a first VL at three months on ART. Phone-based follow-up was implemented for all routine or follow-up VL tests.

Study Population and Period

For the primary objective, the study population includes all ART patients enrolled at one of three decentralised MSF-supported and nurse-managed primary care facilities, who had been on ART for a minimum of six months by December 2017 and had been identified as having immunological or clinical failure or with at least one VL of ≥1000 copies/ml in the city of Kinshasa between January 2007 until December 2017. Follow-up data will be collected until the end of 2017. From the same population, those for whom outcome data are available (i.e. excluding no VL result or transferred out) will be subject to analyse predictors for a favourable outcome (secondary objective (iii)).

For secondary objective (ii), the entire ART cohort enrolled in the three facilities between January 2015 until December 2017 will be included, regardless of VL failure status, in order to assess the compliance with a first viral load done for all patients. In October 2017, the complete cohort was around 1400 patients.

Data variables and definitions

Primary objective: *To describe for patients identified with virologic failure, i.e. at least one viral load ≥1000 copies/ml, between January 2007 and December 2017 and on ART for a minimum of 6 months, proportions at each step of the "failure cascade", i.e. from virologic failure on, as well as treatment outcomes (viral load, retained in care, transferred out, lost-to-follow up (LTFU) and death) at 6, 12, and 24 months (if appropriate) since virologic failure in public sector MSF supported health care facilities in Kinshasa.*

Patient outcome variables will be collected at 6, 12 and 24 months after initial high VL, where possible. Patients will be classified into one of the following categories after VL1 ≥1000 copies/ml;

- VL not done or no results
- Switched to second line
- VL2 done and results available, further divided into;
    - VL 2 ≥1000 copies/ml, further divided into;
        - Switched to second line
        - Not switched
    - VL 2 <1000 copies/ml, further divided into;
        - Referred to fast-track
        - Referred to PODI
        - Remained in normal care

In each of those categories the patient outcomes will be measured and classified as one of the following:

- Retained in care with supressed viral load (<1000 copies/ml)
- Retained in care with unsuppressed viral load (≥1000 copies/ml)
- Retained in care with viral load status unknown
- Death, as confirmed by a family or community member after phone follow-up
- Transferred out, to a clinic outside the MSF supported clinics, as confirmed by the patient in writing
- Lost-to-follow-up (LTFU), when a patient did not return for a follow-up visit 90 days after the scheduled visit and the reason could not be confirmed

To know the patient's position in the cascade the following variables will be collected:

- Date of ART initiation
- If patient had a VL1, date of VL1
- If the patient had a VL2, date of VL2
- If the patient was switched to second-line ART, date of switch to second-line ART
- For patients with re-supressed VL, whether they were referred to a community distribution point (PODI), a fast track system or remained in regular care

A dummy figure to present the patient flow for the outcomes is added in Appendix 1. The outcomes for patients with at least one VL >1000 copies/ml (primary objective) are shown in blue.

Secondary objective (i): *To describe existing protocols and the implementation of decentralization of care to primary care clinics, nurse led HIV care, and viral load monitoring between 2007 and 2017 in these facilities.*

Descriptive information will be used for the narrative of implementation.

Secondary objective (ii): *To describe compliance to protocols existing (first viral load (VL1) done, timing of first viral load, timing of second viral load (VL2), timing between detecting virologic failure criteria and second line switch, correct regimen change) for all patients receiving care in these facilities between 2015 and 2017.*

All patients on ART between 2015 and 2017 will be considered and will be classified into one of the following categories;

- On ART < 6 months in December 2017
- On ART ≥ 6 months in December 2017, further divided into;
    - VL not done or no results
    - VL1 done and results available, further divided into;
        - VL1 < 1000 copies/ml
        - VL1 ≥1000 copies/ml;

Like for the primary objective, patients will be classified into one of the following categories after VL1 ≥1000 copies/ml;

- VL2 not done or no results

- Switched to second line
- VL2 done and results available, further divided into;
    - VL 2 ≥1000 copies/ml, further divided into;
        - Switched to second line
        - Not switched
    - VL 2 <1000 copies/ml, further divided into;
        - Referred to fast-track
        - Referred to PODI
        - Remained in normal care

In addition to the data collected for the primary objective, the time to the next step in the cascade and completion rates will be calculated and compared to existing protocols at that time to analyse compliance.

The dummy figure 2 in appendix 2 shows the patient flow for the secondary objective (ii).

Secondary objective (iii)**:** *To analyse predictors of favourable treatment outcomes in those patients with at least one a VL >1000 copies/ml.*

Additional variables to be collected (where appropriate) include:

- Patient age at initiation on ART
- Patient age at VL1
- Patient gender
- Results of VL1
- Results of VL2
- Facility where enrolled
- First-line ART treatment regimen
- Second-line ART treatment regimen
- Previous ART exposure
- Time on ART at VL1
- CD4 at ART initiation and at VL1
- Delay between diagnosis of virologic failure and initiation of second line ART

A favourable outcome will be defined as retained and suppressed, including those 'retained in care with suppressed viral load' in one of the MSF supported facilities. All other outcomes are classified as 'not retained or suppressed' and include the other outcome possibilities. The analysis will be restricted to those for whom a result is available. The cut-off for availability of VL2 will be put at 12 months.

Indicators that will be explored as possible predictors for a favourable outcome, when possible;

- Patients age at ART initiation and at VL1, gender, ART regimen, facility, VL result known
- VL1 result, VL2 done or not, VL2 result
- Time from VL1 $\geq$ 1000 copies/ml to VL2
- Time between diagnosis of treatment failure (VL2$\geq$1000 copies/ml) and initiation of second line ART
- Previous ART exposure
- CD4 at ART initiation
- Time on ART at VL1, CD4 at VL1

Research procedures and data collection methods

All quantitative data used in this study will already have been collected as part of routine clinical patient follow-up and reporting. Routine clinical data and patient characteristics will have been entered by nurses into each patient's medical record. Viral load measurements will have been done by Abbott® Real-Time Viral Load at the MSF referral hospital, after sample collection in the facility, transported as a dried blood spot. Viral load results will have arrived at the facility as a paper document and are kept in an excel based database. Data clerks daily enter all patient data from the different paper-based clinical record into the MSF project database, the national standard Tier.Net (Tier.Net v1.2.2., 2011). Once the record is entered into MSF project databases, it is de-identified and the patient is assigned an anonymous patient number. Data cleaning on-site will be done to check for inconsistencies in data entry and responses. De-identified patient information will be extracted from the Tier.net database into a specific study excel database.

Descriptive information on the history and chronology of implementation of the different programme aspects will be gathered from review of existing literature, including grey literature, MSF programme documents, and guidelines and documents from the Ministry of Health (MoH). Interviews with key MSF and MoH staff will be conducted to complete the information.

Statistical analysis

All analyses will be performed using Stata/IC 14.1 (StataCorp, Stata Statistical Software: College Station, TX). Participants' baseline characteristics and treatment outcomes at different points in time will be assessed using means with their standard deviations (SD), or medians with corresponding interquartile ranges (IQR) for continuous variables, and frequencies and proportions for categorical data. Comparisons of means and medians will be calculated using t-test or the ANOVA and nonparametric k-sample tests respectively. Differences in proportions between groups will be reported using chi-squared tests or Fisher's exact as appropriate. Multivariate logistic regression will be used for analysis of fixed outcomes predictors. Cox-regression will be used to analyse time bound outcome predictors. A two-sided alpha <0.05 threshold will be considered as statistically significant for all analyses.

Ethical considerations

Ethical approval

The data are routinely collected for programme monitoring and evaluation of the national HIV programme in the DRC and patients enrolling for routine care are not asked for informed consent. Beyond submission to the Institutional Review Board (IRB) of the Ministry of Health in the DRC, full ethics exemption for routinely collected data will be sought from the MSF Ethical Review Board. The protocol will also be submitted for expedited review to the IRB of the University of Cape Town. The principal investigator is responsible for the overall ethical compliance of the study. The study will be conducted in accordance with the

Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-related Research Involving Human Subjects (22) and International Ethical Guidelines for Epidemiological Studies (23). We commit to sharing study results with participants of the study or clinicians who treat them.

Risks and benefits

This retrospective analysis does not cause any physical harm to participants, who did not receive differential treatment as compared to other patients in the DRC, resulting from this study. Nevertheless, use of medical data beyond the immediate clinical care exposes the patient to possible breaches of confidentiality, including the patients' HIV status. Evaluation of nurse adherence to protocols entails a possible risk of negative feedback for those nurses who do not adhere optimally. We plan to mitigate these risks by anonymizing data and allowing only investigators access to data and databases. Facility names will also be coded so that individual facilities cannot be identified in any research outputs.

There are potential benefits for the study participants and for care and treatment for ART patients in general. A better understanding of risk factors for adverse outcomes in second line patients and protocol implementation may lead to better care and patients' outcomes in the included facilities, the DRC and beyond. As there is currently a gap in the literature on nurse-managed care for second-line patients, the results of this study are of key importance for policy and practice nationally and internationally.

Privacy and confidentiality

Investigators who will do the analysis will receive the secondary data anonymised and coded. Participants' names will thus not be used in this study and only aggregate data will be presented. Facility names will not be made public but will be coded. Confidentiality will be maintained by keeping data collection forms locked in a secure cabinet, while the electronic data file will be kept in a password and firewall protected computer. Forms, lists, logbooks and any other lists that link participant codes to other identifying information will

be stored in a separate, locked file in an area with limited access. Data sets will be maintained securely for five years after completion of the study.

Collaborative partnerships

The study will involve collaborating partners from the National HIV programme at the Congolese Ministry of Health. Representatives of the collaborative institutions will be represented on the study manuscript and any publication.

Dissemination

The results of this study will be presented in local and national stakeholder meetings and will be made available to patients and health care workers of the participating facilities. The manuscript will be submitted for publication in a peer-reviewed journal and the findings might be presented at national and international conferences.

Timetable

Table 1 presents the planned timeline for the consequent steps in the finalisation of the mini-dissertation and manuscript.

Table 1: Timetable for finalisation of mini-dissertation and manuscript

	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18
Protocol Preparation	■	■									
Protocol draft to supervisors			■								
Supervisors feedback				■	■						
Protocol Ethical & Departmental Review							■				
Literature review							■				
Data manipulation & Analysis							■	■			
Write-up								■	■		
Submission to UCT									■		
Journal submission											■

Budget

The study will be done using secondary analysis of routinely collected data and no additional costs are anticipated during the study. The student researcher will perform the data manipulation, analysis and write-up free of charge.

References

1. UNAIDS. 90-90-90. An ambitious target to help end the AIDS epidemic. [Internet]. 2014 [cited 2019 Feb 9]. Available from: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf

2. UNAIDS. Progress towards the 90-90-90 targets| 2017 [Internet]. Geneva; 2017 [cited 2019 Feb 9]. Available from: http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf

3. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach [Internet]. 2016 [cited 2019 Feb 9]. Available from: https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf;jsessionid=6F5FC0BC34E6F336F355F9B5DB1C9B6B?sequence=1

4. Kredo T, Adeniyi FBFB, Bateganya M, Pienaar EDED. Task shifting from doctors to non-doctors for initiation and maintenance of antiretroviral therapy (Review). Cochrane Database Syst Rev. 2014;(7).

5. Zachariah R, Ford N, Philips M, S.Lynch, Massaquoi M, Janssens V, et al. Task shifting in HIV/AIDS: opportunities, challenges and proposed actions for sub-Saharan Africa. Trans R Soc Trop Med Hyg. 2009;103(6):549–58.

6. Kranzer K, Govindasamy D, Ford N, Johnston V, Lawn SD. Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review. J Int AIDS Soc. 2012;15(2).

7. Labhardt ND, Ringera I, Lejone TI, Cheleboi M, Wagner S, Muhairwe J, et al. When patients fail UNAIDS' last 90 - the "failure cascade" beyond 90-90-90 in rural Lesotho, Southern Africa: a prospective cohort study. J Int AIDS Soc. 2017;20(1):1–10.

8. McMahon JH, Elliott JH, Bertagnolio S, Kubiak R, Jordan MR. Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries: A systematic review. Bull World Health Organ. 2013;91(5):377–85.

9. Hamers RL, Sigaloff KCE, Kityo C, Mugyenyi P, de Wit TFR. Emerging HIV-1 drug resistance after roll-out of antiretroviral therapy in sub-Saharan Africa. Curr Opin HIV AIDS. 2013;8(1):19–26.

10. Boerma RS, Sigaloff KCE, Akanmu AS, Inzaule S, Boele van Hensbroek M, Rinke de Wit TF, et al. Alarming increase in pretreatment HIV drug resistance in children living in sub-Saharan Africa: a systematic review and meta-analysis. J Antimicrob Chemother. 2017 Feb;72(2):365–71.

11. Bain LE, Nkoke C, Noubiap JJN. UNAIDS 90–90–90 targets to end the AIDS epidemic by 2020 are not realistic: comment on "Can the UNAIDS 90–90–90 target be achieved? A systematic analysis of national HIV treatment cascades." BMJ Glob Heal. 2017;2(2):e000227.

12. Cohen R, Lynch S, Bygrave H, Eggers E, Vlahakis N, Hilderbrand K, et al. Antiretroviral treatment outcomes from a nurse-driven, community-supported HIV/AIDS treatment programme in rural Lesotho: observational cohort assessment at two years. J Int AIDS Soc. 2009 Oct 8;12:23.

13. Johnston V, Fielding KL, Churchyard G. Outcomes Following Virological Failure and Predictors of Switching to Second-line Antiretroviral Therapy in a South African Treatment Programme. JAIDS. 2013;61(3):1–19.

14. Ajose O, Mookerjee S, Mills EJ, Boulle A, Ford N. Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. AIDS. 2012;26(8):929–38.

15. Ciaffi L, Koulla-Shiro S, Sawadogo A, le Moing V, Eymard-Duvernay S, Izard S, et al. Efficacy and safety of three second-line antiretroviral regimens in HIV-infected patients in Africa. Aids. 2015;29(12):1473–81.

16. Rohr JK, Ive P, Robert Horsburgh C, Berhanu R, Shearer K, Maskew M, et al. Marginal structural models to assess delays in second-line HIV treatment initiation in South Africa. PLoS One. 2016;11(8).

17. Johnston V, Fielding K, Charalambous S, Mampho M, Churchyard G, Phillips A, et al. Second-line antiretroviral therapy in a workplace and community-based treatment programme in South Africa: Determinants of virological outcome. PLoS One. 2012;7(5).

18. WHO. The Democratic Republic of the Congo: quantifying the crisis. Bull World Heal Organ. 2009;87:6–7.

19. Gils T, Bossard C, Verdonck K, Owiti P, Casteels I, Mashako M, et al. Stockouts of HIV commodities in public health facilities in Kinshasa: Barriers to end HIV. PLoS One. 2018;13(1):e0191294.

20. Vogt F, Kalenga L, Lukela J, Salumu F, Diallo I, Nico E, et al. Decentralizing ART supply for stable HIV patients to community-based distribution centres: Programme outcomes from an urban context in Kinshasa, DRC. JAIDS. 2016;74(3):1.

21. Programme National de la lutte contre le SIDA. Plan d'urgence traitement ARV. Kinshasa; 2016.

22. CIOMS W. International Ethical Guidelines for Health-related Research Involving Humans [Internet]. Geneva; 2016 [cited 2017 Oct 24]. Available from: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

23. CIOMS. International Ethical Guidelines for Epidemiological Studies [Internet]. Geneva; 2009 [cited 2017 Oct 24]. Available from: https://cioms.ch/wp-content/uploads/2017/01/International_Ethical_Guidelines_LR.pdf

Post manuscript

A number of changes were made to the study that deviate from the original protocol, none of which had ethical implication for patients.

Secondary objective (i)

We did not include secondary objective (i) in the final manuscript as an outcome but added it as part of the setting in the methods section.

Timelines

Due to unanticipated operational delays, and delays in obtaining approval from the relevant ethics bodies, the time schedule was delayed with six months.

Enhanced adherence counselling

We did not analyse proportions of patients who went through EAC, as these data were not available in the Tier.net database.

Fast-track, PODI

We did not report on referrals to fast-track re-fills or PODIs, as these data were not available in the Tier.net database.

SECTION B:

Literature Review

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Introduction

Sub-Saharan Africa carries the highest burden of HIV in the world, and the largest gap in qualified health personnel (1). Cohorts of people living with HIV (PLHIV) requiring lifelong follow-up are growing, due to better diagnostics and provision of antiretroviral treatment (ART) regardless of immunological status. Global focus has been on increasing the number of patients who are stable in the "cascade of care" (i.e. 90% of PLHIV know their status, 90% of these are on treatment, and 90% of those suppress the virus) (2). However, rising resistance to first-line ART has led to growing numbers of patients who enter the "viral load (VL) cascade", i.e. VL testing, adherence sessions, re-testing and regimen changes, particularly in sub-Saharan Africa (3–5). While the World Health Organization (WHO) recommends task shifting of first-line HIV care to nurses, management of the VL-cascade and the decision to switch is still reserved for medical doctors in most African countries (1) .

30% of the worlds AIDS-related deaths and 21% of all new HIV-infections, occur in West- and Central Africa, where treatment coverage was 39% and viral suppression 29% among all PLHIV in 2017 (2,6). All countries in the region are considered low HIV-prevalence (<5%), and HIV competes with other health conditions in terms of financial support, infrastructure and human resources (7). In the Democratic Republic of Congo (DRC), a challenging country to provide health services, VL testing and second-line switch is fully nurse-led in decentralised facilities (8,9). The ministry of health is scaling up routine VL testing and treatment for all PLHIV since 2016 (10).

Benefits of task-shifting and decentralisation of first-line care have been reported, as well as patient outcomes when follow-up after treatment failure is doctor-led (11–13). We propose a study evaluating outcomes from patients after a first elevated VL (FEVL) in an exclusively nurse-managed and decentralised cohort in the DRC (Section A). A literature review is conducted focusing on African studies describing patient outcomes after first-line failure, in observational cohorts, either nurse-or doctor-led.

Objectives

This literature review aims to examine existing literature presenting outcomes, and their determinants, of PLHIV along the VL-cascade in routine settings, in order to put the

proposed study (Section A) into a context of current academic evidence. We focus on mortality, retention in care and virologic outcomes.

The objectives of the review are, for African cohorts,

- To identify all published literature with focus on treatment outcomes of PLHIV along the cascade after first-line failure and predictors for those outcomes
- To appraise the identified evidence in terms of availability, quality and comparability, allowing for critical interpretation of the results,
- To summarize the results, interpret the findings and identify areas where additional research is needed.

Search strategy

A search was conducted using the PubMed interface (United Status National Library of Medicine, National Institutes of Health) of the Medline digital archive using a combination Medical Subject Headings (MeSH) and keywords. No language restriction was applied. The search included published articles until June 30, 2018. The following search terms were used:

Table 1: Search terms for literature review

	((HIV [MeSH] OR HIV Infections [MeSH] OR HIV OR human immune deficiency syndrome OR acquired immune deficiency syndrome OR immunodeficiency syndrome OR HIV/AIDS OR AIDS)
	OR
	(Antiretroviral Therapy, Highly Active [MeSH] OR Anti-HIV Agents [MeSH] OR antiretroviral OR anti-retroviral OR antiviral OR anti-HIV OR anti-HIV OR HAART OR ARV OR ART))
AND	(("second-line outcomes " OR "outcomes after high viral load" OR "second-line treatment outcomes")
	OR
	(Treatment Failure [MeSH] OR Second-line therapy [MeSH] OR second-line therapy OR therapy switch OR treatment failure OR virologic failure OR high viral load OR drug resistance)
	OR
	(cascade of failure OR failure cascade OR second-line cascade OR viral load cascade))
AND	(Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Canary Islands OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Democratic Republic of Congo OR DRC OR Djibouti OR Egypt OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Ivory Coast OR “Cote d'Ivoire” OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR “Sao Tome'' OR Senegal OR Seychelles OR ''Sierra Leone'' OR Somalia OR St Helena OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR ''Western Sahara'' OR Zaire OR Zambia OR Zimbabwe)

Inclusion and exclusion criteria

Inclusion criteria:

- Observational cohort studies in Africa reporting patient outcomes after virologic (VF), immunological (IF) or clinical failure (CF) on first-line treatment
- Earliest start of follow-up was any time from ART start to second-line switch
- ≥1 patient followed after switch to second-line

Exclusion criteria:

- Observation start at/after treatment failure on second-line
- If follow-up started at switch, studies only reporting comparative outcomes between different regimens and not overall outcomes, studies limited to children, and publications limited to TB/HIV co-infected patients were excluded.

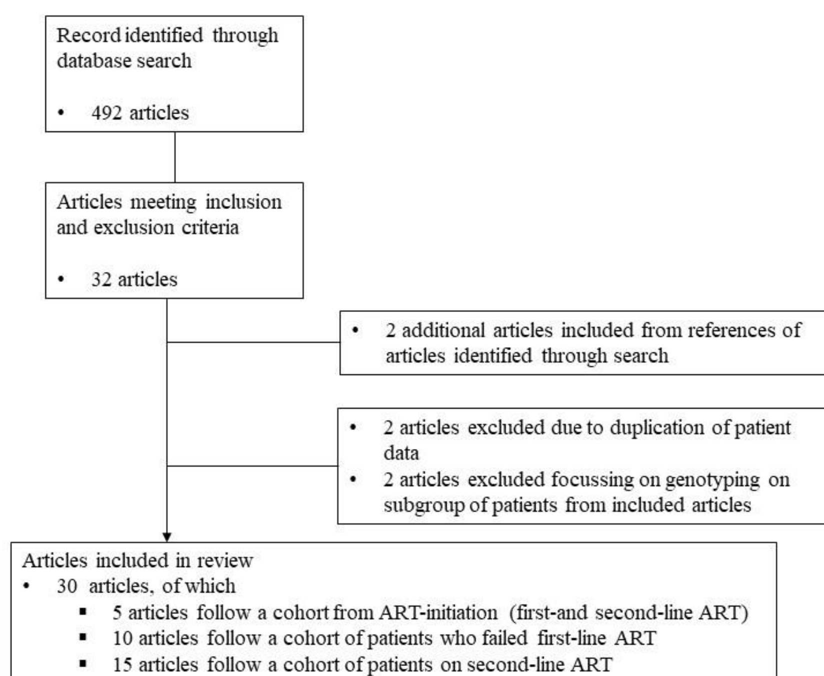

Figure 1: Flow diagram for selection of articles for literature review
ART = antiretroviral treatment

492 articles yielded though the search were scanned by examination of the abstracts; 32 of these met the inclusion criteria (Figure 1). Two additional articles were included based on

the references from articles found with the search criteria. Two articles were excluded due to overlap with another included article (14,15). Two articles which included patients from a second paper by the same author, focusing on genotyping, are discussed but not tabulated (16,17). 30 articles were thus retained.

Characteristics of included studies

Focus in the cascade and general aim

Five included studies follow cohorts through the entire cascade from ART initiation until clinical or virologic outcomes after switch to second-line (Table 1.A). Three of these focused on long-term outcomes (4-10 years) for all patients, including those switched (18–20). The two others were comparative cohort studies, focusing on the impact of switch to second-line on mortality (21,22). Ten articles enrolled patients at FEVL (3,23–26), confirmed virologic failure (VF) (27–29), or immunological failure (IF) (30,31) until ≥1 patient had outcomes after second-line switch (Table 1.B). These articles will be most comparable in scope to the results of our protocol, in particular two covering the full VL-cascade (3,32). The studies mainly focused on the impact of switch (30,31), or delays in switch on clinical outcomes (25,26,29), and one on predictors for switch (27). The remaining 15 articles included cohorts of patients on second-line and report outcomes (Table 1.C).

Role of nurses

11 articles specified in their methods which cadre was responsible for the management of patients. Two articles from the same cohort in Lesotho, specified that care was nurse-led, but switch to second-line required approval by a second-line committee (3,23)[2]. Four articles specified nurse-led programmes (18,33), or including nurse-led clinics (27,34) with management of virologic failure and switch to second-line by doctors. A multi-centered study wrote that nurses, clinical officers or physicians provided care (35). Other authors specified care was provided by medical doctors (21,36), clinicians (29), or that a clinical team was responsible for switch (37). Other studies did not report on the staff cadre managing patients.

[2] clarified through personal correspondence with the author Labhardt, November 2017.

Study setting, population and period

All studies were from sub-Saharan Africa. Five studies including >1 country (range 2-13), one of which included Asian countries (35), presented only overall and not individual country outcomes (22,26,31,38). 13 studies were from South Africa, four more included South Africa among other countries (22,26,35,38) . Six other studies included cohorts in other Southern African countries with an high HIV-prevalence (>10%) (6); in Uganda (29,39), Lesotho (3,23), Malawi (28) and Malawi and Zambia (31). Three cohort studies were conducted in the West- and Central African region[3] (in Senegal (20) and Nigeria (37,40)), and three others included countries from that region among other countries (22,35,38). The remaining studies were from East-Africa (21,30,33,41). Routine conditions in urban Congo probably compare best to other countries in West-and Central Africa for delivery of HIV services. 10 studies were from urban, five peri-urban, and four from rural settings. The Senegalese and Nigerian cohorts, followed by East-African contexts, present a closer contextual comparison to DRC compared to Southern African countries with more advanced HIV-programmes (2). Patients were recruited between 1998 and 2015. Over time, access to VL monitoring and second-line regimens has increased, with many countries shifting from targeted to routine VL monitoring. Earlier studies had more opportunity for longer follow-up. The most recent studies and those covering cohorts in a similar period (2007-2017) are preferred for comparison with our results.

Study design and follow-up

18 studies used retrospectively collected data, all others gathered data prospectively. Prospectively collected studies have a quality advantage, because researchers can *a priori* decide on data to be collected and how to limit the above biases. Follow-up from ART initiation ranged from two to 10 years (Table 4), with follow-up from treatment failure between 24 weeks and around two years. Cohorts starting observation from second-line had 6-36 months follow-up.

[3] I used the United Nations denomination of West-and Central Africa for the region containing 25 countries which have with low HIV-prevalence (<5%), low HIV-coverage (39%), and competing health priorities in common (6).

Criteria for switch to second-line

Criteria for switch to second-line ART are site-and time-dependent, varying e.g. with adoption of WHO guidelines and availability of diagnostic tools. Two studies relied only on IF as switch criteria (30,31). Three studies with different sites used site-specific criteria (22,35,38), four reported that any reason for switch (VF, IF, CF or first-line toxicity) was included (33,37,40,41). Two studies allowed either IF or VF as switch-criteria (20,21), and all other studies based switch on VF; targeted (28,39), one elevated VL (19,42) and toxicity (36) or two elevated VL results, with different thresholds (80-5000 copies/ml) (3,18,23). One study required genotyping results to confirm resistance (24).

Results and discussion

The results are divided up in four parts; characteristics of included patients (Table 3), descriptive proportions of outcomes along the cascade (Table 4), outcomes at different time-points (Table 5), and outcome predictors (Table 6). Table 5.A and 6.A report outcomes after treatment failure, table 5.B and 6.B report outcomes measured after second-line switch, with some articles included twice.

Patient characteristics

Characteristics presented are only those patients with high VL or confirmed VF (Table 2.A), and those on second-line (Table 2.B).

Table 2: Characteristics of included studies

A. Studies including all ART patients and those who fail first-line ART
B. Studies restricted to patients who fail first-line ART
C. Studies restricted to patients who switch to second-line ART

Table 2.A

[a]Côte d'Ivoire, Kenya, Malawi, Rwanda, Senegal, South Africa, Uganda, Zimbabwe

Reference	Study setting and period	Design	Sample size	Inclusion and exclusion criteria (excl.)	Criteria for switch to second-line
Barth et al. 2011 (19)	Rural South Africa, clinic	Retrospective cohort	735 on ART 117 (20% of 583 who > 3 mo FU) failure	-initiated on ART	-1 VL≥ 1000 copies/ml > 3 months after initiation
Boulle et al. 2010 (18)	Peri-urban South Africa, clinics, 2001 - 2007	Prospective cohort	7,323 on ART 152 (14% of RIC at 5 years) failure	-ART-naive at initiation	-2 VL≥ 5000 copies/ml
De Beaudrap et al. 2013 (20)	Senegal, 1998 - 2010	Prospective cohort	366 on ART 79 (24% of those with initial virologic success) failure	-initiated on 2 NRTI +PI/NNRTI - ≥ 6 mo FU - ≥1 VL done after baseline VL	after initial VL <500 copies/ml: -2 consecutive VL ≥1000 copies/ml or -1 VL ≥1000 copies/ml & CD4 & 50% drop in CD4-peak value/ return to ≤ pre-ART CD4 or 1 VL ≥5000 copies/ml
Hawkins et al. 2017 (21)	Urban Tanzania, clinics, initiated 2004-2012	Prospective cohort	47,296 on ART 9,248 (10%) failure	- ≥ 15years - on first-line ART 24 wk after initiation	-1 VL > 10,000 copies/ml ≥ 24 wk on ART and/or -50% drop in CD4-peak value / return to ≤ pre-ART CD4
Keiser et al. 2011 (22)	11 urban programmes in 8 countries[a] initiated 2002 - 2006	Retrospective cohort	16,591 on ART 705 (4%) failure	- ≥ 16 years - ART-naive at initiation - initiation with NNRTI - ≥ 6 mo FU	Site-dependent IF /VF

Table 2.B

[b]All patients on ART were included in descriptive outcomes, but only those with failure were included in analysis

Reference	Study setting and period	Design	Sample size	Inclusion and exclusion criteria (excl.)	Criteria for switch to second-line
Gsponer et al. 2012 (31)	Urban Malawi, Zambia, hospitals, 2004-2009	Retrospective cohort	2,411 (3% of 80,937 on ART)	- > 16 years - IF	- 50% drop in CD4-peak value / return to ≤ pre-ART CD4 / CD4 staying persistently <100 cells/ mm^3
Hosseinipour et al. 2010 (28)	Urban Malawi, clinics 2006 - 2008	Prospective cohort	106 (1.3% of 8,000 on ART)	- > 13 years - VL > 400 copies/ml on first-line after suspicion of failure excl: declined switch	Targeted VL > 400 copies/ml
Johnston et al. 2013 (27)[b]	Urban, peri-urban South Africa, clinics, initiated 2003 - 2008	Retrospective cohort	1,867 (18% of 10,402 with VL) 13,537 on ART	- ≥ 15 years - ≥ 6 mo FU excl: patients from clinics with < 50 patients	Routine VL, 2 VL >1000 copies/ml within 9 mo
Labhardt et al. 2017 (3)	Rural Lesotho, clinics 2014 - 2015	Prospective cohort	138 (8.8% of 1,563 with VL)	- ≥ 16 years - ≥ 6 mo on NNRTI-regimen - First VL≥ 80 copies/ml excl: 7 days ART interruption in 3 mo	Routine VL1 ≥ 80 copies/ml, EAC, VL2 after 3 months ≥ 80 copies/ml
Lejone et al. 2017 (23)	Rural Lesotho, clinics 2014 - 2015	Prospective cohort	53 (28% of 191 with VL)	- <16 years - ≥ 6 mo on NNRTI-regimen	Routine VL1 ≥ 80 copies/ml, EAC, VL2 after 3 months ≥ 80 copies/ml

				Inclusion and exclusion criteria	Criteria for switch
				- First VL≥ 80 copies/ml excl: 7 days ART interruption in 3 months	
Murphy et al. 2010 (24)	Peri-urban South Africa, Hospital 2004 - 2006	Prospective cohort	141	- adults -1 VL≥ 1000 copies/ml = > 3 months after initiation excl: history of mono-or dual therapy	1 VL≥ 1000 copies/ml > 3 months after initiation & major mutation confirmed by genotyping
Petersen et al. 2014 (26)	Urban Uganda & South Africa, clinics Initiated 2002-2011	Prospective cohort	823 (10% of 7,975 on ART)	- on NNRTI-regimen - 2 failing VL >16 weeks after initiation	Routine VL, 2 consecutive VL >1000 copies/ml between 12-24 wk or >400 copies/ml > 24 wk after initiation (≤ 9 mo apart)
Ramadhani et al. 2016 (30)	Tanzania, hospital, 2004 – 2013	Retrospective cohort	637	- adolescents and adults - IF	- 50% drop in CD4-peak value / return to ≤ pre-ART CD4 / CD4 staying persistently <100 cells/ mm3
Rohr et al. 2016 (25)	South Africa, clinics, 2004-2014	Retrospective cohort	5,895	- ≥ 18 years - ART-naive at ART start - NNRTI-regimen - ≥ 12 mo FU excl: - switched to second-line before failure - failed < 12 mo before database closure	2 VL≥ 1000 copies/ml within 12 mo > 3 months after initiation
SSempijja et al. 2017 (29)	Uganda, initiated 2004 – 2013	Retrospective cohort	124 (4% of 3,026 on ART)	- ≥18 years - ≥ 3 mo NNRTI-regimen before VL - 2 VL≥ 1000 copies/ml within 12 mo	2 VL≥ 1000 copies/ml within 12 mo

Table 2.C

[c] East Africa: Kenya, Uganda, Southern Africa: Malawi, Mozambique, South Africa, Zambia, Zimbabwe, West/Central Africa: Burkina Faso, Democratic Republic of the Congo, Nigeria, Asia: Cambodja, Myanmar, Laos

[d] Kenya, Nigeria, South Africa, Uganda, Zambia, Zimbabwe

Reference	Study setting and period	Design	Sample size	Inclusion and exclusion criteria (excl.)	Criteria for switch to second-line
Castelnuovo et al. 2009 (39)	Urban Uganda, referral hospital Switched 2004-2005	Prospective cohort	40 (110 (5% ART patients) switched, first ones enrolled)	- VL >400 copies/ml twice or VL >400 copies/ml once and immunological and/or clinical failure - naive to PIs at switch to PI-based regimen - present at ≥2 scheduled clinic visits in the past 6 mo - residence of Kampala for the past 12 mo - written informed consent	VL confirmed failure after WHO clinical or immunological criteria failure
Court et al. 2014 (43)	South Africa, hospital 2003-2011	Retrospective cohort	274	- ≥ 15 years - second-line ART after 2 VL >1000 copies/ml	-2 VL >1000 copies/ml - first-line side effects
Fox et al. 2010 (44)	Urban South Africa, referral hospital 2004 - 2008	Retrospective cohort	328 (3% of 9,694 on ART)	- ≥ 18 years - second-line ART after standard first-line ART - ≥12 mo FU	-2 VL >1000 copies/ml - first-line side effects
Johnston et 2012 (34)	Urban, peri-urban South Africa, clinics, 2003-2010	Retrospective cohort	417 (79% of 529 with VL result)	- ≥ 18 years - second-line ART after VL >400 copies/ml - ≥15 mo FU	- treatment failure (2 V≥ 1000 copies/ml, /1 VL ≥ 1000 copies/ml & 1 VL 400-999 copies/ml / 1 VL 400-999 copies/ml & 1 VL ≥400 copies/ml or missing)
Levison et al. 2011 (45)	Peri-urban South Africa, clinic	Prospective cohort	202 (3% of 6,339 on ART, 724 failure, 315 on second-line)	-≥ 15 years - switch to PI after 2 VL ≥ 1000 copies/ml or last available VL > 1000 copies/ml - ≥ 6 mo potential FU on PI-based regimen excl: transferred in, ART non-naieve	-2 VL ≥ 1000 copies/ml or last available VL > 1000 copies/ml

Murphy et al. 2012 (42)	Peri-urban South Africa, hospital	Retrospective cohort	136 (156 on second-line)	- adult ≥ 6mo on second-line ART - VL ≥1000 copies/ml on first-line	- VL ≥1000 copies/ml on first-line
Narainsamy et al. 2017(46)	Peri-urban South Africa, hospital 2011-2014	Retrospective cohort	223 (238 switched, 6,500 on ART)	- ≥ 18 years - switched from NNRTI-based to PI-based regimen after 2 documented VL ≥ 1000 copies/ml, 2 months apart excl: switched after 1 VL, no VL data, switched for side-effects	-side -effects -2 VL ≥ 1000 copies/ml, 2 months apart
Onyedum et al. 2013 (37)	Nigeria, university hospital	Retrospective cohort	186 (4% of 4229 on ART)	- ≥ 15 years - ≥ 12 mo on PI-based regimen after NNRT-regimen excl: transferred in on second-line -no data on first-line regimen	-2 VL ≥ 1000 copies/ml after ≥ 6 mo ART - 50% drop in CD4-peak value / return to ≤ pre-ART CD4 / CD4 staying persistently <100 cells/ mm3 after ≥ 12 mo ART - new WHO-stage 3 or 4 OI on ART -ART toxicity
Osinusi-Adekanmbi et al. 2014 (40)	Nigeria, hospital 2008-2010	Prospective cohort	73 (82 switched & screened)	- >18 years - confirmed VL>1000 copies/ml - adherence documented >95% in 3 mo before screening Excl: -opted out - VL undetectable	- CF, IF or VF, as identified by clinic provider
Pujades-Rodríguez et al. 2010 (35) [c]	13 countries, 10 in Africa, 3 in Asia 2001-2008	Retrospective cohort	632 from 27 cohorts (493 from Africa)	- ≥ 15 years - ART-naive at ART start - > 6 mo on second-line PI after NNRT-regimen - known sex information	site-specific
Schoffelen et al. 2013 (36)	Rural South Africa, clinic, 2004-2010	Retrospective cohort	210	- ≥ 12 mo on PI-based second-line PI March in March 2004 - initiated at that clinic	- VL ≥ 1000 copies/ml after suppression < 400 copies/ml - con'd VL > 400 copies/ml after 6 months on ART - adverse effects on first-line
Shearer et al. 2017 (47)	Urban South Africa, clinics	Retrospective cohort	1,236	- >18 years - ART naïve at initiation on first-line ART - start second-line ART < 1 year after VF excl: - on second-line ART during pregnancy - switched to second-line without evidence of failure	- 2 consecutive VL >1000 copies/ml (2 weeks to 6 months apart), ≥ 4 months after initiation
Sigaloff et al. 2012 (38) [d]	6 African countries 2007 – 2009	Prospective cohort	243 (232 with genotyping result)	- switched to second-line ART after VF, IF or CF excl: on PI before switch, pregnant	-site specific
Tsegaya et al. 2016 (41)	Ethiopia, hospital 2006 - 2015	Retrospective cohort	356	- ≥ 15 years - initiated second-line ART at that clinic - ≥ 6 mo on second-line	- VL failure after suspicion of failure - varying definitions of VL failure over time
Wilhelmson et al. 2016 (33)	Ethiopia, hospital, 2014 - 2016	Retrospective cohort	383 (out of 427 eligible)	- PI-based second-line ART after NNRTI-based first-line excl: - documented transfer - initiated second-line in another clinic - missing data	Clinical and/or immunological criteria (new HIV-related conditions or absence of CD4 cell response) for suspected first-line ART failure, since 2010 confirmed with VL testing Or first-line side-effects

ART= anti-retroviral treatment, CF = clinical failure, excl.: exclusion criteria, FU = follow-up, IF = immunological failure, ml = millilitre, mo = month/s, NRTI = nucleotide reverse-transcriptase inhibitor, NNRTI = non-nucleotide reverse-transcriptase inhibitor, OI = opportunistic Infection, PI = protease-inhibitor, RIC = retention (retained) in care, VF = virologic failure, VL = viral load, wk = week/s, WHO = World Health Organisation

Table 3: Characteristics of included patients

A: Characteristics of patients who experience first-line failure (at failure, unless specified)

B: Characteristics of patients who are switched to second-line ART (at switch, unless specified)

Table 3.A: Characteristics of patients who experience first-line failure (at failure, unless specified)

Reference	**Female sex** (N, %)	**Age** (yrs) (median, IQR)	**CD4-count** (cells/mm^3)	**VL** (Log $_{10}$ copies/ml) (median, IQR) or (N, %)	**Time on ART** (median, IQR)	**First-line regimen**	**Second-line regimen**	**WHO-stage**
Barth et al. 2011 (19)[a]	223 (66%)	at ART start: 35 (mean)	at ART start: 54	at ART start: 4.9 (mean)	24-36 mo: 162 (48%) 36-48 mo: 111 (33%) >48 mo: 60 (18%)	EFV: 204 (61%) d4T: 253 (76%)		
Gsponer et al. 2012 (31)	1276 (53%)	29 (25-34) at ART start: 27 (23-32)	<50: 325 (13%) 50-99: 585 (24%) 100-199: 763 (32%) ≥200: 738 (31%)	NR	NR	AZT/3TC + NVP: 1215 (50%), + EFV: 97 (4%) d4T/3TC +NVP: 1005 (42%), + EFV: 89 (4%)	TDF/FTC/LPV: 194 (60%) ABC/ddI/LPV: 65 (20%) AZT/TDF/FTC/LPV: 15 (5%) AZT/TDF/FTC/LPV/r: 14 (4%)	at ART start: I/II: 644(27%) III/IV: 1767 (73%)
Hosseinipour et al. 2010 (28)	59 (54%)	38 (32-46)	at switch (n=101): 65 (22–173)	at switch (n=101): 4.7 (4.2– 5.2)	34 (25–48) mo at switch: 35 (25-49)	EFV or NVP / 3TC / d4T or AZT	LPV/r based	
Johnston et al. 2013 (27)	503 (27%)	42 (17-71) (mean, range)	184 (108-279)	4.3 (3.0-5.7) (mean, range)	17 (13-24) yrs	AZT/3TC/NVP or EFV TDF/FTC/EFV d4T/3TC/EFV or NVP	ABC/ddI/LPV/r AZT/ddI/LPV/r	
Keiser et al. 2011 (22)	473 (67%)	at ART start: Switched (n=382): 35 (30-41) Not switched (n=323): 34 (30-40)	at ART start: Switched (n=282): 73 (23-133) Not switched (n=259): 67 (21-161)	at ART start: Switched (n=73): 5.0 (4.4-5.6) Not switched (n=64): 5.3 (4.6-5.8)	At switch: 17 (11- 25) mo	AZT/ddI/NVP: 296 (42%) d4T/3TC/EFV: 221 (31%) AZT/3TC/NVP: 74 (10%) AZT/3TC/EFV: 74 (10%)	AZT/ddI/LPV/r: 171 (45%) ABC/ddI/LPV/r: 42 (11%) AZT/3TC/LPV/r: 33 (9%) TDF/FTC/LPV/r: 23 (6%) d4T/ddI/ LPV/r: 18 (25%)	at ART start: III/IV: 282 (40%)
Labhardt et al. 2017 (3)	91 (66%)	41 (32–50)	351 (182–520)	3.9 (3.2–4.3)	49 (29–68) mo	AZT/3TC: 70 (51%) TDF/3TC: 67 (49%) ABC/3TC: 1 (1%) NVP: 90 (65%), EFV: 48 (35%)	TDF/3TC/LPV/r AZT/3TC/LPV/r ABC/3TC/LPV/r RAL/LPV/r	
Lejone et al. 2017 (23)	25 (47%)	9.7 (5.6–13.0) At start: 5.1 (1.6-8.5)	41 ≥5 yrs: 690 (432-1015) 12<5yrs CD4 %: 22 (17–32)		44 (25–58) mo	AZT/3TC: 47 (89%) TDF/3TC: 2 (4%) ABC/3TC: 4 (8%) NVP: 14 (26%), EFV: 36 (68%),	TDF/3TC/LPV/r AZT/3TC/LPV/r ABC/3TC/LPV/r LPV: 3 (6%)	
Murphy et al. 2010 (24)	71 (50%)	36 (30-42) (n=122 with mutation) 43 (35-47) (n=19)	≥ 100:110 (78%) <100: 29 (21%)	≥5: 27(19%) <5: 113 (81%)	13 (7-20) (n=122 with mutation) mo 8 (6-12) (n=19) mo	AZT/3TC + NVP: 17 (12%), + EFV: 38 (27%) d4T/3TC/NVP: 9 (6%) + EFV:61 (43%) d4T/ddi/EFV : 2 (1%)		I/II: 47 (33%) II/IV: 64 (45%)
Petersen et al. 2014 (26)	562 (68%)	<30: 228 (28%) 30-39: 396 (48%) ≥40: 199(24%)	<100: 114 (14%) 100-199: 244 (30%) 200-349: 319 (39%) 350-499: 108 (13%) ≥500: 38 (5%)	<0: 103 (13%) 0-3.7 269 (33%) 3.7-4: 97 (12%) 4-5: 263 (32%) >5: 91 (11%)	17 (10--31) yrs	EFV: 428 (52%) NVP: 395 (48%)		At ART start: I/II: 215 (26%) III/IV: 566 (69%)
Ramadhani et al. 2016 (30)	394 (62%)	<30: 134 (21%) 30-55: 454 (71%) ≥55: 49 (8%)	At switch (n = 396) <100: 174 (44%) 100-200: 166 (42%), >200: 56 (14%)		<36 mo: 360 (57%) 36-60 mo: 187 (29%) >60 mo: 90 (14%)			

Table 3.B: Characteristics of patients who are switched to second-line ART (at switch, unless specified)

Reference	Female (N, %)	Age (yrs) (median, IQR)	CD4-count (cells/mm^3)	VL (Log $_{10}$ copies/ml) (median, IQR) or (N, %)	Time on ART (median, IQR)	First-line regimen	Second-line regimen	WHO stage
Castelnuovo et al. 2009 (39)	20 (50%)	39 (36-43)	108 (43-205)	4.8 (4.0-5.4)	22 (19-29) mo	d4T/3TC or AZT/3TC EFV or NVP	AZT/ddI/LPV/r: 36 (90%) d4T/ddI/LPV/r: 4 (10%)	II: 7 (17%) III: 14 (35%), IV: 19 (48%)
Court et al. 2014 (43)	149 (55%)	35 (32-42)	At ART start: 174 (107-265)	At ART start: 4.1 (3.6 -4.7)	27 (15-47) mo			
Fox et al. 2010 (44)	216 (66%)	37 (8) (mean, SD)	203 (128) (mean, SD)		38 (8) (mean, SD) mo	d4T/3TC/EFV: 259 (79%) d4T/3TC/NVP: 46 (14%)		
Hawkins et al. 2017 (21)	1144 (65%)	40 (10) (mean, SD)	239 (205) (mean, SD)	4.4 (1.1) (mean, SD)	34 (17) (mean, SD) mo	NR	ABC/3TC(FTC)/PI: 35 (2%) ABC/ddI/PI: 1232 (70%) TDF/3TC (FTC)/PI: 405 (23%) Other+PI: 70 (4%)	I: 53 (3%) II: 141 (8%) III: 1074 (61%) IV: 493 (28%)
Johnston et al. 2012 (34) workplace (n=205)	17 (8%)	43 (37-49)	169 (97-235) At ART start:166 (91-221)	4.6 (4.1-5.1)	22 (15-34) mo	NR	No new NRTI: 14 (7%), 1: 7 (3%), ≥2: 184 (90%)	At ART start: III/IV: 108 (71%)
community (n=212)	130 (61%)	36 (31-42)	187 (95-270) At ART start:122 (43-195)	4.3 (3.7-4.6)	17 (10-25) mo	NR	No new NRTI: 26 (12%), 1 : 46 (22%), ≥2 : 140 (66%)	At ART start: III/IV: 164 (86%)
Levison et al. 2011 (45)	153 (75%)	34 (7) (mean, SD)	212 (133-289)	4.0 (3.6-4.4)	at failure: 11 (7-18) mo			
Murphy et al. 2012 (42)	88 (65%)	36 (31-43)	153 (89-232) at ART start: 70 (20-118)	4.4 (3.8-4.9)	13 (7-20) mo		AZT/ddI/PI 88 (65%) AZT/3TC/PI: 30 (22%) 3TC/PI alone: 7 (5%) d4T/3TC/PI: 6 (4%)	
Narainsamy et al. 2017 (46)	152 (68%)	at ART start 18-29: 35 (16%) 30-39: 103 (46%) 40-49: 66 (30%) >49: 19 (9%)	at ART start: 0-100: 131 (60%) 101-200: 65 (30%) >200: 23 (11%)	<4: 45 (20%) 4-5: 117 (53%) >5: 61 (27%)	NR	TDF/3TC + EFV: 68 (31%), + NVP 40 (18%) AZT/3TC + EFV : 6 (3%), + NVP : 8 (4%) d4T/3TC +EFV : 55 (25%) + NVP : 45 (21%) ABC/3TC/EFV : 1 (0%)		
Onyedum et al. 2013 (37)	110 (59%)	42 (10) (mean, SD)	At ART start: <200: 112 (60%) 200-499: 63 (34%) ≥500: 11 (6%)	at ART start: 4.5 (3.9-6.3)	17 (8) mo (mean, SD)	d4T/3TC/NVP: 121 (65%) AZT/3TC/NVP : 41 (22%) TDF/FTC/NVP: 11 (6%) TDF/FTC/EFV: 7 (4%)	TDF/3TC/AZT/LPV/r: 186 (100%)	
Osinusi-Adekanmbi et al. 2014 (40)	49 (67%)	35 (30-41)	121		24 (16-32) mo	TDF: 26 (37%) AZT/d4T: 45 (64%)		
Pujades-Rodríguez et al. 2010 (35)	380.9 pyr FU (63%)	35 (30-42)	<50: 126 pyr 50-99: 115 pyr 100-199: 172 pyr ≥200: 196 pyr		24 (16-31) mo	D4T : 445 pyr AZT : 165 pyr EFV : 146 pyr NVP : 463 pyr	LPV/r: 374 pyr NFV: 463 pyr	I/II: 63 pyr (43%) III/IV: 85 pyr (57%)
Schoffelen et al. 2013 (36)	145 (69%)	33 (24-40) 39 (19%) of <15 years	Adults: 187 (93-299) Children: 485 (308-983) At ART start: Adults: 62 (18-139)	4.0 (3.4-4.5)	19 (11-31) mo	d4T/3TC: 146 (70%) AZT/3TC: 61 (29%) TDF/3TC: 1 (1%) NVP: 112 (53%) EFV: 96 (46%)	AZT/3TC/LPV/r: 151 (72%) TDF/3TC/LPV/r: 28 (13%) d4T/3TC/LPV/r: 10 (5%) TDF/FTC/LPV/r : 2 (1%) ABC/3TC/ LPV/r: 1 (1%) other/LPV/r:18 (9%)	
Shearer et al. 2017 (47)	731 (59%)	38 (33–44)	203 (114–305)	4.2 (3.6–4.8)	19 (13–31) mo	TDF/3TC/EFV : 217 (18%) d4T/3TC/EFV: 827 (67%) Other: 192 (16%)	TDF/3TC(FTC)/LPVr : 374 (30%) AZT/3TC/LPVr: 366 (30%) AZT/ddI/LPVr: 496 (40%)	
Sigaloff et al. 2012 (38)	116 (50%)	38(34-45)	126 (66-205)	4.2 (3.3-5.0)	27 (15-44) mo	AZT/3TC/NNRTI: 12 (44%)		

						D4T/3TC/NNRTI : 95 (41%) TDF/FTC/NNRTI : 23 (10%) Triple NNRTI : 4 (2%)		
Tsegaya et al. 2016 (41)	158 (44%)	15-29: 78 (22%) 30-39: 167 (47%) 40-49: 82 (23%) >50: 29 (8%)	<100: 222 (62%) ≥ 100: 134 (38%)		43 (26-64) mo	TDF: 206 (58%) ABC: 102 (29%) AZT: 41 (12%) d4T/ddi : 7 (2%)	LPV/r : 289 (81%) ATV/r : 64 (18%) NFV: 3 (0%)	I/II: 127 (36%) III: 172 (48%) IV: 57 (16%)
Wilhelmson et al. 2016 (33): adults (n=330) <15 yrs (n=53)	180 (55%) 27 (51%)	37 (30-42) 11 (7-14)	126 (66- 226) 154 (88-319)	4.9 (4.5-5.3) 5.0 (4.6-5.5)				I/II: 109 (33%) III/IV: 216 (65.5%)

3TC = lamivudine, ABC = abacavir, ART= anti-retroviral treatment, AZT =zidovudine, d4T = stavudine, ddI = didanosine, EFV = efavirenz, FTC = emtricitabine, FU = follow-up, IQR = interquartile range, LPV = lopinavir, LPV/r = lopinavir/ritonavir, ml = millilitre, NRTI = nucleotide reverse-transcriptase inhibitor, NNRTI = non-nucleotide reverse-transcriptase inhibitor, NVP = nevirapine, OI = opportunistic Infection, PI = protease-inhibitor, RAL = raltegravir, RIC = retention (retained) in care, SD= standard deviation, TDF = tenofovir, VF = virologic failure, VL = viral load. WHO = World Health Organisation, yrs = years

Outcomes

Access to viral load testing and cascade after first-line failure

Table 4 presents steps in the cascade after first-line failure. The proportions of patients with a VL done can only be compared between settings with similar access to VL testing. VL testing coverage ranged from 13% (no routine VL; 82% had CD4 results) (21), to 77% (routine VL (27)). Median time between first high VL and a confirmatory test was reported by five studies, and ranged between 2.6 (IQR, 1.8-3.8) (26) and 6.8 (IQR, 0.1-32) months (46), the latter being a small study in a single clinic (46). A larger study in Uganda also reported 5.6 months (5.1-5.6) as a median, however this might have been influenced by the fact that routine VL was being introduced during the study (29). These results reflect guideline recommendations that varied between 3-6 months between first and second VL. Proportions of patients with confirmed treatment failure out of all on ART varied from 1% (targeted VL setting) to 16% (routine VL), with higher proportions in studies with longer follow-up (19,28). The proportions found seem consistent with systematic reviews reporting >80% on treatment viral suppression in LMIC (48), using thresholds between 300 and 500 copies/ml (49). Reported proportions with VF were lower if only targeted VL testing was used (28) or VL was still being scaled up (22,29). Proportions switched to second-line among failing patients were reported by eight studies, varying between 30% at six months after failure (26,29), 13-45% at 12 months (27,29), 62-73% around 18 months (3,30), and 65% at 2 years (29). Most studies with higher proportions switched were those requiring a confirmatory VL or genotyping to define failure (3,24,25,29), and lower proportions where reported when relying on immunological criteria only (31). Time from FEVL or from failure to switch ranged between 1.9 (IQR, 0.9-4.6) (47) and 36 (IQR, 18-54) months (20). Two studies with low switch proportions and long delays reported reluctance of clinicians to switch, for fear of wasting the regimens due to poor adherence (19–21,27).

Mortality

Reported mortality after treatment failure ranges between 4% (2) at 18 and 14% (25) at 12 months (23,28)**.** After second-line switch, reported mortality ranged from 1% at 2 years (42) to 10% after one year (28). One systematic review, considered mortality up to 11% by 12 months after switch as low (12). With this criterion, mortality after failure and after switch in the included cohorts is overall low (below 10%). One exception is the Malawi cohort (28),

where 14% of those with failure and 10% of patients on second-line died. The latter died in the first six months (six in the first three months) after switch. Early mortality is common when patients present with advanced stage of disease and/or low CD4-counts (19,28).

Loss-to-follow-up and retention in care

Loss-to follow-up (LTFU) was defined and reported inconsistently, with different definitions (Table 5). After treatment failure, authors report LTFU of 9% at six months (24), 21% at 18 months (3) and 60% by the end of follow-up (follow-up time not reported) (25). Six months after second-line switch, authors report LTFU between 4% (14) and 17% (44). 12 to 18 months after switch, LTFU ranged between 3% (42) and 15% (23,34). Retention in care after switch was reported by eight studies, reporting 83%-92% at six months (43,45), 83-93% at 12 months (42,43), and 53% at 24 months to (43) 81% (33) at 22 (median) months. Systematic review data from sub-Saharan Africa from 2010 reported a mean retention on first-line ART of 65% at three years (50). More recent articles indicate it might be lower in growing cohorts needing long-term retention after ART start (4). In our studies, after treatment failure, LTFU was highest in Lesotho (21%) at 18 months (3) and in a long-term (>10 years) study in South Africa, where 60% of patients left the cohorts through LTFU. LTFU after switch was 30% in the same study, with a median follow-up after switch of 17 months (IQR, 9-29) (25). One other study in South Africa reported 31% LTFU in a cohort with a median follow-up of 24 months (IQR, 14-36). Like in other studies (12,35,40), patients with high VL and low CD4 were more likely to be lost, and LTFU is thus likely to mask mortality (47).

Virologic Outcomes

Of patients who failed first-line, reported re-suppression proportions were between 19% (in children), and 85% (adults) at one year after failure (3,23,28). After switch, proportions re-suppressing varied between 41%-79% (24,37) 46%-87% (25,34,38) at 6 and 12 months post-switch respectively, with similar results at longer durations These results are consistent with systematic review data in LMIC in which pooled estimates were 22% and 23% virologic failure at six and 12 months on second-line ART (12). Pujades-Rodriguez report only 2% immuno-virologic failure but 12% of any failure after switch (14). Lejone et al. reported only 38% re-suppression (VL≤80 copies/ml) 18 months after switch in children in Lesotho (23). One study reported a virologic increase (in 0.5 log10 VL versus VL at failure) of 9/100 pyr

after 2 years (38). The one study which reported over 90% re-suppression used genotyping to investigate drug-resistance and guide choice of second-line regimens (24). Particularly low re-suppression rates (<50%) were found in Lesotho (3,23) and in one study in South Africa (45). The Lesotho studies had small sample sizes, and a weak health system and a reluctance to switch patients according to the defined criteria, in this decentralised nurse-led programme, were given as reasons for poor outcomes (3). Only 38% of children in the Lesotho cohort re-suppressed at 12 months, but many retained the same NRTI on second-line, which might be have been sub-optimal (23). This result is worse than a multicenter analysis in LMIC, in which only 16.4% of children had virologic failure 2 years after switch (13).

Table 4: The cascade from ART initiation until re-suppression on second-line ART

[a] First-line failure = VF unless specified. All time measured are presented in months. Denominator for first-line failure is all on ART, unless specified. Denominator for switched is those with failure, unless specified.

Reference	Total on ART	VL done (CD4)	Months VL1-VL2	First-line failure [a]	Switched	Months failure-switch	Re-suppressed after switch
Barth et al. 2011 (19)	735			117 (16%)	31 (26%)		25/31 (81%)
Boulle et al. 2010 (18)	7,323			14% (at 5 yrs)	12.2% all (at 5 yrs)	5.3 (2.2-11.2)	22/29 (76%) at 5 yrs
Castelnuovo et al. 2009 (39)	2,340				110 (5%) all	9 (3-11) from VL1	75% at 12 mo (ITT)
Court et al. 2014 (43)					274		169/228 (86%) at 12 mo
De Beaudrap et al. 2013 (20)	366			79/324 (24% VS)	65 (18%) (48 VF)	36 (18-54) from VL1	43/53 (81%) (median FO 6 mo)
Fox et al. 2010 (44)	10,022				328 (3%) all	2.8 (1.1-6.1)	203/262 (77%) at 12 mo
Gsponer et al. 2012 (31)	80,937	655 (27%)		IF: 2,411 (3%)	324 (13%)		
Hawkins et al. 2017 (21)	47,296	5,949 (13%) (39,490 (82%))		VF: 1,459 (3%), IF: 7,825 (17%)	1760	15.6 (13.2) (mean, SD)	
Hosseinipour et al. 2010 (28)	~8,000			109 (1%)	101 (93%)		85% of 101 at 12 mo
Johnston et al. 2013 (27)	13,537	10,402 (77%)	4.9 (2.8-6.1)	1,867 (13%), 18% of VL	361 (22%) of incl.		291/361 (81%) end FU
Johnston et al. 2012 (34)	14,779				529 (4%) all		250/330 (76%) at 15 mo
Keiser et al. 2011 (22)	16,591			705 (4%) VF, IF or CF	382 (54%)		
Labhardt et al. 2017 (3)		1,563 (VL1, 9% high)		80 (5%), (69%) of 116 VL2	58 (73%)		32/58 (55%) at 12 mo
Lejone et al. 2017 (23).		191 (VL1, 28% high)		36 (19%), (74%) of 49 VL2	24 (67%)		9/24 (38%) at 12 mo
Levison et al. 2011 (45)	6,339			724 (11%)	315 (44%)	5 (3-8)	85/167 (51%) at 6 mo
Murphy et al. 2010 (24)				141	107 (76%)		100 (93%) at 6 mo
Murphy et al. 2012 (42)					136		94/126 (75%) at 12 mo
Narainsamy et al. 2017 (46)			6.8 (0.1-32)		238	6.4 (0-43.3)	176/223 (79%) at 18 mo
Onyedum et al. 2013 (37)	4,229				186 (4%) all		56 (82%) at 12 mo
Osinusi-Adekanmbi et al. 2014 (40)					73		48 (66%) at 12 mo
Petersen et al. 2014 (26)	7,975		2.6 (1.8-3.8)	823 (10%)	358 (43%)	3.9 (2.1-6.6)	
Pujades-Rodríguez et al. 2010 (35)					632		507 (81%) (med FU 12 mo)
Ramadhani et al. 2016 (30)				IF: 637	396 (62%)	(233) 59% < 3 mo	
Rohr et al. 2016 (25)			2.9 (1.9-4.9)	5,895	3,706 (63%)	3.4 (11-8.7)	14% VF (med FU 17 mo)
Schoffelen et al. 2013 (36)					210	6 (3-11)	92/128 (72%) at 12 mo
Shearer et al. 2017 (47)					1,236	1.9 (0.9-4.6)	75% at 12mo
Sigaloff et al. 2012 (38)					243		180/208 (87%) at 12 mo
SSempijja et al. 2017 (29)	3,036		5.6 (5.1-5.6)	124 (4%)	82 (66%)	8.1 (3.7-17.0)	
Tsegaya et al. 2016 (41)					365		289 (79%) (median FU 32 mo)

ART = antiretroviral therapy, FU= follow-up, IF = immunological failure, ITT= intention-to-treat, mo = month/s, SD = standard deviation, VL= viral load, VL1 = first high VL, VL2 = confirmatory VL, VF = virologic failure, VS= virologic success

Table 5: Outcomes

A. After treatment failure on first-line ART
B. After switch to second-line ART

Table 5.A: Outcomes after treatment failure on first-line treatment

[a]Re-suppression means viralogical suppression on second-line or overall, unless specified that it is first-line.

Reference	Follow-up period After failure	Mortality	Virological[a] (VL in copies/ml)	Immunological (CD4 in cells/mm³)	LTFU/RIC	Switch	Other outcome/ Comments
Gsponer et al. 2012 (31)	3932 pyr	76 (3%) 19 (15-24)/1000 pyr			177 (7%) LTFU 55(37-52)/1000 pyr	324 (13%) 82 (74-92) /1000 pyr	LTFU: not returning ≥ 12 mo
Hosseinipour et al. 2010 (28)	12 mo	15 (14%)	re-sup: 85% (13 others: 6 never sup, 7 rebound)	CD4 increase: 142			re-sup: VL <400 copies/ml
Johnston et al. 2013 (27)	19 (10-5) mo	107 (6%)	296 (18%) re-sup on first-line		312 (19%) LTFU 49 (3%) TO 67 (4%) left 476 (29%) admin cens	361 (22%)	Denominator: 1921.8 pyr failure LTFU= no clinic contact > 6 mo re-sup: VL <400 copies/ml
	12 mo	5%	13% re-sup on first-line			17%	Cumulative incidence/ Competing Risks
Keiser et al. 2011 (22)		Cum 12 mo: 4% second-line (5/100 pyr) 2% non-failing first-line (3/100 pyr) 12% on failing first-line (13/100 pyr)			LTFU per 100 pyr: 5 second-line 2 non-failing first-line 14 failing first-line		LTFU: >1 yr between last visit and cohort closure
Labhardt et al. 2017 (3)	18 mo	10 (7%)	56 (58%) re-sup		29 (21%) LTFU	58/80 (73%)	LTFU: status unknown re-sup: VL<80 copies/ml
Lejone et al. 2017 (23)	18 mo	2 (4%)	10 (19%) re-sup		8 (15%) LTFU	24/36 (67%)	
Murphy et al. 2010 (24)	6 mo	6% (2-9)	99 (70%) <400 copies/ml 91 (65%) <50 copies/ml	50%: 30% CD4-increase Med increase: 88 (7-168) Med CD4: 249 (166-343) 33% had CD4 <200	9% (4-13) LTFU		
Petersen et al. 2014 (26)	med 25 mo	49 (6%) 2.5/1000 pyr				1, 3, 6 mo: 3%, 16%, 30%	
Ramadhani et al. 2016 (30)	med 17 (8-32) mo					396 (62%)	OI: TB, pneumonia, KS, CM, HZ OI: 115 (18%), 7% pneumonia, 6% TB
Rohr et al. 2016 (25)	end FU: max 10 yrs	298 (5%) end FU			3555 (60%) LTFU 2042 (35%) RIC	3706 (63%)	
SSempijja et al. 2017 (29)	24 mo	8 (7%)	Vir increase: 24/270 pyr 9/100 pyr	Imm decline: 30/259 pyr 12/100 pyr		49/100 pyr second-line 30.2%, 44.6%, 65.0% at 6,12,24 mo	Imm decline: to 50 from CD4 at failure Vir increase: to 0.5 log_{10} from VL at failure

Table 5.B: Outcomes after second-line switch

Reference	Follow-up period after switch	Mortality	Virologic	Immunological (CD4 in cells/mm³)	LTFU/RIC	Clinical	Other outcome/ Comments
Barth et al. 2011 (19)	24-48 (since ART) mo		Re-sup 25/31 (81%)				re-sup: <50 copies/ml
Boulle et al. 2010 (18)	150 (since ART) mo		Re-sup 22/29 (76%)				re-sup: VL <400 copies/ml
Castelnuovo et al. 2009 (39)	36 mo	1 (3%) (2 we)	ITT: 12,24,36 mo: 75%, 85%, 82% re-sup 3 VF at 36 mo	Med CD4: 279 (239-461) Med increase: 214 (128-295)		25 (62%) toxicity	40 patients, failure; VL>400 copies/ml Adherence >95 % at 12, 24, 36 mo: 92%, 97%, 97%
Court et al. 2014 (43)	med 27 mo		VL at 6, 12, 18, 24, 30, 36, 42, 48 mo (% of VL results). VL<50: 159 (71%), 155 (79%), 115 (72%), 97 (78%), 77 (79%), 58 (74%), 48 (70%), 33 (73%) VL < 400: 195 (87%), 169 (86%), 132 (83%), 107(86%), 88(91%), 69(88%), 60(87%), 40(89%) VL ≥1000: 22 (10%), 26 (13%), 26 (16%), 16 (13%), 7 (7%), 7 (9%), 2 (3%), 4 (8%)		RIC at 6, 12, 18, 24, 30, 36, 42, 48 mo: 252 (92%), 228 (83%), 180 (66%), 146 (53%), 112(41%), 87(32%), 72(26%), 54(20%)		
De Beaudrap et al. 2013 (20)	45 (since ART) mo		6 mo: 43 (81%) VL <500 copies/ml 6, 12, 24 mo: 18%, 20%, 27% VF				12 relapsed after resupression: all 12 patients has dual class resistance 8 were resistant to second-line drug VF : 2x 1000 copies/ml
Fox et al. 2010 (44)	12 mo	17 (5%) after 4 mo (1-8)	262 (81%) VL done 203 (77%) Re-sup at 12 mo, (18 (9%) rebound)	Med increase 6 mo: 59 (37-80) 12 mo: 133 (106-160)	243 (78%) RIC 53 (17%) LTFU after 6 mo (4-9) 15 TO (excluded)		Compared to first-line outcomes, second-line were slightly less likely to be RIC re-sup: VL<400 copies/ml
Hawkins et al. 2017 (21)		2.4/100pyr			9.0 /100 pyr		LTFU: >90 days since last clinic visit, no contact >120 days before cut-off or death
Hosseinipour et al. 2010 (28)	12 mo	10 (10%)	75% alive re-sup			34 (34%): HIV-events	(N=101) re-sup: VL <400 copies/ml
Johnston et al. 2012 (34)	15 mo 12 mo	12 (6%) workplace 12(6%) community	Workplace: VS 89 (48%), 26% rebound Community: VS 152 (72%), 13% rebound Med 5 VL done Workplace: VS: 59 (46%) Community VS: 116 (72%)	Med increase: 68 (40-95) workplace 127 (101-154) community	Workplace: RIC 179 (74%), LTFU: 29 (14%) Community: RIC 151 (84%), LTFU: 15 (7%), TO: 5 (3%)		VS= VL <400 copies/ml
Labhardt et al. 2017 (3)	18 mo	2 (3%)	32 (55%) re-sup		8 (14%) LTFU		(n=58) re-sup: VL<80 copies/ml
Lejone et al. 2017 (23).	18 mo	1 (4%)	9 (38%) re-sup		8 (15%) LTFU		(n=24) re-sup: VL<80 copies/ml
Levison et al. 2011 (45)	6 mo	4 (2%)	VL >400: 82 (41%)	Med increase: 90 (-4-177)	7 (4%) TO 24 (12%) LTFU 167 (83%) RIC		
Murphy et al. 2010 (24)	6 mo		70 (41%) re-sup				(N =107), re-sup:VL <400 copies/ml
Murphy et al. 2012 (42)	24 mo	1 (1%)	VL >1000 at 6, 12, 18, 24 mo:	Med CD4 at 6, 12, 18, 24 mo: 228 (157–329, 276	RIC 6, 12, 18, 24 mo 136 (100%) 126 (93%) 112 (82%) 99 (73%)		

			36 (26%),32 (25%) 23 (21%), 25 (25%)	(201–404), 315 (207–436), 330 (230–481)	LTFU: N/A, 4 (3%), 11 (9%), 17 (15%) TO: N/A, 6 (4%), 13 (10%), 19 (17%)		
Narainsamy et al. 2017 (46)	18 mo		47 (21%) VF				VF: VL>1000 copies/ml
Onyedum et al. 2013 (37)	12 mo		re-sup: 3, 6, 12 mo: 93 (82%), 70 (79%), 56 (82%)	IS 3, 6, 12 mo: 91 (56%), 107 (71%), 81 (79%)			re-sup= <400 copies/ml after switch IS = increase ≥50% vs CD4 at switch
Osinusi-Adekanmbi et al. 2014 (40)	>24 mo	5 (7%)	VS at 6-9, 12, 12-24, >24 mo: OT: 88%, 91%, 91%, 91% ITT: 73%, 66%, 58%, 58%		LTFU: 6 (8%) Withdrew 5 (7%)		VS: VL <1000 copies/ml
Pujades-Rodríguez et al. 2010 (35)	741 pyr	34 (5%) at 15 (12-26 mo) At 30 mo: 44/1000 pyr	I/VF:12, 24 mo: 2%, 8%, any failure: 12%,18% 53, 46 1000 pyr		23 (4%) LTFU at 6 mo At 30 no: 33/1000 pyr		Any failure: 12mo, 24 mo: 12%, 28% 119 (19%) at 12 (9-17mo)
Rohr et al. 2016 (25)	med 17 (9-29) mo	2%	14% VF		42% RIC without VF 30% LTFU		(n=3706) VF: 2x VL>1000copies/ml LTFU last visit > 6 mo before cut-off
Schoffelen et al. 2013 (36)	20 (11-35) mo	11 (6%) of which 6 in first 12 mo	En of FU: VS: 111 (58%) VL 6,12,18,24 mo: VL <400: 95 (71%), 92 (72%), 82 (69%), 63 (75%) VL<50: 74 (55%), 78 (61%), 70 (59%), 54 (64%)	Increase: ad: 152(-4-398) Child: 27 (-172-210)	RIC: 139 (73%) 15 (8%) TO	24% CF	VS: VL <50 copies/ml VL Cross-sectional data
Shearer et al. 2017 (47)	12 mo	22 (2%)	75% re-sup 12 mo		123 (11%) LTFU		LTFU: ≥ 3 mo late for scheduled visit
	med 24 (14-36) mo	14% end FU			31% LTFU end FU		re-sup: ≥ 400 copies/ml
Sigaloff et al. 2012 (38)	12 mo	11 (5%)	201 VL results 28 (14%) VF 180 (87%) re-sup	21 (12%) IF	208 RIC (90%), 19 (8%) LTFU, 4 (2%) TO	WHO stage IV/TB : 13 (6%) CF	LTFU (no def) VF ≥ 400 copies/ml after switch
Tsegaya et al. 2016 (41)	med 32 (15-53) mo 1085 pyr	21 (6%)		24 (7%) IF	11 (3%) LTFU	11 (3%) CF	Overall failure (death, IF, CF, LTFU): 67 (19%) or 62/1000 pyr Cum inc: 12, 24, 60, 96 mo: 65, 14%, 24%, 42%) LTFU: no ART for ≥ 3 mo, no info
Wilhelmson et al. 2016 (7)	med 22 mo ad: 22 mo child: 24 mo	ad: 2(1%) child: 0 (0%)			81% RIC, 19% LTFU ad: 256 (80%) RIC, 63 (20%) LTFU, 9 TO child: 42 (86%) RIC, 7 (14%) LTFU, 4 TO		LTFU: Missed scheduled appointment ≥ 90days

ART= anti-retroviral treatment, dl = decilitre, CF = clinical failure, FU = follow-up, IF = immunological failure, IVF = immunovirologic failure, IQR = interquartile range, ITT = Intention-to-treat, LTFU: lost-to-follow-up, med = median, ml = millilitre, mo = month/s, OI = opportunistic Infection, re-sup = re-suppressed, pyr = person-years, RIC = retention (retained) in care, SD= standard deviation, TO = transferred out, VF = virologic failure, VS = viral suppression VL = viral load, yrs = year/s

Determinants for outcomes

In line with the objectives of the protocol, only articles presenting predictors for outcomes after first-line treatment failure or after second-line switch, and excluding switch to second-line or time to switch as an outcome, are presented (Table 6). Measures of association are reported if they yielded a statistically significant association ($p < 0.05$).

11 articles reported on determinants of outcomes after treatment failure (Table 5.A). Most studies considered death, LTFU or a combination as the primary outcome(s), two studies looked at predictors for survival (30,31), one virologic failure (24), one OIs (30), and two studies documented retained and suppressed (VL<80copies/ml) as primary outcome (3,23). Most studies looked at the impact of switching to second-line on outcomes, all finding a positive effect for those switching after treatment failure. Those who switched were less likely to die compared to those not switched after failure (22,26,29–31) less likely to be LTFU (21,22,31), to have an OI or a combination of these negative outcomes (21,30) and more likely to be retained and suppressed at 18 months (3,23). Rohr et al. found a lower but not statistically significant adjusted hazard of death in those who switched between 0 and 1,5 month after failure versus > 12 months (HR[a]: 1.21 (95% CI: 0.95-1.54)) (25). Hosseinipour et al. found a significant negative effect of clinical failure and low body-mass index on mortality and of low CD4-count on mortality or LTFU (28). The study by Murphy et al. found that those patients with a mutation were more likely to re-suppress (VL<400 copies/ml) (69% vs 37% (p=0.01)) at six months and less likely to be dead (4% vs 16% (p=0.02)) compared to patients with wild-type virus, most of whom did not received second-line treatment (24).

19 articles presented determinants for outcomes after switch to second-line ART (Table 6.B). Most considered virologic outcomes, such as virologic suppression or failure. Some articles used a composite end-point for failure, including immunological and clinical failure (35), and/or death or LTFU (38) in addition to virologic failure. Many different predictors were assessed and found significant, detailed in table 6.B. The most important ones are discussed. Seven articles found an association between some indicator of adherence and outcomes and two did not (20,34); two articles found positive associations between different adherence measures and viral suppression, in univariable (51) and multivariable analysis (44). Four articles found that lower adherence was associated with virologic or

other definitions of failure (28,35,38,43,46). Five articles found time to switch to be significantly associated with outcomes, all indicating benefits of a shorter time between failure and switch. Johnston et al. found that viremia for less than a year was associated with viral re-suppression in multivariable analysis (34), and Gsponer et al. found a positive survival trend with shorter time to switch (31). Others found that a time to switch of over one month (45), one and a half months (25), and over six months (46) (> versus faster switch) were associated with failure on second-line. SSempijja et al. found that the hazard of immunological decrease, virologic increase and an endpoint combining the two were higher in patients switched more than one year after failure versus sooner (29).

Most studies analysed measures of HIV-progression at ART initiation and/or at switch to second-line ART as predictor, such as CD4-count, VL or WHO-stage, and findings suggest that more advanced disease at start and at switch predicts worse outcomes. While it is hard to compare, levels of disease progression in patients in the reviewed papers seemed to be advanced at ART initiation, slightly better at failure and again more advanced at switch. At initiation, CD4-counts were low, with medians between 62 (IQR, 18-139)(36) and 174 (IQR, 107-265) cells/mm^3 (43). Median CD4 counts at failure were relatively low between 184 (IQR, 108-279) (27) and 351 (IQR, 182-520) cells/mm^3 (3). At switch, median CD4-counts were lower again, between 65 (IQR, 22-173) and 212 (IQR, 133-289) cells/mm^3(28,45). Median/mean $\log_{10}$ VL (copies/ml) ranged between 4.1 (IQR, 3.6 -4.7) to >5 at ART start (22,43), 3.9 (IQR, 3.2-4.3) to 4.3 (range, 3.0-5.7) (3,27) at failure, and 4.0 (IQR, 3.6-4.4) to 4.9 (IQR, 4.5-5.3) (adults) and 5.0 (IQR, 4.6-5.5) (children) at switch (33,45) Of studies reporting WHO clinical stage, proportion of advanced clinical stages (III/IV) varied between 40%-86% (22,34) at ART-initiation, 32% or 45% (24,29) at failure, and 57%- 89% (21,35) at switch. Different multivariable analyses showed that higher CD4 at ART start was positively associated with viral re-suppression (44), negatively with failure on second-line (43) and LTFU (33), and WHO-stage IV at start was found associated with any type of failure (38). Other multivariable models suggested that lower VL and higher CD4 at switch predict suppression (34), patients with lower CD4 at switch or WHO-stage IV at switch are more likely to experience death or any failure (35,41), and higher VL at switch predicts attrition (47).

Two studies found that female sex showed a significant association with VF (>400copies/ml, OR[a]: 2.25 (95% CI: 1.03-4.88) (45), and any type of failure (adjusted for adherence: IRR[a]: 1.56 (0.99-2.44)) but in the latter women were less likely to die on second-line (35) (HR[a]: 0.45 (95% CI: 0.23- 0.91)). This could mean that among survivors women were less likely to fail, but could have similar results to men if death were included among failures. Two studies found a significant effect of age in multivariable regression. One study found those with older age were less likely to reach viral re-supression (age, per five yrs increase: RR[a]: 0.87 (95% CI: 0.79-0.95) (34), a second study found a that attrition was higher in <30 (versus ≥45) years of age (HR[a]: 0.48 (95% CI: 0.27-0.84) (47).

A positive impact on death, retention in care and clinical disease, as well as viral suppression resulting from switching to second-line, and of switching early is found across the included studies. Different authors also found that a range of measures of poor adherence predict virologic failure and failure overall after switch. A study done on a subset of patients from Johnston et al. (34) found that non-adherence (measured as subtherapeutic drug concentrations) more than NNRTI-resistance (determined through genotyping), contributed to failure after second-line switch (16). Levison et al. also performed genotyping on a group of patients on second-line ART, finding that most (67%) patients failing second-line had no resistance (17). Murphy also found that second-line treatment yielded better outcomes in patients with first-line resistance (24). The 2012 systematic review in LMIC also found that poor adherence rather than resistance drove first-line failure in the included studies (5/19 included studies are also part of this review) (12). First-line adherence predicts second-line adherence, and treatment interruptions predict failure (52,53).

Table 6: Determinants for outcomes

A. After treatment failure on first-line ART

B. After switch to second-line ART All measures of association are presented with their 95% confidence interval. [a]Adjusted. [b] if the reference category is not specified, it is versus "not"

Table 6.A: After treatment failure on first-line ART

Reference	Main outcome	other predictors assessed	Predictors identified[b]	Comments
Gsponer et al. 2012 (31)	LTFU	Baseline	Switched: 14(7-26) 51(43-59)/1000 pys (p<0.001)	
	Death		Switched: HR[a]: 0.25 (0.09-0.72)	
	Survival 5 yrs		Switched 98% vs 91% not switched	Weighted cox models in women <30 yrs
Hawkins et al. 2017 (21)	Death or LTFU	ABC vs TDF second-line	Switched : HR[a]: 0.78 (0.65-0.95)	Restricted to switch after VF (presented)
	LTFU		Switched : HR[a]: 0.81 (0.66-0.99)	Marginal structure models
Hosseinipour et al. 2010 (28)	Death at 6/12 mo	Hb, duration ART, VL value	Clinical failure OR[a]: 3.47 (1.14-10.59)	
			BMI <18.5 m^2/kg: OR[a]: 4.43 (1.15-17.12)	
	Death or Morbidity at 6 mo		CD4 <50 cells/mm3 OR[a]: 3.13 (1.05-9.31)	
Keiser et al. 2011 (22)	Death		non-failing first-line = 1	Adjust age, sex, nadir CD4
			second-line = HR[a]: 1.60 (0.82-3.14)	
			failing first-line = HR[a]: 3.24 (1.82-5.76)	
	LTFU		non-failing first-line = 1	
			second-line = HR[a]: 2.10 (0.94-4.67)	
			failing first-line = HR[a]: 5.41 (2.70-10.85)	
Labhardt et al. 2017 (3)	Suppressed & retained at 18 mo	Gender, age, travel time, education, VL 1, VL2, first line resistance, facility type	Switched: OR[a]: 7.17 (1.90-27.04) VL <80 copies/ml after EAC: OR[a]: 5.02 (1.14-22.09)	Multivariable incl. VL1 result Suppressed: VL ≤ 80 copies/ml
Lejone et al. (23).	Suppressed & retained at 18 mo		Switched: 38% vs 0% (p= 0.016)	Suppressed: VL ≤ 80 copies/ml
Murphy et al. 2010 (24)	Death at 6 mo	Gender, resistance, second-line regimen, VL failure, WHO-stage failure	NNRTI-based second-line: 15% vs 2% (p=0.02)	Univariable analysis, none retained in multivariable analysis
			CD4 ART start<100: 17% vs 2% (p=0.005)	
			Mutation (vs no mutation) : 4% vs 16% (p=0.02)	ITT
	VL ≤400 copies/ml at 6 mo		Mutation (vs no mutation) : 69% vs 37% (p=0.01)	ITT
Petersen et al. 2014 (26)	Death	first vs second-line, supression prior to failure, WHO stage, ART start to failure, time since last visit	Age (+10yrs) OR: 1.80 (1.30–2.51)	Univariable analysis
			Male: OR: 1.93 (1.09–3.43)	
			Nadir CD4: OR: 0.56 (0.36–0.88)	
			Most recent CD4: OR: 0.53 (0.37–0.76)	
			CD4 decline since failure: 1.17 (1.09–1.27)	
			VL at failure: OR: 1.78 (1.22–2.61)	Also VL at peak, nadir & most recent are siginificant (not presented)
			Seen 90 days prior: 1.82 (1.02–3.27)	
	Death		OR[a]: not switched: 2.1 (1.1-4.2)	Adjusted for confounders
Ramadhani et al. 2016 (30)	Survival		Switched: 2.3 (1.2-3.9) yrs FU vs 1.0 (0.5-1.4)	Kaplan Meier curve
	OI	Gender, age, duration on ART, site of care, adherence	Switched: 38 (5/100pyr) vs 77 (16/100 pyr)	
			Prob 6,12 mo: switched 0.03, 0.07 vs 0.12, 0.36 (p<0.001)	
			Switched HR[a]: 0.4 (0.2-0.6)	
			Switched: HR[a]: 0.2 (0.1-0.2)	Logistic using propensity scoring
	OI or death		Switched: HR[a]: 0.4 (0.2-0.7)	

Rohr et al. 2016 (25)	Death		HR[a]: 1.21 (0.95-1.54) switched >12 mo vs 0-1.5 mo	Marginal structure models, per time of switch (incl. not switched), more pronounced in lower CD4 at failure
SSempijja et al. 2017 (29)	Death at 24 mo		Not switched: 12% vs 1% (p=0.009)	

Table 6.B: After switch to second-line ART

Reference	Main outcome	other predictors assessed	Predictors identified (	Comments
Court et al. 2014 (43)	VL > 1000 copies/ml	Time on second-line, gender, age , VL at baseline	Adherence of 4 months (per 10% increase): OR[a]: 0.73 (1.34- 0.12) Square root CD4 ARTtart: OR[a]: 0.22 (0.35- 0.09)	Multivariable presented, retained from univariable models
De Beaudrap et al. 2013 (20)	VL > 1000 copies/ml	Adherence level (pill count)	/	
Fox et al. 2010 (44)	VL <400 copies/ml at 12 mo	TB history, BMI at ART start	CD4 >200 ART start: HR[a]: 1.96 (1.21-3.17) 2 detectable VL before switch: HR[a]: 1.68 (1.08-2.61) Switch for non-compliance, no: HR[a]: 1.83 (1.14-2.93)	
Gsponer et al. 2012 (31)	Survival 5 yrs		Time of switch after failure 6, 12, 18: 97%, 96%, 95%	Weighted cox models in women <30 yrs
Hosseinipour et al. 2010 (28)	VL >400 copies/ml at 12 mo	Age, gender, time on ART, TB, BMI, Hb, missed visits, missed dose, resistance	CD4 switch <50 cells/mm3 vs >200: OR: 8.6 (2.40-30.78) WHO CF switch: OR: 11.54 (14.5-202.7) WHO IF switch: OR: 54.21 (14.5-202.7) No active NRTI: OR: 0.17 (0.03-0.94) Nr of missed visits: OR: 2.50 (1.35-4.63) Ever missed dose: OR[a]: 5.70 (1.16-27.93)	Univariable analysis Multivariable analysis
Johnston et al. 2012 (34)	VL< 400 copies/ml	VS, first-line ART, non-adherence on first-line ART, reason for switch, year of switch, new NRTIs in switch regimen, reported non-adherence second-line ART, gender	$\log_{10}$ VL switch 4 vs.5 RR[a] : 1.59 (1.09-2.34) Age (+5 yrs) RR[a] : 0.87 (0.79-0.95) Duration of viremia <12 mo: RR[a]: 1.22 (1.03–1.44) Transferred in: RR[a]: 1.33 (1.11-1.61) CD4 switch: 100-199 vs 100: RR[a]: 1.37 (1.05-1.78)	Workplace, multivariable Community, multivariable
Levison et al. 2011 (45)	VL >400 copies/ml at 6 mo	Age, CD4 count, VL at switch	Female: OR[a]: 2.25 (1.03-4.88) Time to switch (+1 mo): OR[a]: 1.07 (1.01-1.14)	Multivariable
Murphy et al. 2012 (42)	VL <50 copies/ml at 12 mo Adherence ≥ 90% at 12 mo	Age, gender, adeherence last 6 mo, CD4 at second-line , NRTI	Adherence 12 mo second-line : OR: 2.5 (1.3-4.8) /	
Narainsamy et al. 2017 (46)	2x VL≥ 1000 copies/ml	Gender, age, VL at switch, TB history, pregnancy, regimen modif, EFV-based first-line	Patients defaulted appointment: RR = 1.9 (1.1-3.2) Delay switch>6 mo: RR:1.7 (0.8-3.8), RR[a]: 1.6 (0.7-3.5)	
Osinusi-Adekanmbi et al. 2014 (40)	VL ≥ 1000 copies/ml at 12 mo	Gender, age, CD4, genotyping sensitivity score, TDF first-line,	First-line duration ≤24 mo: 13 (34%) vs 19 (54%) (p=0.08)	
Pujades-Rodríguez et al. 2010 (35)	Any failure second-line (CF, IF, VF)	Geography, urbanisation, routine VL, gender, use of VL for confirmation, age, calender year second-line start, clinical stage at first and second-line start, CD4 ART start	Hospitals vs clinic: IRR[a]: 1.61 (1.01-2.57) CD4 switch vs > 200: 100-199/mm3: IRR[a]: 1.59 (0.78- 3.25) <50/mm3: IRR[a]: 3.32 (1.81-6.08) Women, adj for adherence: IRR[a]: 1.56 (0.99-2.44) Change 2 NRTI switch: IRR[a]: 0.64 (0.42-0.96) On second-line 6-11 vs >18 mo: IRR[a]:1.90 (1.19-3.02) Adherence <80% vs ≥ 90%: IRR[a] 3.14 (1.67-5.90) Second-line no LPV/r IRR[a]: 1.61 (0.73- 3.56)	Sensitivity analysis: definition of immuno-logical failure as a CD4 cell count of less than 50/mm3 instead of less than 100/mm3 gave similar results Dissappears after adjustment for adherence

	Death Cohort attrition		Rural vs urban: HR[a]: 0.33 (0.12-0.91) Women HR[a]: 0.45 (0.23- 0.91) CD4 switch <100/mm3 HR[a]: 2.83 (1.38-5.80) CD4 switch <50/mm3 HR[a]: 2.74 (1.35-5.58) Immunovirologic failure: HR[a]: 3.17 (1.18-8.50) Change of second-line regimen HR[a]: 0.42(0.22-0.80)	Sensitivity analysis: + predictors mortality
Rohr et al. 2016 (25)	2x VL ≥1000 copies/ml		HR[a]: 2.26 (1.12-4.55) switched 1.5-3 mo vs 0-1.5 mo HR[a]: 2.13 (1.01-4.47) switched 3-6 mo vs 0-1.5 mo	Marginal structure models, in CD4<100 Effect dissappear with longer time, survival bias
Schoffelen et al. 2013 (36)	VF	Gender, CD4 switch, time second-line	/	
Shearer et al. 2017 (47)	Attrition at 12 mo	Gender, BMI, anemia, TB , regimen	35-39 yrs vs <30: HR: 0.40 (0.23-0.70) VL switch ≥ 100,000 vs >5000: HR: 2.19 (1.38-3.46) CD4 switch <50 vs ≥ 200: HR: 2.19 (1.38-4.46) TB: HR: 2.41 (1.31-4.46)	Univariable , In multivariable (not presented) VL less significant and CD4 not
	Attrition end of FU	Gender, BMI, anemia, TB , regimen	CD4 switch <50 vs ≥ 200: HR[a]: 1.85 (1.03-3.32) Started in 2007-8 (vs 5-6): HR[a]: 1.64 (1.04-2.60) Age ≥45 vs <30: HR[a]: 0.48 (0.27-0.84)	Multivariable
	VL≤400 copies/ml at 12 mo	Gender, BMI, anemia, TB ,	TDF vs d4T first-line: RR[a]: 1.22 (1.07-1.39) VL switch ≥ 100,000 vs >5000: RR[a]: 0.79 (0.68-0.92)	Multivariable
	VL≤400 copies/ml end of FU	Gender, BMI, anemia, TB , regimen	VL switch ≥ 100,000 vs >5000: RR: 0.79 (0.64-0.97) CD4 switch <50 vs ≥ 200: RR: 0.62(0.44-0.87)	Univariable , VL no longer significant in multivariate
Sigaloff et al. 2012 (38)	VL <400 copies/ml, death, LTFU, third-line Any failure (VF, IF, CF, LTFU, death, TO)	Active regimens, gender, at switch: CD4,VL, substitutions, 3-day adherence, pills missed,	Age (yrs): OR 0.94 (0.90-0.98) WHO stage IV at start: OR[a]: 5.25 (1.55-17.7) 30-day adherence <95%: OR[a]: 4.08 (1.45-11.5)	Univariable logistic regression Multivariable logistic regression
SSempijja et al. 2017 (29)	Imm. Decline Vir. Increase Composite end-point	Gender, age, clinic, at initiation: year, WHO, CD4, at VF: CD4, VL, year	Time to switch: ≥25 mo: HR: 4 (1-17) 13-24 mo HR: 10 (2-53), ≥25 mo: HR: 14 (3-73) 13-24 mo HR: 5 (1-19), ≥25 mo: HR: 5 (1-17)	Cox prop. Marginal structure model, ref=0-6 mo Univariable , all remained significant in multivariable (not presented)
Tsegaya et al. 2016 (41)	Failure: Death, LTFU, CF, IF	Age, Isoniazide, NRTI first-line	Weight + 1kg: HR[a]: 0.92 (0.88-0.95) WHO switch IV: HR[a]: 2.0 (1.1-4.1) cfr I/II CD4 switch <100: HR[a]: 2.0 (1.2-3.5) cfr ≥ 100	Multivariate, no significant in univariable
Wilhelmson et al. 2016 (7)	LTFU	Age, gender, marital status, running water, electricity, WHO stage	CD4 ART start <100: HR: 1.93 (1.16-3.20) Unable to work: HR: 1.97 (1.17-3.33) First-line failure confirmed by VL: HR:2.11 (1.16-3,83) No education: HR: 1.74 (0.97-3.13)	Univariable Cox (p< 0.3)
			CD4 ART START <100: HR[a]: 2.36 (1.36-4.09) First-line failure confirmed by VL: HR[a]: 2.08 (1.09-3.98)	Multivariable Cox

3TC = lamivudine, ABC = abacavir, ART= anti-retroviral treatment, AZT =zidovudine, BMI = body-mass index, CF = clinical failure, cop= copies, d4T = stavudine, ddI = didanosine, dl = decilitre, EFV = efavirenz, FTC = emtricitabine, FU = follow-up, g = gram, Hb = haemoglobin, HR = hazard ratio, IQR = interquartile range, ITT = intention-to-treat, LPV = lopinavir, LPV/r = lopinavir/ritonavir, LTFU = Lost-to-follow-up, ml = millilitre, mo = month/s, NRTI = nucleotide reverse-transcriptase inhibitor, NNRTI = non-nucleotide reverse-transcriptase inhibitor, NVP = nevirapine, OI = opportunistic Infection, OR = Odds ratio, PI = protease-inhibitor, prob = probability, RAL = raltegravir, RIC = retention (retained) in care, RR = Risk Ratio, SD= standard deviation, TAM = thymidine-analogue mutation, TB = tuberculosis, TDF = tenofovir, VF = virologic failure, VL = viral load.VL1 = first VL after initiation, VL2 = second VL, WHO = World Health Organisation, yrs = years

Summary, interpretation and needs for further research

The 30 included studies were heterogeneous in focus, settings, definitions and reported outcomes, limiting comparability. Nevertheless, trends could be seen in the outcomes. Failure proportions were comparable to existing evidence, and higher in cohorts with longer observation time. Switch rates were moderate to low, and higher when patients were sicker (e.g. CF) or when confirmation of failure was performed in some way (i.e. genotyping, second elevated VL). Switched to second-line ART versus not switching yielded positive outcomes (survival, retention, virologic suppression, CD4) across included articles. The timing between failure and switch was overall high, and longer delays predicted failure after switch. Overall mortality was low, and higher early after failure. LTFU was moderate to high, and likely LTFU masked mortality. Viral re-suppression after second-line switch was acceptable, with exceptions from smaller studies. Patients generally had advanced stages of disease at initiation on first- and second-line, and both predicted negative treatment outcomes. Poor adherence led to adverse outcomes after switch.

Among all identified studies, none reported on cohorts exclusively managed by nurses. Only six studies reported the complete cascade since ART until re-suppression on second-line, and only two among them documented first high VL and confirmatory VL as separate steps (3,23). We found few cohort studies from West-and-Central Africa, where progress towards 90-90-90 targets is lower than anywhere else in the world, and HIV-related mortality is high (6). Among these, only one describes the VL-cascade until viral re-suppression, but not each step, in a long-term cohort including first-line patients (20).

To inform task-shifting of care for growing groups of patients needing VL monitoring and second-line care to nurses, research is needed documenting patient outcomes and their determinants, particularly regions with scarcity of skilled staff, such as in West-and Central Africa. Those studies should explore each step of the cascade after failure, and determinants of outcomes. Such as was done for first-line ART, studies need to establish whether nurse-led care is non-inferior to doctor-led care (54). The protocol proposed in Section A will, to our knowledge, be the first study to document a completely nurse-led cascade until viral suppression on second-line, contributing to the necessary evidence to support nurses managing treatment failure.

References

1. World Health Organization. Task Shifting Global Recommendations and Guidelines HIV/AIDS [Internet]. Geneva; 2008 [cited 2019 Feb 9]. Available from: https://www.who.int/healthsystems/TTR-TaskShifting.pdf

2. UNAIDS. Progress towards the 90-90-90 targets| 2017 [Internet]. Geneva; 2017 [cited 2019 Feb 9]. Available from: http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf

3. Labhardt ND, Ringera I, Lejone TI, Cheleboi M, Wagner S, Muhairwe J, et al. When patients fail UNAIDS' last 90 - the "failure cascade" beyond 90-90-90 in rural Lesotho, Southern Africa: a prospective cohort study. J Int AIDS Soc. 2017;20(1):1–10.

4. Kranzer K, Govindasamy D, Ford N, Johnston V, Lawn SD. Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review. J Int AIDS Soc. 2012;15(2).

5. Estill J, Ford N, Salazar-Vizcaya L, Haas AD, Blaser N, Habiyambere V, et al. The need for second-line antiretroviral therapy in adults in sub-Saharan Africa up to 2030: a mathematical modelling study. lancet HIV. 2016;3(3):e132-9.

6. UNAIDS. Miles to Go. Closing gaps. Breaking Barriers. Righting Injustices. [Internet]. 2018 [cited 2019 Feb 9]. Available from: http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf

7. Médecins Sans Frontières. Out of Focus. How millions of people in West-and Central Africa are being left out of the global HIV response. [Internet]. 2016 [cited 2019 Feb 9]. Available from: https://www.msf.org.za/system/tdf/publications/out_of_focus_english2.pdf?file=1&type=node&id=3026&force=

8. Boillot F, Serrano L, Muwonga J, Kabuayi JP, Kambale A, Mutaka F, et al. Implementation and Operational Research: Programmatic Feasibility of Dried Blood Spots for the Virological Follow-up of Patients on Antiretroviral Treatment in Nord Kivu, Democratic Republic of the Congo. JAIDS. 2016;71(1):e9–15.

9. Global Fund. Global Fund Grants to the Democratic Republic of the Congo [Internet]. 2016 [cited 2019 Feb 9]. Available from: http://data.worldbank.org/indicator/SI.POV.NAHC/countries/CD?display=default

10. Programme National de la lutte contre le SIDA. Plan d'urgence traitement ARV. Kinshasa; 2016.

11. Kredo T, Adeniyi FBFB, Bateganya M, Pienaar EDED. Task shifting from doctors to non-doctors for initiation and maintenance of antiretroviral therapy (Review). Cochrane Database Syst Rev. 2014;(7).

12. Ajose O, Mookerjee S, Mills EJ, Boulle A, Ford N. Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. AIDS. 2012;26(8):929–38.

13. Boerma RS, Bunupuradah T, Dow D, Fokam J, Kariminia A, Lehman D, et al. Multicentre analysis of second-line antiretroviral treatment in HIV-infected children: Adolescents at high risk of failure. J Int AIDS Soc. 2017;20(1):1–9.

14. Pujades-Rodríguez M, Arnould L, Brinkhof MAW. Receiving Second-Line HIV Therapy in Resource-Limited Countries. JAMA. 2010;304(3):303–12.

15. Fox MP, Maskew M, Brennan AT, Evans D, Onoya D, Malete G, et al. Cohort profile: The Right to Care Clinical HIV Cohort, South Africa. BMJ Open. 2017;7(6):1–8.

16. Johnston V, Cohen K, Wiesner L, Morris L, Ledwaba J, Fielding KL, et al. Viral suppression following switch to second-line antiretroviral therapy: Associations with nucleoside reverse transcriptase inhibitor resistance and subtherapeutic drug concentrations prior to switch. J Infect Dis. 2014;209(5):711–20.

17. Levison JH, Orrell C, Gallien S, Kuritzkes DR, Fu N, Losina E, et al. Virologic failure of protease inhibitor-based second-line antiretroviral therapy without resistance in a large HIV treatment program in South Africa. PLoS One. 2012;7(3):3–7.

18. Boulle A, Van Cutsem G, Hilderbrand K, Cragg C, Abrahams M, Mathee S, et al. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. AIDS. 2010;24(4):563–72.

19. Barth RE, Tempelman HA, Moraba R, Hoepelman AIM. Long-term outcome of an HIV-

treatment programme in Rural Africa: Viral suppression despite early mortality. AIDS Res Treat. 2011;2011:1–5.

20. De Beaudrap P, Thiam M, Diouf A, Toure-Kane C, Ngom-Guèye NF, Vidal N, et al. Risk of virological failure and drug resistance during first and second-line antiretroviral therapy in a 10-year cohort in senegal: Results from the ANRS 1215 cohort. J Acquir Immune Defic Syndr. 2013;62(4):381–7.

21. Hawkins C, Hertzmark E, Spiegelman D, Muya A, Ulenga N, Kim S, et al. Switching to second-line ART in relation to mortality in a large Tanzanian HIV cohort. J Antimicrob Chemother. 2017;72(7):2060–8.

22. Keiser O, Tweya H, Braitstein P, Dabis F, Mac Phail P, Boulle A, et al. Mortality after failure of antietroviral therapy in sub-Saharan Africa. Trop Med Int Heal. 2011;15(2):251–8.

23. Lejone TI, Ringera I, Cheleboi M, Wagner S, Muhairwe J, Klimkait T, et al. The treatment cascade in children with unsuppressed viral load - a reality check in rural Lesotho, Southern Africa. JAIDS. 2017;77(3):250–6.

24. Murphy RA, Sunpath H, Lu Z, Chelin N, Losina E, Gordon M, et al. Outcomes after virologic failure of first-line ART in South Africa. AIDS. 2010;24(7):1007–12.

25. Rohr JK, Ive P, Robert Horsburgh C, Berhanu R, Shearer K, Maskew M, et al. Marginal structural models to assess delays in second-line HIV treatment initiation in South Africa. PLoS One. 2016;11(8).

26. Petersen ML, Tran L, Geng EH, Reynolds SJ, Kambugu A, Wood R, et al. Delayed switch of antiretroviral therapy after virologic failure associated with elevated mortality among HIV-infected adults in Africa. AIDS. 2014;28(14):2097–107.

27. Johnston V, Fielding KL, Churchyard G. Outcomes Following Virological Failure and Predictors of Switching to Second-line Antiretroviral Therapy in a South African Treatment Programme. JAIDS. 2013;61(3):1–19.

28. Hosseinipour MC, Kumwenda JJ, Weigel R, Brown LB, Mzinganjira D, Mhango B, et al. Second-line treatment in the Malawi antiretroviral programme: high early mortality, but good outcomes in survivors, despite extensive drug resistance at baseline. HIV Med. 2010;11(8):510–8.

29. Ssempijja V, Nakigozi G, Chang L, Gray R, Wawer M, Ndyanabo A, et al. Rates of switching to second-line antiretroviral therapy and impact of delayed switching on immunologic, virologic, and mortality outcomes among HIV-infected adults with virologic failure in Rakai, Uganda. BMC Infect Dis. 2017;17(1):1–10.

30. Ramadhani HO, Bartlett JA, Thielman NM, Pence BW, Kimani SM, Maro VP, et al. The Effect of Switching to Second-Line Antiretroviral Therapy on the Risk of Opportunistic Infections Among Patients Infected With Human Immunodeficiency Virus in Northern Tanzania. Open Forum Infect Dis. 2016;3(1):1–7.

31. Gsponer T, Petersen M, Egger M, Phiri S, Maathuis MH, Boulle A, et al. The causal effect of switching to second-line ART in programmes without access to routine viral load monitoring. AIDS. 2012;26(1):57–65.

32. Hosseinipour MC, Gupta RK, Van Zyl G, Eron JJ, Nachega JB. Emergence of HIV drug resistance during first- and second-line antiretroviral therapy in resource-limited settings. J Infect Dis. 2013;207(SUPPL.2).

33. Wilhelmson S, Reepalu A, Balcha TT, Jarso G, Björkman P. Retention in care among HIV-positive patients initiating second-line antiretroviral therapy: A retrospective study from an Ethiopian public hospital clinic. Glob Health Action. 2016;9(1):1–8.

34. Johnston V, Fielding K, Charalambous S, Mampho M, Churchyard G, Phillips A, et al. Second-line antiretroviral therapy in a workplace and community-based treatment programme in South Africa: Determinants of virological outcome. PLoS One. 2012;7(5).

35. Pujades-Rodríguez M. Treatment Failure and Mortality Factors in Patients Receiving Second-Line HIV Therapy in Resource-Limited Countries. JAMA. 2010;304(3):303.

36. Schoffelen AF, Wensing AMJ, Tempelman HA, Geelen SPM, Hoepelman AIM, Barth RE. Sustained Virological Response on Second-Line Antiretroviral Therapy following Virological Failure in HIV-Infected Patients in Rural South Africa. PLoS One. 2013;8(3):1–8.

37. Onyedum CC, Iroezindu MO, Chukwuka CJ, Anyaene CE, Obi FI, Young EE. Profile of HIV-infected patients receiving second-line antiretroviral therapy in a resource-limited setting in Nigeria. Trans R Soc Trop Med Hyg. 2013;107(10):608–14.

38. Sigaloff KCE, Hamers RL, Wallis CL, Kityo C, Siwale M, Ive P, et al. Second-line antiretroviral

treatment successfully resuppresses drug-resistant hiv-1 after first-line failure: Prospective cohort in sub-saharan africa. J Infect Dis. 2012;205(11):1739–44.

39. Castelnuovo B, John L, Lutwama F, Ronald A, Spacek LA, Bates M, et al. Three-year outcome data of second-line antiretroviral therapy in Ugandan adults: Good virological response but high rate of toxicity. J Int Assoc Physicians AIDS Care. 2009;8(1):52–9.

40. Osinusi-Adekanmbi O, Stafford K, Ukpaka A, Salami D, Ajayi S, Ndembi N, et al. Long-term outcome of second-line antiretroviral therapy in resource-limited settings. J Int Assoc Provid AIDS Care. 2014;13(4):366–71.

41. Tsegaye AT, Wubshet M, Awoke T, Addis Alene K. Predictors of treatment failure on second-line antiretroviral therapy among adults in northwest Ethiopia: A multicentre retrospective follow-up study. BMJ Open. 2016;6(12).

42. Murphy RA, Sunpath H, Castilla C, Ebrahim S, Court R, Nguyen H, et al. Second-line antiretroviral therapy: long-term outcomes in South Africa. JAIDS. 2012;61(2):158–63.

43. Court R, Leisegang R, Stewart A, Sunpath H, Murphy R, Winternheimer P, et al. Short term adherence tool predicts failure on second line protease inhibitor-based antiretroviral therapy: An observational cohort study. BMC Infect Dis. 2014;14(1):1–7.

44. Fox MP, Ive P, Long L, Maskew M, Sanne I. High rates of survival, immune reconstitution, and virologic suppression on second-line antiretroviral therapy in South Africa. JAIDS. 2010;53(4):500–6.

45. Levison JH, Orrell C, Losina E, Lu Z, Freedberg KA, Wood R. Early outcomes and the virologic impact of delayed treatment switching on second-line therapy in an antiretroviral roll-out program in South Africa. Antivir Ther. 2011;16(6):853–61.

46. Narainsamy D, Mahomed S. Delays in switching patients onto second-line antiretroviral treatment at a public hospital in eThekwini, KwaZulu-Natal. South Afr J HIV Med. 2017;18(1):1–5.

47. Shearer K, Evans D, Moyo F, Rohr JK, Berhanu R, Van Den Berg L, et al. Treatment outcomes of over 1000 patients on second-line, protease inhibitor-based antiretroviral therapy from four public-sector HIV treatment facilities across Johannesburg, South Africa. Trop Med Int Heal. 2017;22(2):221–31.

48. Boender TS, Sigaloff KCE, Mcmahon JH, Kiertiburanakul S, Jordan MR, Barcarolo J, et al. Long-term virological outcomes of first-line antiretroviral therapy for HIV-1 in low- and middle-income countries: A systematic review and meta-analysis. Clin Infect Dis. 2015;61(9):1453–61.

49. McMahon JH, Elliott JH, Bertagnolio S, Kubiak R, Jordan MR. Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries: A systematic review. Bull World Health Organ. 2013;91(5):377–85.

50. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: Systematic review. Trop Med Int Heal. 2010;1(1):1-15

51. Murphy RA, Marconi VC, Gandhi RT, Kuritzkes DR, Sunpath H. Coadministration of Lopinavir/Ritonavir and Rifampicin in HIV and Tuberculosis Co-Infected Adults in South Africa. PLoS One. 2012;7(9):5–10.

52. Ramadhani HO, Bartlett JA, Thielman NM, Pence BW, Kimani SM, Maro VP, et al. Association of first-line and second-line antiretroviral therapy adherence. Open forum Infect Dis. 2014 Sep;1(2):1–8.

53. Kranzer K, Ford N. Unstructured treatment interruption of antiretroviral therapy in clinical practice: A systematic review. Trop Med Int Heal. 2011;16(10):1297–313.

54. Sanne I, Orrell C, Fox MP, Conradie F, Ive P, Zeinecker J, et al. Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial. Lancet (London, England). 2010 Jul 3;376(9734):33–40.

SECTION C:

Manuscript

Nurse-led management of antiretroviral treatment failure: Outcomes from Kinshasa, Democratic Republic of Congo[4]

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[4] This manuscript is presented following instructions for authors from the journal Tropical Medicine and International Health (Appendix 4), deviating from the author guideline in three ways for the purpose of this dissertation:

(i) Authors and affiliations are not included in the title page but addressed in the acknowledgements
(ii) Supplementary tables and figures are provided and referred to in the text
(iii) Strict word count is 3,500 words, unless there are several objectives, in which case 4,000 words are allowed. We considered a 4,000-word limit, which is also the recommended word count for the dissertation by the University of Cape Town.

Abstract

Objectives: In a decentralised nurse-led antiretroviral therapy (ART) programme, to assess compliance with guidelines for viral load (VL) monitoring and management of treatment failure as well as outcomes after a first elevated viral load (VL)≥1000 copies/ml (FEVL), and predictors for a "favourable outcome " defined as retained with supressed VL (<1000 copies/ml), transferred out or censored at database closure after a suppressed VL.

Methods: We included patients starting first-line ART from 2007-2017 with a FEVL in three facilities in Kinshasa, Democratic Republic of Congo (DRC). We used logistic regression to identify predictors of favourable outcomes in adults.

Results: Of 294 adults with FEVL who did not switch to second-line before confirmatory VL, 82% had a second VL (VL2) done within 24 months of FEVL at a median (interquartile range [IQR]) of 4.0 (3.1-5.6) months) after FEVL. Among patients with VL2 done, 69% had VL2≥1000copies/ml, of whom 75% switched to second-line a median of 1.1 (IQR, 0.7-2.0) months after VL2. Among 85% of patients not deceased, LTFU or transferred out by 6 months after second-line switch, 82% had VL<1000 copies/ml. Undergoing VL2 >6 versus ≤3 months after FEVL (adjusted odds ratio [aOR]: 0.26; 95% Confidence Interval [CI]:0.11-0.67) and switching 1-3 versus ≤1 month after VL2≥1000copies/ml (aOR: 0.30; 95%CI:0.10-0.88) were independently associated with lower odds of a favourable outcome .

Conclusion: Nurse-management of the VL-cascade yielded acceptable outcomes in DRC. Early detection and fast switch can help improve retention and viral suppression following virologic failure.

Introduction

Scarcity of human resources for health hampers provision of quality health care in developing countries such as in West- and Central Africa, including for people living with HIV (PLHIV) (1). One in three HIV-related deaths happen in West- and Central Africa, where antiretroviral therapy (ART) coverage was only 39% and viral suppression 29% in 2016 (2,3). A catch-up plan to reach global targets is facing an 81% funding gap, reflecting competing priorities in a region ravished by political tension, epidemics and fragile health systems (2). Decentralisation and task-shifting of treatment and follow-up of PLHIV on first-line ART to nurses and expert patients has contributed to progress toward global targets along the HIV 90-90-90 "care cascade" (i.e. 90% of patients know their HIV status, 90% of these are on treatment, and 90% of ART patients suppress the virus) (4).

Notwithstanding, treatment failure threatens achievement of care cascade targets (5). Both pre-treatment and acquired drug resistance are increasing, with >15% of PLHIV not suppressing the virus by 12 months on ART (6–8). Uptake of viral load- (VL) informed care has allowed for faster identification of treatment failure and switch to second-line protease-inhibitor (PI) based regimens, but implementation is challenging (9). Patients identified with a first high VL, who might already face barriers to treatment adherence, enter an additional elevated "VL-cascade" including intensive counselling, VL re-testing after 3-6 months, switch to second-line if VL remains elevated and return to the original cascade once re-supressed (10). While the World Health Organisation (WHO) has recommended nurse-led care for 'stable patients' (i.e. patients with suppressed VL) since 2008 (11), nurse-led management of first-line failure and decision making about second-line switch has thus far not been recommended. This poses a challenge in settings with limited human resources such as the Democratic Republic of Congo (DRC), where decentralised health services are exclusively nurse-run (12). Of note, in a referral hospital in DRC 84% of admitted patients had advanced HIV disease and only 22% of them were ART-naive, showing the need for early detection of virologic failure (VF) and switch (13).

To our knowledge, outcomes of the complete cascade after an unsuppressed VL (from high VL to re-suppression on second-line ART) have not been documented in West-and Central Africa, nor for an exclusively nurse-ran programme. Two studies from Lesotho described the

VL-cascade for patients in decentralised nurse-led facilities, but second-line switch required advice of a central second-line committee (14,15). We aimed to describe the cascade of care and outcomes of patients following a first VL≥1000 copies/ml at three nurse-led primary health care clinics in Kinshasa, DRC, and to identify predictors for subsequently being retained in care and virologically suppressed (<1000 copies/ml). We also examined compliance with existing protocols for identification of VF and switch to second-line.

Methods

Design

In this retrospective cohort study, we used clinical information that had been routinely collected from ART patients in three urban primary health care facilities from 2007 until June 2018 in Kinshasa, DRC.

Setting

The health system in DRC is fragile and under constant pressure from disease outbreaks and political instability (16). Despite national HIV prevalence of 1.2%, there were nearly 22,000 HIV-related deaths in 2015 (4). In 2017, estimated ART coverage was 34% (children aged <15 years) and 58% (adults) (2). The National Programme for the Fight against AIDS and Sexually Transmittable Diseases in the DRC is responsible for HIV services and started to treat all PLHIV and provide routine annual VL testing in 2016 (17,18). Médecins Sans Frontières (MSF) has supported ART care in the capital Kinshasa since 2002, decentralisation of ART services since 2005 and routine VL monitoring since mid-2015 (13,19). The patients in this study were enrolled in facilities with exclusive decentralised nurse-led care and treatment and clinical mentoring support by MSF.

Decentralisation

Decentralisation of HIV care to primary health care facilities was piloted in 2005, and is accompanied by training, mentoring and supervision of nurses responsible for implementation (Supplementary Table S1). Currently, four to six nurses are trained per facility on 12 clinical themes, with a weekly training session and three months of intense mentoring

of the trainee per theme. High staff turn-over, and high workload of nurses, not limited to HIV care, are challenges restricting continuous mentoring activities. The first community ART dispensing points (PODI) in Kinshasa were piloted in 2010. PODI are dispensaries managed by patient networks, who provide peer support and ART refills to stable patients between 6-monthly clinic visits, with good patient retention (19).

Viral load monitoring

Before 2015, identification of treatment failure was based on clinical and/or immunological criteria confirmed with targeted VL. Routine VL monitoring was implemented mid-2015 in MSF-supported facilities. A central VL platform was installed at the referral hospital, with sample collection at facility level. The initial routine VL protocol prescribed that all newly initiated patients on ART undergo VL testing at six months on ART (or when coming for a routine clinical visit if on ART for longer), and yearly thereafter. Patients with a FEVL received enhanced adherence counselling (EAC) and were re-tested three months later. If patients had a second elevated VL≥1000 copies/ml (SEVL), they were switched to second-line; if the VL was <1000 copies/ml they were referred to a facility fast-track circuit or a PODI. Since January 2017, the protocol was adapted to provide a first VL at three months on ART. Phone-based follow-up was implemented to communicate VL results. The major challenges concern transport logistics, maintenance of the platform and stockouts of laboratory materials and medicines.

Study population

We used two cohorts for the analysis. The primary objective was describing patient outcomes after FEVL, and a secondary objective was to identify predictors for those outcomes (outcome cohort). The other secondary objective was assessing compliance with protocols for VL monitoring and switch to second-line in all ART patients (protocol cohort). The “outcome cohort” included all patients who started ART between 2007 and 2017, with ≥1 VL ≥1000 copies/ml >75 days after ART initiation and ≥6 months potential follow-up thereafter. We excluded patients on PI-based regimens before FEVL. The analysis of predictors of a favourable outcome following FEVL was restricted to adults not censored for any reason ≤135 days after FEVL to ensure a reasonable time for clinical interventions to

have occurred and impacted outcomes (e.g. 2nd VL, EAC, second-line switch). The "protocol cohort" included all patients who started ART on a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen between January 2015 and April 2018 after implementation of routine VL monitoring, and with >135 days potential follow-up before database closure (end June 2018), and thus enough time for a first VL (VL1) measurement to have been done.

Study variables and definitions

The primary outcome for the "outcome cohort" was a "favourable outcome " at 12 months after FEVL defined as either (i) alive and in care with ≥1 VL <1000 copies/ml by 12 months (window of 75-450 days) after FEVL or (ii) transferred out or censored <270 days after FEVL with last VL <1000 copies/ml between 75-270 days after FEVL. Patients were considered deceased if death was confirmed by a family or community member after telephonic follow-up. Patients were documented as "transferred out" (TO) if they confirmed in writing that they had transferred to a clinic outside the MSF supported clinics or to a PODI. Lost-to-follow-up (LTFU), was defined as no return for a follow-up visit 90 days after the scheduled visit without documented TO or death.

We defined VL at ART start as a VL result within 30 days after ART initiation, CD4 at ART start as a CD4 result within [-180 to +7] days of ART initiation, VL1 as the first VL done >30 days after ART initiation, and VL2 as the VL measurement after VL1 ≥1000 copies/ml. The time windows used were defined as: 1 month; [0-30] days, 2 months; [30-75] days, 3 months; [76-135] days, 6 months; [136-270] days, 12 months; [271-450] days, 18 months; [451-630] days, 24 months; [631-810] days. For instance, "in the 6-month window" means between 126-270 days, while by 6 months means ≤270 days. Using these time windows, for compliance to protocols, VL1 was considered "on time" if done 31 days to 6 months after ART initiation, VL2 was "on time" if done <6 months after a VL1 ≥1000 copies/ml. Switch to second-line was considered "on time" within a 2-month window after VL2 ≥1000 copies/ml. The cut-off for considering a VL2 "done" was within a 24-month window.

Data collection and analysis

Clinical data were routinely entered by nurses into individual medical records. Data clerks entered all paper-based patient records into the national database daily (Tier.Net v1.2.2., 2011). An epidemiologist conducted monthly file reviews to improve data accuracy and where possible, complete missing data. De-identified data were extracted from Tier.Net for this analysis. All analyses were performed using Stata/IC 14.1 (StataCorp, Stata Statistical Software: College Station, TX). We described characteristics at ART initiation and FEVL using medians and interquartile ranges and proportions for continuous and categorical variables respectively. We used logistic regression to identify predictors of a favourable outcome at 12 months after FEVL. The variables facility, age at FEVL, months on ART at FEVL and sex were included in the model *a priori*. Additional variables were added if statistically significant ($p < 0.05$) in univariable analysis. If there was collinearity between variables, only one was kept in the model. We compared models using Likelihood Ratio tests for nested models, model Akaike information criterion and pseudo-R^2 for goodness of fit.

Ethical approval

We were granted approval to conduct the study by the National Health Ethics Committee at the Ministry of Health in the DRC and the Human Research Ethics Committee of the University of Cape Town. We obtained exemption from ethical review for routinely collected data from the Ethics Review Board of MSF.

Results

Outcomes of the viral load cascade following first elevated viral load

Among 2550 patients who started ART between 2007 and 2017, 373 (15%) had a FEVL. 316 patients, including 22 (7%) children, met the inclusion criteria for analysis of outcomes after FEVL (Table 1.A).

Table 1: Characteristics of patients in three primary health care clinics in Kinshasa, Democratic Republic of Congo

A. with a first elevated viral load (VL) ≥1000 copies/ml after starting first-line ART between 2007 and 2017 (Outcome cohort)

B. who started first-line ART after implementation of routine viral load monitoring between January 2015 and April 2018 (Protocol cohort)

Characteristic			A. Outcome cohort		B. Protocol cohort	
			Adults (n=294)	**Children[a] (n=22)**	**Adults (n=791)**	**Children (n=54)**
Female (n, %)			217 (74%)	8 (36%)	555 (70%)	23 (43%)
Median age (yrs) (IQR) at ART initiation			37 (31-44)	7 (3-11)	41 (33-48)	6 (2-12)
Median age (yrs) (IQR) at FEVL			41 (34-47)	9 (6-13)		
Age (yrs) category at ART initiation, n (%)		[0 - 5]		8 (36%)		24 (44%)
		]5 - 15]	8 (3%)	14 (64%)		30 (56%)
		]15 - 30]	53 (18%)		128 (16%)	
		]30 - 45]	167 (57%)		386 (49%)	
		]45 - 65]	66 (22%)		266 (34%)	
		]65 - 85]			11 (1%)	
Facility (n, %)[b]		1	140/961 (15%)	8/961 (1%)	456 (58%)	34 (63%)
		2	94/879 (11%)	10/879 (1%)	200 (25%)	9 (17%)
		3	60/710 (8%)	4/710 (1%)	135 (17%)	11 (20%)
Year ART start(n, %)		2007-2010	42 (14%)	1 (5%)		
		2011-2014	132 (45%)	10 (45%)		
		2015-2017	120 (41%)	11 (50%)		
WHO stage at ART initiation (n, %)		1	30 (10%)	4 (18%)	238 (30%)	23 (43%)
		2	72 (24%)	4 (18%)	86 (11%)	7 (13%)
		3	173 (59%)	10 (45%)	361 (46%)	20 (37%)
		4	14 (5%)	4 (18%)	104 (13%)	3 (6%)
		Not recorded	5 (2%)	/	2 (0%)	1 (1%)
Median CD4 (cells/mm^3) (IQR) at ART initiation[c]			153 (73-273)	389 (68-519)	201 (87-360)	418 (298-879)
Median CD4 (cells/mm^3) (IQR) at FEVL[d]			180 (86-325)	273 (22-486)		
Median log VL (copies/ml) (IQR) at ART initiation[e]			4.7 (2.4-5.2)		1.6 (1.6-2.3)	2.0 (1.6-2.4)
Median log FEVL (copies/ml) (IQR)			4.4 (3.8-5.0)	4.4 (3.6-4.8)		
Median time (mo) on ART (IQR) at end of follow-up			46 (28-69)	39 (32-64)	13 (6-20)	13 (4-23)
Median time (mo) on ART (IQR) at FEVL			28 (12-52)	19 (11-39)		
Regimen at ART initiation (n, %)	NRTI	AZT	186 (63%)	20 (91%)	84 (11%)	36 (67%)
		TDF	102 (35%)	2 (9%)	697 (88%)	14 (26%)
		d4T/ABC	6 (2%)		10 (1%)	4 (7%)
	NNRTI	EFV	160 (54%)	17 (77%)	737 (93%)	20 (37%)
		NVP	134 (46%)	5 (23)	54 (7%)	34 (63%)

ABC = abacavir, ART = antiretroviral treatment, AZT = zidovudine, EFV = efavirenz, ml = milliliter, mm= millimeter, mo = month/s, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, IQR = interquartile range, TDF = tenofovir, VL = viral load, FEVL = VL ≥1000 cop/ml minimum 75 days after ART-start, yrs= years.

[a] In A: Children are defined as those of age ≤15 years at FEVL.
[b] In A: Facility proportions are presented as proportions of all ART patients on ART between 2007 and 2017 in those facilities, also for children, who are defined by age at FEVL.
[c] In A: n=204 for adults and n=16 for children. In B: n=505 for adults and n= 30 for children
[d] In A: n=101 for adults and n=6 for children
[e] In A: n=23 for adults and n= 0 for children. In B: n=317 for adults and n=9 for children

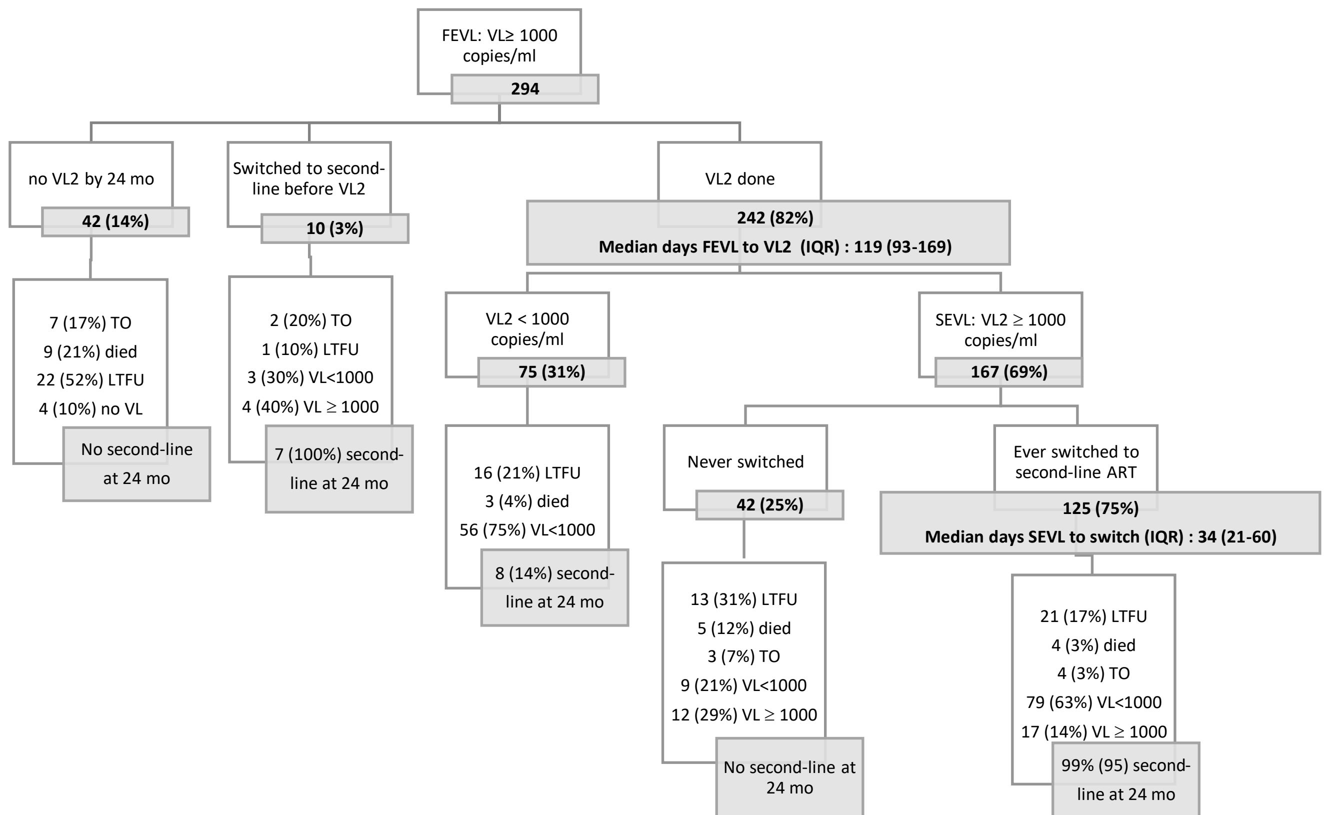


Figure 1: Viral load cascade and outcomes at 24 months for adults >15 years old at first VL ≥1000 copies/ml between 2007 and 2017 in three primary health care clinics in Kinshasa, Democratic Republic of Congo.

VL results and second-line switch at 24 months include patients in care and administratively censored.

FEVL = first elevated VL; first VL ≥ 1000 copies/ml minimum 75 days after ART-start, IQR = interquartile range, mo = months, LTFU = lost-to follow-up, TO = transferred out, VL = viral load, VL2 = first VL after FEVL, SEVL = second elevated VL

Adults

Among adults who had not reached administrative censoring, 204 (74%), 146 (61%), 99 (48%), and 35 (24%) respectively were alive and in care by 6, 12, 18 and 24 months after FEVL (Figure 2, Supplementary table S2). Overall, by the same time points, 9 (3%), 12 (4%), 16 (5%) and 16 (5%) of adults had been transferred out, and 47 (16%), 62 (21%), 71 (24%), and 73 (25%) had been LTFU. 16 (5%) had died by 6 months, 21 (7%) by 12 months.

Table 2: Outcomes per time-window for adults who ever switched to second-line ART after two elevated viral loads (≥1000 copies/ml) between 2007 and 2017 in three primary health care clinics in Kinshasa, Democratic Republic of Congo.

Time after FEVL	By 6-months	By 12-months	By 18-months	By 24-months
In care or administratively censored (n, % of 125)	**122 (98%)**	**108 (86%)**	**97 (78%)**	**96 (77%)**
VL2 done (n, %)	111 (91%)	107 (99%)	96 (99%)	96 (100%)
Switched to second-line ART (n, %)	100 (82%)	106 (98%)	96 (99%)	95 (99%)
Ever re-suppressed (n, %)	34 (28%)	73 (68%)	77 (79%)	79 (82%)

ART = Antiretroviral treatment, FEVL = first VL≥1000 copies/ml >75 days after ART-start. VL2 = VL after FEVL.

252 (86%) of 294 adult patients either had VL2 done (n=242) or were switched to second-line after FEVL without a confirmatory VL (VL2) (n=10) (Figure 1). Cumulatively, by 6, 12, and 24 months, 231 (79%), 247 (84%), and 252 (86%) of the total 294 adults had a VL2 result (Figure 2). Of the 242 patients with a VL2 result, 167 (69%) had a second elevated VL ≥1000 copies/ml (SEVL). Among all patient with a SEVL irrespective of final outcome (death, TO, LTFU), 120 (77%), 141 (82%), 142 (83%), and 144 (83%) had ever been switched to second-line ART by 6, 12, 18 and 24 months. Table 2 presents outcomes of 125 patients with SEVL who switched to second-line ART over SEVL (one switched >24 months after FEVL).

Outcomes after switch

Of patients on second-line ART who were not administratively censored, 105 (85%) and 74 (72%) were in care by 6 and 12 months after switch, 99 (94%) and 72 (97%) had ≥1 VL result, of whom 86 (87%) and 63 (88%) had VL<1000 copies/ml. Overall, by 6 and 12 months, 2 (1%) and 4 (3%) were transferred out, 12 (8%) and 21 (15%) were LTFU, and 4 (3%) died by 6 months after switch.

Children

Of 22 included children, 21 (96%) had a VL2 result with a median of 133 (IQR, 112-189) days between FEVL and VL2 (Supplementary figure S3). 16/22 (76%) had a SEVL, 15 (94%) of whom were switched to second-line at a median of 30 (IQR, 19-66) days after SEVL. Of those children not administratively censored by 6 and 12 months, 17 (89%) and 12 (80%) were alive in care. Overall, 3 (14%) were LTFU by 12 months, none died. Of those in care 6 and 12 months after switch to second-line, 8 (80%) and 7 (78%) had a VL≤ 1000 copies/ml.

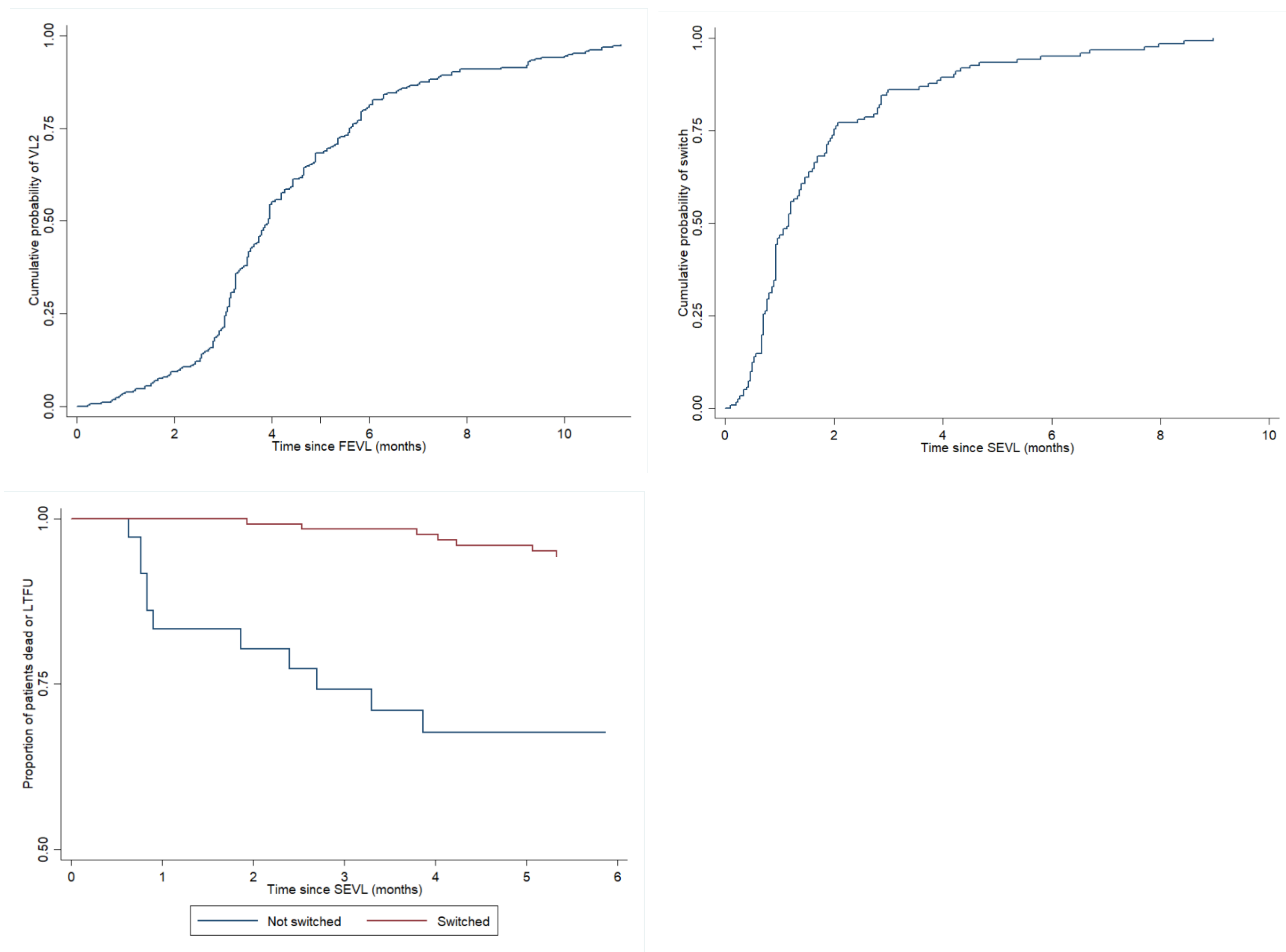


Figure 2: Kaplan-Meier estimates of proportions of adult patients with first elevated VL ≥1000 copies/ml between 2007 and 2017 in three primary health care clinics in Kinshasa, Democratic Republic of Congo

A. **Of having a VL2 done after FEVL among those with FEVL** (upper left panel)
B. **Of switching to second-line ART after SEVL among those with SEVL** (upper right panel)
C. **Of death or LTFU after SEVL, by switched or not switched to second-line ART among those with SEVL** (lower left panel)

FEVL = first elevated VL; first VL ≥ 1000 copies/ml minimum 75 days after ART-start, IQR = interquartile range, mo = months, LTFU = lost-to follow-up, VL = viral load, VL2 = first VL after FEVL, SEVL = second elevated VL; VL2≥ 1000 copies/ml

Table 3: Predictors for a favourable outcome at 12 months after a first VL ≥1000 copies/ml in three primary health care clinics in Kinshasa, Democratic Republic of Congo.

A favourable outcome is not being dead, LTFU or transferred out or administratively censored with a last VL ≥1000 copies/ml. Predictors with a significant effect are presented in bold.

Characteristics		N, column % or median (IQR)	**All patients** (n=250)		**Patients with second VL** (n=240)		**Patients on second-line** (n=120)	
			aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Male sex		56 (26%)	0.59 (0.32-1.08)	0.087	0.60 (0.32-1.15)	0.123	0.62 (0.21-1.82)	0.379
Median (IQR) age (yrs) at FEVL		41 (33-47)	1.02 (0.99-1.04)	0.169	1.02 (0.99-1.05)	0.149	**1.06 (1.01-1.11)**	**0.013**
Facility	1	113 (45%)	1		1		1	
	2	85 (34%)	1.44 (0.78-2.68)	0.242	1.22 (0.63-2.35)	0.556	1.88 (0.61-5.79)	0.269
	3	52 (21%)	1.23 (0.61-2.47)	0.560	0.84 (0.40-1.78)	0.655	0.40 (0.13-1.27)	0.120
WHO stage at ART initiation:	1	24 (10%)	1		1		1	
	2	63 (25%)	**0.24 (0.07-0.80)**	**0.021**	0.29 (0.08-1.00)	0.051	0.24 (0.03-1.85)	0.171
	3/4	160 (64%)	**0.27 (0.08-0.84)**	**0.024**	0.36 (0.11-1.15)	0.087	0.69 (0.10-4.57)	0.237
	not recorded	3 (1%)	0.08 (0.01-1.21)	0.068	0.09 (0.01-1.35)	0.081	omitted	
Log FEVL		4.3 (3.7-4.9)	0.77 (0.56-1.06)	0.104	**0.69 (0.49-0.98)**	**0.037**	0.83 (0.51-1.73)	0.829
Time (mo) on ART at FEVL	≤ 24 mo	108 (43%)	1		1		1	
	24 - 48 mo	69 (28%)	0.99 (0.52-1.91)	0.979	0.92 (0.46-1.82)	0.809	1.48 (0.46-4.72)	0.510
	> 48 mo	73 (29%)	0.87 (0.46-1.67)	0.684	0.86 (0.43-1.70)	0.660	1.75 (0.60-5.10)	0.304
Time (mo) between FEVL and second VL[a]:	≤ 3 mo	38 (16%)			1		1	
	3 - 6 mo	151 (63%)			0.76 (0.34-1.68)	0.500	0.70 (0.19-2.56)	0.588
	> 6 mo	51 (21%)			**0.26 (0.11-0.67)**	**0.005**	0.30 (0.04-2.13)	0.232
Time (mo) between second VL and switch[b]:	≤ 1 mo	57 (48%)					1	
	1 - 3 mo	43 (36%)					**0.30 (0.10-0.88)**	**0.029**
	> 3 mo	10 (8%)					0.32 (0.05-1.73)	0.186
	switch before second VL	10 (8%)					0.20 (0.04-1.09)	0.123

ART= antiretroviral treatment, CI = confidence Interval, FEVL = first VL 75 days after ART start≥ 1000 copies/ml, IQR = interquartile range, mo = month/s, aOR =Adjusted Odds ratio, VL = viral load, WHO = World Health Organization, yrs = years.

[a] restricted to 240 patients with a second VL

[b] restricted to 120 patients switched to second-line maximum ≤270 days after FEVL

Table 4: Compliance to guidelines for identification of virologic failure and switch to second-line ART in patients started on ART between January 2015 and April 2018 in three primary health facilities in Kinshasa, Democratic Republic of Congo.

The timing of the steps in the protocol for virologic failure identification and switch to second-line ART are presented cumulatively as performed by the end of the time window. Results that meet the timing or switching criteria are presented in bold.

VL1 done		**VL2 done**		**Switch to second-line ART**			
618/845 (73%) [a]		67/97 (69%) [b]		27/41 (66%) [c]			
Timing VL1 after ART-start		**Timing VL2 after VL1**		**Timing switch after VL2**		**NRTI before and after switch**	
266 (43%)	**3 mo**	**45 (67%)**	**3 mo**	**2 (7%)**	**Before VL2**	**2 (7%)**	**AZT - ABC**
521 (84%)	**6 mo**	**64 (96%)**	**6 mo**	**14 (52%)**	**1 mo**	**5 (19%)**	**AZT - TDF**
593 (96%)	12 mo	67 (100%)	12 mo	**20 (81%)**	**2 mo**	**3 (11%)**	**TDF - ABC**
618 (100%)	> 12 mo			26 (96%)	3 mo	**14 (52%)**	**TDF - AZT**
				27 (100%)	6 mo	3 (11%)	TDF - TDF

ABC = abacavir, ART = antiretroviral treatment, AZT = zidovudine, EFV = efavirenz, ml = milliliter, mo = month/s, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, TDF = tenofovir, VL = viral load, VL1 = first VL minimum 30 days after ART-start, VL2 = first VL after VL1

[a] excluding VL less than 30 days after ART start

[b] among those with VL1 ≥1000 copies/ml

[c] among those with VL2 ≥1000 copies/ml

Analysis of predictors for favourable treatment outcomes

250 adult patients with a FEVL and ≥135 days subsequent follow-up were included in the analysis of outcome predictors (Table 1.B). 142 (57%) had a favourable outcome at 12 months. Only WHO stage was associated with a favourable outcome: Stage 2 (vs 1) (aOR):0.24 (95% CI: 0.07-0.80)) and Stage 3/4 (vs 1) (aOR):0.27 (95% CI: 0.08-0.84) (Table 3). In 240 patients with a VL after FEVL, 142 (59%) had a favourable outcome at 12 months. >6 months between FEVL and VL2 (vs ≤3) (aOR: 0.26 (95% CI: 0.11-0.67)) and $\log_{10}$ FEVL (aOR: 0.69 per unit increase (95% CI: 0.49-0.98)) were independently associated with reduced likelihood of a favourable outcome at 12 months after FEVL. In 120 patients who switched to second-line <270 days after FEVL, 78 (65%) had a favourable outcome at 12 months. Switching 1-3 months (vs ≤1 month) after FEVL reduced (aOR: 0.30 (95% CI: 0.10-0.88) and a higher age at FEVL ((aOR: 1.06 per year (95% CI: 1.01-1.11)) slightly increased the odds of a favourable outcome.

Compliance to protocols for identification of virologic failure and switch to second-line ART

Of 845 patients in the "protocol cohort" (Table 1.B), 618 (73%) had a VL1 (507 (84%) on time) (Table 4). Out of 97 patients with a VL1 ≥1000 copies/ml, 67 (69%) had a VL2 done (64 (96%) on time). 27 (66%) of patients with a VL2 ≥1000 copies/ml were switched to second-line (20 (81%) switched on time; 24 (89%) changed NRTI appropriately).

Discussion

Our study showed acceptable compliance with the VL-cascade in a nurse-ran programme in Kinshasa (82% of those with VL1≥1000 copies/ml had VL2 done before switch, 91% within 6 months, 75% of those with SEVL were switched to second-line, 91% within 3 months), and those who switched to second-line had good outcomes. After routine VL implementation, coverage was lower but timing was well adhered to (73% had a VL1 done, 84% within 6 months after initiation, 69% of those with a VL1≥1000 copies/ml had VL2 done, 96% within 6 months, 66% of those with a SEVL switched to second-line, 96% within 3 months). Nurses switched patients with confirmed elevated viral load quickly, which was associated with better outcomes; patients switching within a month of SEVL being significantly more likely to be retained and virologically suppressed by 12 months after SEVL.

Fifteen per cent of patients started on ART had a first high VL, in line with published estimates of first-line failure in LMIC (20). Similar to our results were findings from Lesotho, where 84% of adults and 93% of children with a FEVL had a second VL result (14,15). Two large studies in South Africa found shorter (2-3 months) time from FEVL to confirmatory VL than ours, others reported longer delays (21–25). Proportions switched among patients with SEVL were similar or better in comparison to studies using the same switch criteria (14,21,24). Higher proportions switched were reported in a study using genotyping as confirmation (76%) and targeted VL testing (93%) (26,27). Confirmation of the test result, with adherence support between tests, could give health-care workers more confidence to switch without fear of "wasting" regimens on patients with poor adherence. Time from failure to switch in the "outcome cohort" was particularly short, with recent studies reporting between 2-8 months

in South Africa and up to 15 months in Tanzanian clinics (24,28,29). Similar to studies which were doctor-led, high proportions of adults (88%) and children (78%) re-suppressed after switch (30–33). One study with genotyping-informed regimen-switch reported 93% (26). In comparison, in the nurse-led study in Lesotho, only 32% of adults and 38% of children re-supressed (14,15). Overall, VL-cascade results were less positive in the "protocol cohort", but comparable to doctor-led studies, and timelines and correct NRTI-change were mostly respected. Because VL was targeted until 2015, a VL was more likely to be done in patients who already had advanced disease which could have urged nurses to switch faster if VL was found to be high (24). Notably, the "outcome cohort" had lower CD4 at initiation and more advanced WHO clinical stage than the "protocol cohort".

Mortality was low with higher early mortality, which has been documented elsewhere to be related to advanced HIV at ART initiation (27,34,35). LTFU was high, especially early, with 16% lost 6 months and 25% two years after FEVL respectively, and 15% LTFU one year after switch. Studies report LTFU after failure ranging from 9% at 12 to 21% at 18-19 months (14,23,26), and after switch from 4-17% at 6 and 8-14% at 12-15 months respectively (30,31,36–38). One DRC study found retention on first-line ART of 65% and 57% at 1 and 2 years (39), and patients who have failed first-line are likely to have worse retention (35). As mortality is low and LTFU is high and early, LTFU is may mask (early) mortality (35).

We did not find an independent association between switch and a favourable outcome , despite extensive reporting of this in the literature (14,15,29,41). As we include all patients who had a FEVL in the analysis, the lack of association could be due to some patients re-suppressing without switch. Also, we had too few patients and outcomes to use causal analysis methods, and there is likely confounding by indication whereby sicker patients are more likely to be switched, which could attenuate the effect of switch on outcomes. Older patients had a slightly higher chance of a favourable outcome in the second-line group. Older patients also had a lower hazard of attrition (Age ≥45 vs <30: adjusted hazard ratio: 0.48 (95% CI: 0.27-0.84)) in a South African study (28). Younger patients could be less likely to adhere well to second-line ART due to developmental and lifestyle factors associated with youth.

Longer time to confirmatory VL in those with VL2 (>6 vs ≤3 months) and between VL2 and switch (1-3 months vs <1 month) in those switched predicted negative outcomes. Although

we found no significant negative association with >3 months versus <1 month between SEVL and switch and being retained and suppressed, the direction of effect was similar to a 1-3 months vs <1-month delay and the number of patients switching after 3 months was very small. Delays in switch have been extensively shown to predict adverse virologic outcomes (25,30,36,38). Time compliance for confirmatory VL testing and switch is thus essential for good health outcomes, and it is very reassuring that nurses in this routine programme in Kinshasa adhered to time guidelines.

Reaching all patients for initial VL after routine implementation was challenging, and likely reflects troubleshooting at implementation, such as maintenance of the VL platform, reagent supply gaps, sample transport, return of results and limited initial experience of nurses. Funding gaps and supply challenges have been reported to disrupt HIV-services in the DRC, including VL testing (12,42). Electoral tensions also led to disruptions in health services in Kinshasa in recent years, which is not uncommon in the DRC (16). A systematic review showed inconsistent results from decentralised ART monitoring in LMIC, highlighting the need for point-of-care VL testing (43).

This is the first study of an exclusively nurse-managed VL-cascade including switch, and the first study in West-and Central Africa to report different steps in the VL-cascade, necessary to address bottlenecks to reaching universal targets to end HIV (35,43). Data from routine conditions represent the reality for most patients in national programmes, which cannot be derived from controlled conditions. Nevertheless, our study has several limitations. The retrospective design did not allow measurement of other factors that could have helped to explain the results, and missing data could not be retrieved. For instance, we could not report on the numbers of EAC sessions held, a and did not have data on adherence or genotyping to better understand reasons for failure. Replacement of CD4-monitoring with VL-monitoring after VL-scale-up led to CD4-counts not being done for all patients at initiation nor at FEVL. The fact that neither were significant as outcome predictors could be linked to the incompleteness of data. The retrospective design also limits accuracy of data, leading to potential bias. For instance, missing VL results could reflect a VL not done, a missing VL result in the patient file, or an encoding error, not always identifiable through file review. A first VL 31 days after ART-start could be too early for the second VL to be a relevant measurement for viral re-suppression, but no patient had a first VL done between

31 and 75 days after ART-start. Due to lack of a control group we could not establish non-inferiority between nurse-and doctor led care. The high LTFU and high numbers of patients administratively censored throughout the follow up lead to selection bias. The high LTFU could have many reasons. Patients present with advanced disease in Kinshasa, and advanced disease predicts LTFU which masks mortality (13). The highly stigmatised status HIV in the DRC could lead patients to drop in and out of different clinics, and re-present non-ART-naive and severely ill (20). Other patient-level barriers to retention can be cost, time, transportation (44). Although officially HIV-care provided free-of-charge, laboratory tests and medicines other than antiretrovirals are often subject to user fees (45). Health system factors such as high workload of poorly remunerated nurses, and regular shortages of medicines and lab supplies, all Kinshasa reality, contribute to patients' disengagement with care (42,44). Selection bias may explain part of the association between delays between VL-cascade steps and outcomes, as those more adherent to clinic visits and returning faster, are more likely to have had a second VL and switch done earlier, hence more likely to re-suppress. Finally, the support from MSF, even if limited to logistics support and mentoring, could have helped to improve results, such as timing between SEVL and switch.

Growing numbers of patients with VF in need of second-line ART urge for task-shifting of management of the VL-cascade. Our study shows that a nurse-led decentralised programme in a challenging context can yield comparable results to doctor-led studies in similar or more developed contexts. Appropriate logistical support and continued quality training and mentoring for nursing staff, accompanied by adequate funding, are conditions to successful implementation. Task-shifting could allow more time for doctors to deal with complex cases, for example related to PI-induced drug toxicities or drug-drug interactions. While our study focuses on nurse-led care, task-shifting from doctors can occur to other cadres such as clinical officers, depending on context-specific availability (43). As pre-treatment drug resistance is increasing, many countries consider dolutegravir-based regimens for ART-naive and ART-non-naive patients. Dolutegravir has a high genetic barrier, and evidence suggests it is superior and it better tolerable than NRTI and PI-based regimens (46). Appropriate monitoring of long-term outcomes and resistance, with the human resources available, will be essential to preserve this drug for future generations. More research, including studies

comparing nurse- to doctor-led care, is needed to show feasibility and results of nurse-led programmes in rural areas and other contexts. Nurse-led management of the VL-cascade contributes to reach global targets in the HIV-response and should be widely implemented.

References

1. Zachariah R, Ford N, Philips M, S.Lynch, Massaquoi M, Janssens V, et al. Task shifting in HIV/AIDS: opportunities, challenges and proposed actions for sub-Saharan Africa. Trans R Soc Trop Med Hyg. 2009;103(6):549–58.

2. UNAIDS. Miles to Go. Closing gaps. Breaking Barriers. Righting Injustices. [Internet]. 2018 [cited 2019 Feb 9]. Available from: http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf

3. UNAIDS U. Step Up the Pace: Towards an AIDS-free generation in West and Central Africa [Internet]. Geneva; 2017 [cited 2019 Feb 10]. Available from: https://www.unicef.org/publications/files/Step_Up_the_Pace_West_and_Central_Africa.pdf

4. UNAIDS. Progress towards the 90-90-90 targets| 2017 [Internet]. Geneva; 2017 [cited 2019 Feb 9]. Available from: http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf

5. Kredo T, McCaul M, Volmink J. Task-shifting from doctors to non-doctors for initiation and maintenance of antiretroviral therapy. S Afr Med J. 2015;105(8):626–7.

6. Boerma RS, Sigaloff KCE, Akanmu AS, Inzaule S, Boele van Hensbroek M, Rinke de Wit TF, et al. Alarming increase in pretreatment HIV drug resistance in children living in sub-Saharan Africa: a systematic review and meta-analysis. J Antimicrob Chemother. 2017 Feb;72(2):365–71.

7. Hamers RL, Sigaloff KCE, Kityo C, Mugyenyi P, de Wit TFR. Emerging HIV-1 drug resistance after roll-out of antiretroviral therapy in sub-Saharan Africa. Curr Opin HIV AIDS. 2013 Jan;8(1):19–26.

8. World Health Organization, Centre for Disease Control and Prevention, The Global Fund. HIV Drug Resistance Report [Internet]. Geneva; 2017 [cited 2019 Feb 10]. Available from: https://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf?sequence=1

9. Stockdale AJ, Saunders MJ, Boyd MA, Bonnett LJ, Johnston V, Wandeler G, et al. Effectiveness of Protease Inhibitor/Nucleos(t)ide Reverse Transcriptase Inhibitor-Based Second-line Antiretroviral Therapy for the Treatment of Human Immunodeficiency Virus Type 1 Infection in Sub-Saharan Africa: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018;66(12):1846–57.

10. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach

[Internet]. 2016 [cited 2019 Feb 9]. Available from: https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf;jsessionid=6F5FC0BC34E6F336F355F9B5DB1C9B6B?sequence=1

11. World Health Organization. Task Shifting Global Recommendations and Guidelines HIV/AIDS [Internet]. Geneva; 2008 [cited 2019 Feb 9]. Available from: https://www.who.int/healthsystems/TTR-TaskShifting.pdf

12. Boillot F, Serrano L, Muwonga J, Kabuayi JP, Kambale A, Mutaka F, et al. Implementation and Operational Research: Programmatic Feasibility of Dried Blood Spots for the Virological Follow-up of Patients on Antiretroviral Treatment in Nord Kivu, Democratic Republic of the Congo. JAIDS. 2016;71(1):e9–15.

13. Ousley J, Niyibizi AA, Wanjala S, Vandenbulcke A, Kirubi B, Omwoyo W, et al. High Proportions of Patients with Advanced HIV Are Antiretroviral Therapy Experienced: Hospitalization Outcomes from 2 Sub-Saharan African Sites. Clin Infect Dis. 2018;66(Suppl 2):S126–32.

14. Labhardt ND, Ringera I, Lejone TI, Cheleboi M, Wagner S, Muhairwe J, et al. When patients fail UNAIDS' last 90 - the "failure cascade" beyond 90-90-90 in rural Lesotho, Southern Africa: a prospective cohort study. J Int AIDS Soc. 2017;20(1):1–10.

15. Lejone TI, Ringera I, Cheleboi M, Wagner S, Muhairwe J, Klimkait T, et al. The treatment cascade in children with unsuppressed viral load - a reality check in rural Lesotho, Southern Africa. JAIDS. 2017;77(3):250–6.

16. World Health Organization. The Democratic Republic of the Congo: quantifying the crisis. Bull World Heal Organ. 2009;87:6–7.

17. Programme National de la lutte contre le SIDA. Plan d'urgence traitement ARV. Kinshasa; 2016.

18. Programme National de la Lutte contre le SIDA et les lST. Guide de Prise en Charge Integrée du VIH en République Démocratique du Congo. Kinshasa; 2016.

19. Vogt F, Kalenga L, Lukela J, Salumu F, Diallo I, Nico E, et al. Decentralizing ART supply for stable HIV patients to community-based distribution centres: Programme outcomes from an urban context in Kinshasa, DRC. JAIDS. 2016;74(3):1.

20. McMahon JH, Spelman T, Ford N, Greig J, Mesic A, Ssonko C, et al. Risk factors for unstructured treatment interruptions and association with survival in low to middle income countries. AIDS Res Ther. 2016;13:25.

21. Rohr JK, Ive P, Robert Horsburgh C, Berhanu R, Shearer K, Maskew M, et al. Marginal structural models to assess delays in second-line HIV treatment initiation in South Africa. PLoS One. 2016;11(8).

22. Petersen ML, Tran L, Geng EH, Reynolds SJ, Kambugu A, Wood R, et al. Delayed switch of antiretroviral therapy after virologic failure associated with elevated mortality among HIV-infected adults in Africa. AIDS. 2014;28(14):2097–107.

23. Johnston V, Fielding KL, Churchyard G. Outcomes Following Virological Failure and Predictors of Switching to Second-line Antiretroviral Therapy in a South African Treatment Programme. JAIDS. 2013;61(3):1–19.

24. Ssempijja V, Nakigozi G, Chang L, Gray R, Wawer M, Ndyanabo A, et al. Rates of switching to second-line antiretroviral therapy and impact of delayed switching on immunologic, virologic, and mortality outcomes among HIV-infected adults with virologic failure in Rakai, Uganda. BMC Infect Dis. 2017;17(1):1–10.

25. Narainsamy D, Mahomed S. Delays in switching patients onto second-line antiretroviral treatment at a public hospital in eThekwini, KwaZulu-Natal. South Afr J HIV Med. 2017;18(1):1–5.

26. Murphy RA, Sunpath H, Lu Z, Chelin N, Losina E, Gordon M, et al. Outcomes after virologic failure of first-line ART in South Africa. AIDS. 2010;24(7):1007–12.

27. Hosseinipour MC, Kumwenda JJ, Weigel R, Brown LB, Mzinganjira D, Mhango B, et al. Second-line treatment in the Malawi antiretroviral programme: high early mortality, but good outcomes in survivors, despite extensive drug resistance at baseline. HIV Med. 2010;11(8):510–8.

28. Shearer K, Evans D, Moyo F, Rohr JK, Berhanu R, Van Den Berg L, et al. Treatment outcomes of over 1000 patients on second-line, protease inhibitor-based antiretroviral therapy from four public-sector HIV treatment facilities across Johannesburg, South Africa. Trop Med Int Heal. 2017;22(2):221–31.

29. Hawkins C, Hertzmark E, Spiegelman D, Muya A, Ulenga N, Kim S, et al. Switching to second-line ART in relation to mortality in a large Tanzanian HIV cohort. J Antimicrob Chemother. 2017;72(7):2060–8.

30. Sigaloff KCE, Hamers RL, Wallis CL, Kityo C, Siwale M, Ive P, et al. Second-line antiretroviral treatment successfully resuppresses drug-resistant hiv-1 after first-line failure: Prospective cohort in sub-saharan africa. J Infect Dis. 2012;205(11):1739–44.

31. Pujades-Rodríguez M. Treatment Failure and Mortality Factors in Patients Receiving Second-Line HIV Therapy in Resource-Limited Countries. JAMA. 2010;304(3):303.

32. Onyedum CC, Iroezindu MO, Chukwuka CJ, Anyaene CE, Obi FI, Young EE. Profile of HIV-infected patients receiving second-line antiretroviral therapy in a resource-limited setting in Nigeria. Trans R Soc Trop Med Hyg. 2013;107(10):608–14.

33. Court R, Leisegang R, Stewart A, Sunpath H, Murphy R, Winternheimer P, et al. Short term adherence tool predicts failure on second line protease inhibitor-based antiretroviral therapy: An observational cohort study. BMC Infect Dis. 2014;14(1):1–7.

34. Barth RE, Tempelman HA, Moraba R, Hoepelman AIM. Long-term outcome of an HIV-treatment programme in Rural Africa: Viral suppression despite early mortality. AIDS Res Treat. 2011;2011:1–5.

35. Ajose O, Mookerjee S, Mills EJ, Boulle A, Ford N. Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis.

AIDS. 2012;26(8):929–38.

36. Levison JH, Orrell C, Losina E, Lu Z, Freedberg KA, Wood R. Early outcomes and the virologic impact of delayed treatment switching on second-line therapy in an antiretroviral roll-out program in South Africa. Antivir Ther. 2011;16(6):853–61.

37. Fox MP, Ive P, Long L, Maskew M, Sanne I. High rates of survival, immune reconstitution, and virologic suppression on second-line antiretroviral therapy in South Africa. JAIDS. 2010;53(4):500–6.

38. Johnston V, Fielding K, Charalambous S, Mampho M, Churchyard G, Phillips A, et al. Second-line antiretroviral therapy in a workplace and community-based treatment programme in South Africa: Determinants of virological outcome. PLoS One. 2012;7(5).

39. Koole O, Kalenga L, Kiumbu M, Menten J, Ryder RW, Mukumbi H, et al. Retention in a NGO supported antiretroviral program in the Democratic Republic of Congo. PLoS One. 2012;7(7):1–10.

40. Wilhelmson S, Reepalu A, Balcha TT, Jarso G, Björkman P. Retention in care among HIV-positive patients initiating second-line antiretroviral therapy: A retrospective study from an Ethiopian public hospital clinic. Glob Health Action. 2016;9(1):1–8.

41. Gsponer T, Petersen M, Egger M, Phiri S, Maathuis MH, Boulle A, et al. The causal effect of switching to second-line ART in programmes without access to routine viral load monitoring. AIDS. 2012;26(1):57–65.

42. Gils T, Bossard C, Verdonck K, Owiti P, Casteels I, Mashako M, et al. Stockouts of HIV commodities in public health facilities in Kinshasa: Barriers to end HIV. PLoS One. 2018;13(1):e0191294.

43. Pham MD, Romero L, Parnell B, Anderson DA, Crowe SM, Luchters S. Feasibility of antiretroviral treatment monitoring in the era of decentralized HIV care: A systematic review. AIDS Res Ther. 2017;14(1).

44. Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: A systematic review. AIDS. 2012;26(16):2059–67.

45. Maini R, Van Den Bergh R, Van Griensven J, Tayler-Smith K, Ousley J, Carter D, et al. Picking up the bill - Improving health-care utilisation in the Democratic Republic of Congo through user fee subsidisation: A before and after study. BMC Health Serv Res. 2014;14(1):1–11.

46. Waal R De, Lessells R, Hauser A, Kouyos R, Davies M, Egger M, et al. HIV drug resistance in sub-Saharan Africa : public health questions and the potential role of real-world data and mathematical modelling. J Virus Erad. 2018;4(Supplement 2):55–8.

Supplementary tables and figures

Supplementary Table S1: Chronology of decentralisation process and important protocol changes in an anti-retroviral treatment programme supported by Médecins Sans Frontières, Kinshasa, Democratic Republic of Congo.

Timing	MSF supported programme Kinshasa	National protocols, policy changes
2002	HIV-testing and treatment of opportunistic infections at ambulatory treatment centre Kabinda	
2003	Start of ART at centre Kabinda	
2005	Decentralisation of ART patients to four health centres, integration of ART care in nurse-led primary health care Hand-over to Ministry of health of 3000 patients from centre Kabinda (1400 on ART)	
2008	Start hospitalisation unit Centre Hospitalier Kabinda (CHK) with 24 beds	
2010	Start of three ART dispensing points in the community (PODI) (19)	
2012	CHK becomes referral centre, all stable patients are decentralised	
2013	Further decentralisation towards 10 health centres in the health zone of Masina I	
2014	Start community ART groups, fast-track refills	
2015	Increased capacity for CHK to 41 beds Start of viral load platform at CHK First VL done at 6 months on ART	Rationalisation process separating support to clinics providing ART per donor First-line becomes TDF/3TC/EFV instead of AZT/3TC/NVP, leading to stock-outs of former (42)
2016	Start test & treat and clinical mentoring activities Hand-over 2 PODIs to partners	Acceleration plan (17,18): Test and treat and routine viral load testing with first VL after 6 months on ART. VL replaces CD4 for monitoring of ART patients.
2017	Protocol change: first VL after 3 months on ART	
2018	Clinical mentoring in CHK, two general hospitals and health centres (including studied facilities)	

3TC = lamivudine, ART = Antiretroviral Treatment, AZT = zidovudine, CHK = Centre Hospitalier Kabinda, EFV = efavirenz , NVP = nevirapine, TDF = tenofovir. VL = viral load

Supplementary Table S2: Cumulative outcomes per time-window of patients after a first viral load ≥1000 copies/mL between 2007 and 2017 in three primary health care clinics in Kinshasa, Democratic Republic of Congo.

A. **All patients.** Stratified per adults and children.
B. **Patients with two consecutive VL results ≥ 1000 copies/ml (SEVL) after ART start who were switched to second-line.** Stratified per adults and children.
C. **All adult patients.** Stratified per ever switched to second-line and never switched to second-line

A. All patients	**End of 6-months window**			**End of 12-months window**			**End of 18-months window**			**End of 24-months window**		
Status	Total	Re-sup/ VL done	Switched/ Total	Total	Re-sup/ VL done	Switched/ Total	Total	Re-sup/ VL done	Switched/ Total	Total	Re-sup/ VL done	Switched/ Total
Alive in care	69% (204)	24% (92/177)	54% (110/204)	50% (146)	76% (106/140)	68% (99/146)	34% (99)	88% (84/96)	69% (68/99)	12% (35)	91% (31/34)	63% (22/35)
Admin. censored	6% (18)	59% (10/17)	33% (6/18)	18% (53)	72% (36/50)	42% (22/53)	30% (87)	76% (64/84)	47% (41/87)	51% (149)	81% (118/146)	59% (88/149)
Transferred out	3% (9)	0% (0/3)	0% (0/9)	4% (12)	20% (1/5)	17% (2/12)	5% (16)	33% (3/9)	38% (6/16)	5% (16)	33% (3/9)	38% (6/16)
Dead	5% (16)	29% (2/7)	6% (1/16)	7% (21)	42% (5/12)	19% (4/21)	7% (21)	42% (5/12)	19% (4/21)	7% (21)	42% (5/12)	19% (4/21)
LTFU	16% (47)	71% (12/27)	6% (3/47)	21% (62)	53% (21/40)	23% (14/62)	24% (71)	59% (29/49)	32% (23/71)	25% (73)	61% (31/51)	33% (24/73)
Total adults	**100% (294)**	**50% (116/231)**	**41% (120/294)**	**100% (294)**	**68% (169/247)**	**48% (141/294)**	**100% (294)**	**74% (185/250)**	**48% (142/294)**	**294**	**75% (188/252)**	**49% (144/294)**
Alive in care	77% (17)	21% (3/14)	35% (6/17)	55% (12)	73% (8/11)	83% (10/12)	36% (8)	71% (5/7)	88% (7/8)	14% (3)	100% (3/3)	67% (2/3)
Alive, end of follow-up	14% (3)	33% (1/3)	67% (2/3)	32% (7)	33% (2/6)	43% (3/7)	50% (11)	50% (5/10)	64% (7/11)	64% (14)	62% (8/13)	71% (10/14)
Transferred out										5% (1)	100% (1/1)	100% (1/1)
Dead												
LTFU	9% (2)	100% (1/1)	0% (0/2)	14% (3)	67% (2/3)	33% (1/3)	14% (3)	67% (2/3)	33% (1/3)	18% (4)	50% (2/4)	50% (2/4)
Total children	**100% (22)**	**28% (5/18)**	**36% (8/22)**	**100% (22)**	**60% (12/20)**	**64% (14/22)**	**100 % (22)**	**60% (12/20)**	**68% (15/22)**	**100% (22)**	**67% (14/21)**	**68% (15/22)**

B. Patients who switched after SEVL	**End of 6-months window**			**End of 12-months window**			**End of 18-months window**			**End of 24-months window**		
Status	Total	Re-sup/ VL done	Switched/ Total	Total	Re-sup/ VL done	Switched/ Total	Total	Re-sup/ VL done	Switched/ Total	Total	Re-sup/ VL done	Switched/ Total
Alive in care	94% (117)	32% (34/106)	81% (95/117)	74% (93)	71% (65/92)	98% (91/93)	53% (66)	85% (55/65)	98% (65/66)	17% (21)	90% (19/21)	95% (20/21)
Alive, end of follow-up	4% (5)	0% (0/5)	100% (5/5)	12% (15)	53% (8/15)	100% (15/15)	25% (31)	71% (22/31)	100% (31/31)	60% (75)	80% (60/75)	100% (75/75)
Transferred out				1% (1)	0% (0/1)	100% (1/1)	3% (4)	50% (2/4)	100% (4/4)	3% (4)	50% (2/4)	100% (4/4)
Dead	1% (1)	0% (0/1)	100% (1/1)	3% (4)	50% (2/4)	100% (4/4)	3% (4)	50% (2/4)	100% (4/4)	3% (4)	50% (2/4)	100% (4/4)
LTFU	2% (2)	0% (0/2)	100% (2/2)	5% (6)	50% (6/12)	100% (12/12)	16% (20)	65% (13/20)	100% (20/20)	17% (21)	67% (14/21)	100% (21/21)
Total adults	**100% (125)**	**30% (34/114)**	**82% (103/125)**	**100% (125)**	**65% (81/124)**	**98% (123/125)**	**100% (125)**	**76% (94/124)**	**99% (124/125)**	**100% (125)**	**76% (97/125)**	**99% (124/125)**
Alive in care	87% (13)	15% (2/13)	85% (11/13)	73% (11)	73% (8/11)	91% (10/11)	47% (7)	71% (5/7)	100% (7/7)	13% (2)	100% (2/2)	100% (2/2)
Alive, end of follow-up	13% (2)	0% (0/2)	100% (2/2)	20% (3)	0% (0/3)	100% (3/3)	47% (7)	43% (3/7)	00% (7/7)	67% (10)	60% (6/10)	100% (10/10)
Transferred out										7% (1)	100% (1/1)	100% (1/1)
Dead												
LTFU				7% (1)	0% (0/1)	100% (1/1)	7% (1)	0% (0/1)	100% (1/1)	13% (2)	0% (0/2)	100% (2/2)
Total children	**100% (15)**	**13% (2/15)**	**87% (13/15)**	**100% (15)**	**53% (8/15)**	**93% (14/15)**	**100% (15)**	**53% (8/15)**	**100% (15/15)**	**100% (15)**	**60% (9/15)**	**100% (15/15)**

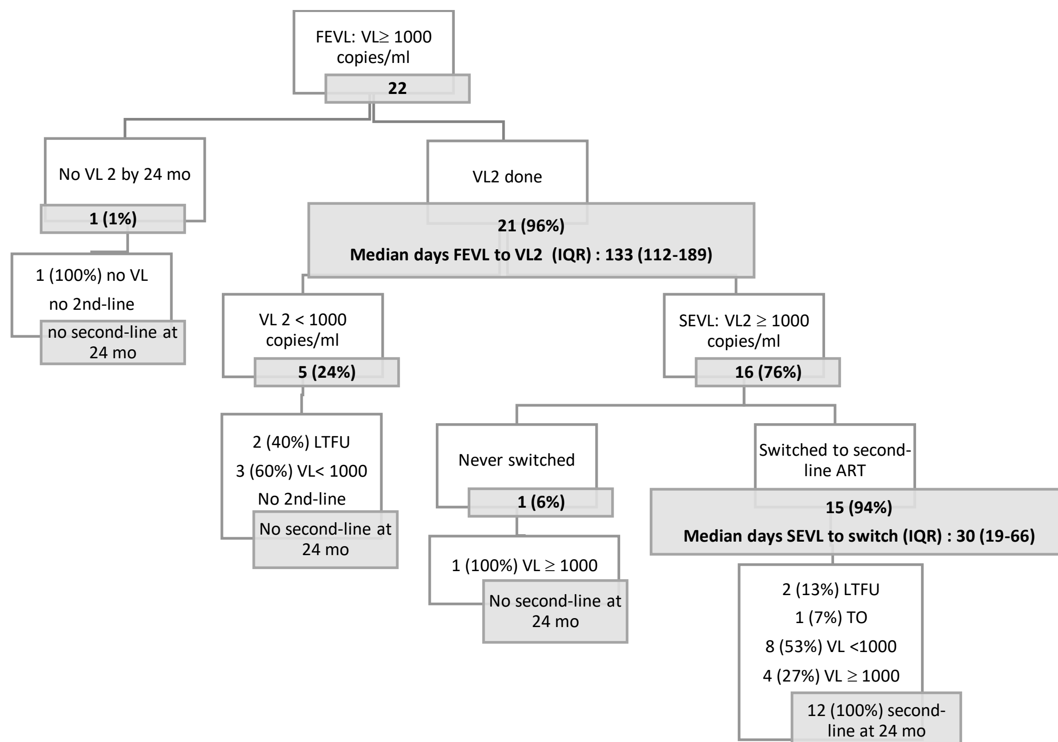
C. All Adult patients	End of 6-months window			End of 12-months window			End of 18-months window			End of 24-months window		
Status	Total	Re-sup/ VL done	Switched/ Total	Total	Re-sup/ VL done	Switched/ Total	Total	Re-sup/ VL done	Switched/ Total	Total	Re-sup/ VL done	Switched/ Total
Alive in care	93% (135)	37% (46/123)	81% (110/135)	71% (103)	69% (70/101)	96% (99/103)	49% (71)	83% (58/70)	96% (68/71)	16% (23)	96% (22/23)	96% (22/23)
Alive, end of follow-up	4% (6)	17% (1/6)	100% (6/6)	15% (22)	64% (14/22)	100% (22/22)	28% (41)	73% (30/41)	100% (41/41)	61% (88)	78% (69/88)	100% (88/88)
Transferred out				1% (2)	50% (1/2)	100% (2/2)	4% (6)	50% (3/6)	100% (6/6)	4% (6)	50% (3/6)	100% (6/6)
Dead	1% (1)	0% (0/1)	100% (1/1)	3% (4)	50% (2/4)	100% (4/4)	3% (4)	50% (2/4)	100% (4/4)	3% (4)	50% (2/4)	100% (4/4)
LTFU	2% (3)	0% (0/3)	100% (3/3)	10% (14)	50% (7/14)	100% (14/14)	16% (23)	65% (15/23)	100% (23/23)	17% (24)	67% (16/24)	100% (24/24)
Total ever second-line	**100% (145)**	**35% (47/133)**	**83% (120/145)**	**100% (145)**	**66% (94/143)**	**97% (141/145)**	**100% (145)**	**75% (108/144)**	**98% (142/145)**	**100% (145)**	**77% (111/145)**	**99% (144/145)**
Alive in care	46% (69)	85% (46/54)		29% (43)	92% (36/39)		19% (28)	100% (26/26)		8% (12)	91% (10/11)	
Alive, end of follow-up	8% (12)	82% (9/11)		21% (31)	79% (22/28)		31% (46)	79% (34/43)		41% (61)	85% (49/58)	
Transferred out	6% (9)	0% (0/3)		7% (10)	0% (0/3)		7% (10)	0% (0/3)		7% (10)	0% (0/3)	
Dead	10% (15)	33% (2/6)		11% (17)	38% (3/8)		11% (17)	38% (3/8)		11% (17)	38% (3/8)	
LTFU	30% (44)	50% (12/24)		32% (48)	54% (14/26)		32% (48)	54% (14/26)		33% (49)	56% (15/27)	
Total never second-line	**100% (149)**	**70% (69/98)**		**100% (149)**	**72% (75/104)**		**100% (149)**	**73% (77/106)**		**100% (149)**	**72% (77/107)**	

Admin = administratively. ART = antiretroviral treatment. Re-sup = ever re-suppressed, or at least one VL < 1000 copies/ml after the VL1 ≥ 1000 copies/ml. SEVL = second elevated VL, VL = viral load

Supplementary Figure S3: Viral load cascade and outcomes at 24 months for children <15 years old at first VL ≥1000 copies/ml between 2007 and 2017 in three primary health care clinics in Kinshasa, Democratic Republic of Congo.

VL results and second-line switch at 24 months include patients retained in care and administratively censored.

ART = anti-retroviral treatment, FEVL = first elevated VL; first VL ≥ 1000 cop/ml minimum 75 days after ART-start, IQR = interquartile range, mo = months, LTFU = lost-to follow-up, TO = transferred out, VL = viral load, VL2 = first VL after FEVL. SEVL = VL after FEVL ≥1000 copies/ml.



Supplementary Table S4: Univariable analysis of predictors for a favourable outcome at 12 months after a first VL ≥1000 copies/ml in three primary health care clinics in Kinshasa, Democratic Republic of Congo.

A favourable outcome is not being dead, LTFU or transferred out or administratively censored with a last VL ≥1000 copies/ml. Predictors with a significant effect are presented in bold.

Characteristics		N, column % or median (IQR)	OR (95% CI)	p-value
Male sex		56 (26%)	0.66 (0.37 - 1.17)	0.153
Median (IQR) age (yrs) at FEVL		41 (33-47)	1.01 (0.99 -1.03)	0.415
Facility	1	113 (45%)	1	
	2	85 (34%)	1.54 (0.86 - 2.74)	0.142
	3	52 (21%)	1.03 (0.53 -1.99)	0.929
Cohort	2007-2014	99 (40%)	1	
	2015-2017	151 (61%)	0.77 (0.46-1.29)	0.326
WHO-stage at ART initiation:	1	24 (10%)	1	
	2	63 (25%)	**0.23 (0.07-0.77)**	**0.016**
	3/4	160 (64%)	**0.24 (0.08-0.73)**	**0.012**
	not recorded	3 (1%)	0.10 (0.01-1.38)	0.086
Non-ART-naive at start		38 (15%)	1.19 (0.59-2.42)	0.615
Median (IQR) CD4 at ART initiation (n=173)		171 (81-282)	1.00 (0.99-1.00)	0.735
CD4 at FEVL (n=87)		188 (95-332)	1.00 (1.00-1.00)	0.927
Log FEVL		4.3 (3.7-4.9)	0.74 (0.54-1.00)	0.052
Time (mo) on ART at FEVL	≤24 mo	108 (43%)	1	
	24 - 48 mo	69 (28%)	1.12 (0.61-2.08)	0.700
	> 48 mo	73 (29%)	0.93 (0.51-1.69)	0.823
Time (mo) on first-line ART		40 (22-62)	1.00 (0.99-1.01)	0.516
Regimen at start containing TDF (vs ABC/AZT)		79 (32%)	1.48 (0.85-2.56)	0.166
Regimen at start containing NVP (vs EFV)		119 (48%)	0.69 (0.42-1.15)	0.153
Ever on second-line : yes		145 (58%)	1.19 (0.72-1.98)	0.495
Number of visits/year		7.5 (4.7-10.4)	1.01 (0.95-1.07)	0.676
Number of VL/year		0.9 (0.6-1.4)	1.09 (0.68-1.74)	0.728
Time (mo) between FEVL and second VL[a]:	≤ 3 mo	38 (16%)	1	
	3 - 6 mo	151 (63%)	0.81 (0.38-1.72)	0.577
	> 6 mo	51 (21%)	**0.30 (0.12-0.72)**	**0.007**
Second-line regimen containing TDF[b]		86 (72%)	1.22 (0.53-2.78)	0.641
Time (mo) between second VL and switch[b]:	≤ 1 mo	57 (48%)	1	
	1 - 3 mo	43 (36%)	0.45 (0.19-1.06)	0.069
	> 3 mo	10 (8%)	0.49 (0.12-1.98)	0.316
	switch before second VL	10 (8%)	**0.22 (0.05-0.88)**	**0.033**

ABC = abacavir, ART= antiretroviral treatment, AZT = zidovudine, CI = Confidence Interval, mo = month/s, EFV = efavirenz , FEVL = first VL ≥ 1000 copies/ml >75 days after ART start, IQR = interquartile range, NVP = nevirapine, TDF = tenofovir, WHO = World Health Organization, yrs = years.

[a] restricted to 240 patients with a second VL.

[b] restricted to 120 patients switched to second-line ≤270 days after FEVL.

Appendices

APPENDIX I: Approval of the Human Research Ethics Committee, University of Cape Town, Cape Town, South Africa, for the study: Nurse-led management of antiretroviral treatment failure: Patient outcomes from Kinshasa, Democratic Republic of Congo

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338
Email: lamees.emjedi@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

07 August 2018

HREC REF: 473/2018

A/Prof MA Davies
Centre for Infectious Disease Research
Public Health & Family Medicine
Room 3.49, Falmouth Building

Dear A/Prof Davies

PROJECT TITLE: NURSE-LED MANAGEMENT OF ANTIRETROVIRAL TREATMENT FAILURE: PATIENT OUTCOMES FROM KINSHASA, DEMOCRATIC REPUBLIC OF THE CONGO (Masters Candidate - Dr Tinne Gils)

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 August 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledges that the following Masters Candidate, Dr Tinne Gils will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

APPENDIX II: Approval of the National Ethics Committee of Health, Ministry of Health, Kinshasa, Democratic Republic of the Congo, for the study: Nurse-led management of antiretroviral treatment failure: Patient outcomes from Kinshasa, Democratic Republic of Congo

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REPUBLIQUE DEMOCRATIQUE DU CONGO
MINISTERE DE LA SANTE PUBLIQUE
COMITE NATIONAL D'ETHIQUE DE LA SANTE – CNES –

Arrêté Ministériel n°1250/CAB/MIN/S/ZKM/043/MC/2006 du 18 Décembre 2006
N° d'enregistrement au U.S. Department of health and Human Services (HHS) : IORG0008558/ IRB
N° d'enregistrement au Federalwide Assurance (FWA) : 00026293

Avis du Comité national d'éthique de la santé N°070/CNES/BN/PMMF/2018/ du 25/06/2018

Kinshasa, le 25 Juin 2018

A Monsieur TINNE GILS
Investigateur Principal de l'étude
1, Avenue de la révolution
Q/Socimat - C/Gombe
Ville de Kinshasa- RDCongo

Concerne : Approbation de l'étude sur « La gestion d'échec thérapeutique antirétroviral par les infirmiers. Résultats de patients de Kinshasa, RDCongo»

Monsieur l'Investigateur Principal,

Le Comité National d'Ethique de la Santé du Ministère de la Santé Publique de la République Démocratique du Congo a bien reçu votre demande d'approbation de l'étude dont le titre est repris en marge et vous en remercie.

Après l'examen de votre protocole d'étude selon les lignes directrices nationales d'éthique de la recherche impliquant des êtres humains du Ministère de la santé publique de la RDCongo, le Comité national d'éthique de la santé a donné son approbation à cette étude. Il a autorisé sa mise en œuvre dans les Cliniques publiques de la Ville de Kinshasa pour la période allant du 25 juin 2018 au 24 Juin 2019.

Veuillez agréer, Monsieur l'Investigateur Principal, l'expression de nos sentiments les meilleurs.

Professeur Félicien MUNDAY MULOPO
Président du Comité National d'Ethique de sant
République Démocratique du Congo

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Siège Administratif : Immeuble PNMLS, 1er Niveau, Local 5, Commune de Kasa-Vubu
Contact :(+243) 99 84 19 8 16, cnesrdcongo@gmail.com , feli1munday @yahoo.fr

APPENDIX III: Exemption of review by the Ethics Review Board, Médecins Sans Frontières, Cape Town, South Africa, for the study: Nurse-led management of antiretroviral treatment failure: Patient outcomes from Kinshasa, Democratic Republic of Congo

Médecins Sans Frontières, Brussels Operational Centre
Democratic Republic of Congo

PRINCIPLE INVESTIGATOR:	Mary-Ann Davies, MBChB, MMed, PhD, FC
COUNTRY:	**DRC**
SITE:	**KINSHASA**
TITLE:	Nurse-led management of antiretroviral treatment failure: patient outcomes from Kinshasa, Democratic Republic of The Congo.

COLLABORATING PARTNERS

Student researcher
Tinne Gils, Mpharm, DTM&H

Médecins Sans Frontières:
Pulchérie, MD
Rebecca Harrison, MSC
Ramzia Moudachirou, MD, MPH
Gilles Van Cutsem, MD, DTM&H, MPH

The study is based on routinely collected programmatic data and meets the following criteria for exemption from the MSF ERB review:

1. **Studies/articles are based on routinely-collected program data.**

The study entitled '**Nurse-led management of antiretroviral treatment failure: patient outcomes from Kinshasa, Democratic Republic of Congo'** is entirely is based on routinely collected data from the health centres of Kimia, Lisanga and Roi Beaudoin in Kinshasa, DRC. The data used for the analysis are data on patients on antiretrovirals (ART) attending these clinics, which are routinely entered into their medical records and transferred to the electronic Tier.net database, which is the national database for all ART patients.

2. **They are either descriptive/evaluative or targeted evaluations.**

This is a descriptive evaluation of data of ongoing program data. The study looks at outcomes of patients who are routinely enrolled, treated and managed in decentralised facilities by nurses, particularly patients who have resistance to first line treatment. The study will also describe the framework of activities of the Kinshasa project to decentralize care, implement viral load monitoring, provide second-line treatment, and task-shifting of the activities to nurses.

The results will be used to inform policy around task shifting of second line switch and care in the DRC and beyond, with the potential to benefit patients and health care workers worldwide.

3. **Confidentiality is respected; no individual patient identifiers are revealed or used.**

Investigators who will do the analysis will receive the secondary data anonymised and coded. These data will be imported into Stata and kept in a de-identified form. Participants names will thus not be used in this study and only aggregate data will be presented. Facility names will not be made public but will be coded. Confidentiality will be maintained by keeping data collection forms locked in a secure cabinet, while the electronic data file will be kept in a password and firewall protected computer. Forms, lists, logbooks and any other lists that link participant code to other identifying information will be stored in a separate, locked file in an area with limited access. Data sets will be maintained securely for five years after completion of the study.

4. **Harm is minimal but acknowledged where relevant.**

This retrospective analysis does not cause any physical harm to participants, who did not receive differential treatment as compared to other patients in the DRC, resulting from this study. Nevertheless, use of medical data beyond the immediate clinical care exposes the patient to possible breaches of confidentiality, including the patients' HIV status. Evaluation of nurse adherence to protocols entails a possible risk of retaliation for those nurses who do not adhere optimally. These risks ar minimised by anonymizing data and allowing only investigators access to data and databases.

5. **Potential benefits to both the program and the community are described. Since the goal is publication, the relevance to a wider audience is described.**

There are no direct benefits resulting from study participation. There are potential benefits for patients attending the analysed facilities under investigation and beyond, and for care and treatment for ART patients in general. A better understanding of risk factors for adverse outcomes in second line patients and protocol implementation may lead to better care and patients' outcomes in the included facilities, the DRC and beyond.

protocol implementation may lead to better care and patients' outcomes in the included facilities, the DRC and beyond. As there is currently a gap in the literature on nurse-managed care for second-line patients, the results of this study are of key importance for policy and practise nationally and internationally.

1. **Collaborative involvement and, if applicable, authorship from a local authority or partner (Ministry of Health, DHO, other NGO) is encouraged. If relevant and applicable, consultation with a body representing the community is desirable.**

In this case, the study is a retrospective analysis of program data and larger collaboration was not done a priori. However, engagement will be sought of the Ministry of Health in the DRC for critical reading of the manuscript and findings from the study will be shared widely with Ministry of Health counterparts in DRC as well as inform MSF program strategy in the decentralised facilities.

2. **If the decision for exemption from review is taken by the respective medical director, the responsibility to ensure that ethical requirements are met lies with MSF. This, however, does not exempt MSF from complying with any relevant regulatory requirements in the country from where the data originate. In some countries, local ethical review may still be required.**

The protocol will be submitted for full review by the Comite d'Ethique of the Ecole de Santé Public of the University of Kinshasa. It will also be submitted for full review by the Institutional Review Board of the University of Cape Town, South Africa.

This research fulfilled the exemption criteria set by the Médecins Sans Frontières Ethics Review Board for a posteriori analyses of routinely collected clinical data and thus did not require MSF ERB review. It was conducted with permission from the Medical Director, Operational Centre Brussels, Belgium.

Signature Removed

Dr Petros Isaakidis - Operational Research Coordinator

Médecins Sans Frontières | Doctors Without Borders |

Southern Africa Medical Unit (SAMU)

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