

How accurately do routinely reported HIV viral load suppression proportions reflect progress towards the 90-90-90 target in the population on ART in Khayelitsha, South Africa?

by Jonathan George Euvrard
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Supervisor: Associate Professor Mary-Ann Davies
Co-supervisor: Dr Tanja Schulz


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Abstract

In 2014, UNAIDS published “90-90-90: An ambitious treatment target to help end the AIDS epidemic”, in which goals for HIV testing, initiation and treatment are described. Briefly, the goals are for 90% of all people living with HIV to know their HIV status, 90% of all people diagnosed with HIV to receive sustained antiretroviral treatment (ART) and 90% of all people receiving ART to have achieved viral suppression.

Since these targets were published, many studies have assessed progress towards them in different settings. Studies reporting on the third 90 are described and synthesised in the Literature Review (Part B). We found significant heterogeneity in data sources, outcome definitions, methods and results across different studies, and we highlighted important themes and identified further research that is required.

The Khayelitsha Cohort in Cape Town is one of the oldest and largest HIV cohorts in South Africa, where ART was initially rolled out in partnership with Médecins Sans Frontières in 2001. With about 22 000 patients on ART and in care in the cohort in 2016, Khayelitsha reported almost 89% VL suppression on routine quarterly reports, but also reported 56% recorded completion of VL tests.

This low reported completion did not necessarily imply low actual completion, but it did raise questions about the validity of the reported suppression proportion and about the reasons for low reported completion. A series of steps must be completed for a VL test result to be included in routine data and thus contribute to the suppression and completion proportions reported. Among those in whom a VL is expected, a blood sample must be collected and tested, the result must be filed in the folder, noted by the clinician and captured electronically. We call this the “VL cascade”.

In order to address these questions about suppression and completion, a retrospective cohort was constructed including all patients on ART and in care at provincial healthcare facilities in Khayelitsha with a routine VL expected in the year from 1 July 2015 to 30 June 2016. The Protocol (Part A) was granted ethical approval by the University of Cape Town Human Research Ethics Committee.

We used 3 data sources to assess completion at each step in the VL cascade. Electronic data were requested from the Primary Healthcare Information System (PHCIS), which contains routine data digitised from the physical folder by clerks working on-site at healthcare facilities, and the Provincial Health Data Centre (PHDC), which contains data on all laboratory tests done in Khayelitsha. We manually reviewed 1 035 physical patient folders.

The suppression proportion at various thresholds was calculated a) using only data digitised into PHCIS and b) using all data from the PHDC, and these proportions were compared. Logistic

regression was used to determine factors associated with the outcomes of a) VL tests being done and b) VL tests completing the VL cascade to be included in routine reports. Healthcare facility was included in the model, as well as age category and pregnancy status, as different models of care are provided for children and pregnant women in Khayelitsha.

The results of the study are reported in the Manuscript (Part C). Of 22 991 patients with a routine VL due, 84% were done, 79% filed, 76% noted, and 55% captured. Using all laboratory data, VL suppression was estimated to be 82%, 87%, 89% and 91% at the 50, 200, 400 and 1 000 copies/mL thresholds respectively, but reported suppression using captured results would have been 80%, 86%, 88% and 89% at those thresholds. Routine VL were more likely to be done among children <15 years old (aOR 1.89, 95%CI 1.45–2.48) and pregnant women (aOR 1.90, 95%CI 1.28–2.81) compared to adult men, adjusted for facility.

We concluded that, despite low reported completion, actual VL testing completion was high. Reported suppression in routine data was very similar to suppression calculated using all laboratory data, thus providing an accurate measure of progress towards the third 90-90-90 target. More work is needed to reach the 16% of patients missed by routine testing.

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PART A: Protocol

Synopsis

Title

How accurately do routinely reported HIV viral load suppression proportions reflect progress towards the 90-90-90 target in the population on ART in Khayelitsha, South Africa?

Primary objective

To determine how accurately the viral load (VL) suppression proportion reported in the routine antiretroviral treatment (ART) programme data reflects the suppression proportion in the population on ART, given the low reported completion proportions.

Secondary objective

To identify the steps in the VL cascade that impact negatively on completion proportions and quantify their impact, in order to inform future interventions to improve the completion proportion.

Sample size

Part 1: all routine VLs expected during the study period (one year) for patients on ART and in care in Khayelitsha (about 22 000).

Part 2: about 1 000 expected viral loads that were reported as not done.

Study population

Patients on ART and in care at provincial primary healthcare facilities in Khayelitsha.

Study sites

Khayelitsha (Site B) CHC, Michael Mapongwana CDC, Nolungile CDC.

Background

The Provincial Government of the Western Cape (PGWC) reports high viral suppression proportions but low completion proportions, about 90% and 60% respectively for Khayelitsha in the study period. Given the low completion proportion, it is unknown how representative the reported suppression proportion is. Furthermore, there is no evidence base on which to design interventions to improve completion proportions.

The proposed study

This study will use three data sources – the Primary Healthcare Information System (PHCIS), the Provincial Health Data Centre (PHDC) and physical folder review – to assess completion and

suppression at each step in the viral load cascade and quantify failure to progress through each step. The Provincial Department of Health (DoH) collects routine ART programme data and only these routine data elements will be used; no additional non-routine elements will be collected. Use of these routine data for the Khayelitsha Cohort has already been approved by the University of Cape Town Human Research Ethics Committee (HREC REF Number 395/2005, updated annually).

The primary risk of this study is to patient privacy and confidentiality, and every effort to mitigate this risk will be taken, as detailed under “Privacy and confidentiality” in the protocol. Briefly: the review of folders for missing viral load results not captured electronically constitutes a data cleaning exercise as these results should have been captured as part of routine DoH data collection to PHCIS anyway. Only staff with existing approved access to these systems and these data will work on this study; no new access will be granted. Results of the folder review will be stored directly to an encrypted password-protected electronic database; no paper records will be generated. This study will be conducted with direct oversight from the substructure Medical Officer who will monitor study activities closely. As such, the risk to patient privacy and confidentiality is perceived to be minimal.

Background

In 2014, UNAIDS published “90-90-90: An ambitious treatment target to help end the AIDS epidemic”, in which goals for HIV testing, initiation and treatment are described.⁽¹⁾ Briefly, the goals are for 90% of all people living with HIV to know their HIV status, 90% of all people diagnosed with HIV to receive sustained ART and 90% of all people receiving ART to have achieved viral suppression.

VL testing is the gold standard in HIV treatment monitoring.⁽²⁾⁽³⁾⁽⁴⁾ The VL test used in the provincial ART programme measures the amount of HIV-1 genetic material in a sample of an HIV-positive patient’s blood, reported as copies per millilitre (copies/ml). Viral suppression is the direct goal of ART, so VL testing provides a direct measure of treatment success. (This remains true despite some new calls to look beyond viral suppression to health-related quality of life; viral suppression is a necessary prerequisite.)⁽⁵⁾

A patient is said to be virally suppressed if their VL is below a certain threshold. In South Africa, this threshold is 400 copies/ml, but the UNAIDS threshold for 90-90-90 is generally taken to be 1000 copies/ml. If a patient has a high VL this indicates that treatment is not effective, usually due either to poor adherence (the patient is not taking their antiretroviral medication consistently) or resistance (the virus in this patient is no longer as susceptible to the specific combination of antiretroviral medication the patient is taking).⁽²⁾⁽⁶⁾

Both suppressed and unsuppressed VL results can inform patient management and clinical care. A suppressed VL may be used along with other indications to identify patients for recruitment to differentiated models of care. For example, the guidelines from the PGWC state that patients are eligible for recruitment to an ART adherence club if they are on ART for 6 months, have no comorbidities that require more frequent clinical visits and have a suppressed VL.(7) Recruitment of stable patients to adherence clubs is seen by many patients as beneficial to them individually as it decreases the frequency and duration of visits. And it is beneficial to the ART programme as it reduces the load on clinicians and facilities and is therefore seen as an essential part of making increases in ART coverage (the second 90-90-90 target) sustainable in the context of an already overburdened healthcare system.

An unsuppressed VL result indicates to a clinician that the virus is replicating. A replicating virus may lead to a compromised immune system, drug resistance and increased risk of the patient transmitting the virus to others. Preventing this replication is the direct purpose of ART. If ART is not successfully suppressing replication then an intervention is required, usually adherence counselling and continued treatment followed by further testing and possibly switching of ART regimen if required. Failure or delay in switching patients who remain unsuppressed on their existing regimens has been shown to have a negative impact at the individual and programme levels. It can lead to increased risk of resistance,(8) opportunistic infections,(9) HIV transmission and transmission of resistant strains.(10)

As stated in the Western Cape Consolidated Guidelines for HIV Treatment, one of the specific objectives of the Western Cape ART Programme is to “promote viral load testing as a preferred approach for monitoring ART success and diagnosing treatment failure”.(11) The guidelines recommend performing routine VL tests in all patients at four months after starting lifelong ART, then again at 12 months on ART and every 12 months thereafter. The guidelines have further recommendations for more frequent testing following a high VL, for patients on 2nd and 3rd line regimens, patients with comorbidities, infants, and for pregnant and breastfeeding mothers.

The Primary Healthcare Information System (PHCIS) is a networked, central database-driven electronic health information system developed by the PGWC. Workstations running PHCIS are located in the registries at facilities where clerks electronically capture HIV programme information on a daily basis from the paper stationery in the patient folder to PHCIS. For monitoring and evaluation of routine VL testing, PHCIS calculates patient-specific windows of time around each expected VL test due date, based on the ART start date captured for each patient (Figure 1). These windows are contiguous, such that any VL taken after three months duration on ART will be counted

in one window or another. In other words, a patient’s 12 monthly cycle may be brought forwards or pushed backwards (often to align with their adherence club’s testing schedule), but as long as they continue to have a VL taken every 12 months then this will fulfil the minimum routine VL completion requirements. Using these routine VL due windows, a VL completion proportion is calculated and reported alongside the suppression proportion. For the reporting period of Q3 2015 to Q2 2016, the PGWC reported a completion proportion in Khayelitsha of 55.9% and a suppression proportion of 89.8%. There are many plausible explanations for this low reported coverage but to date there is no evidence-based research to confirm or quantify the causes.

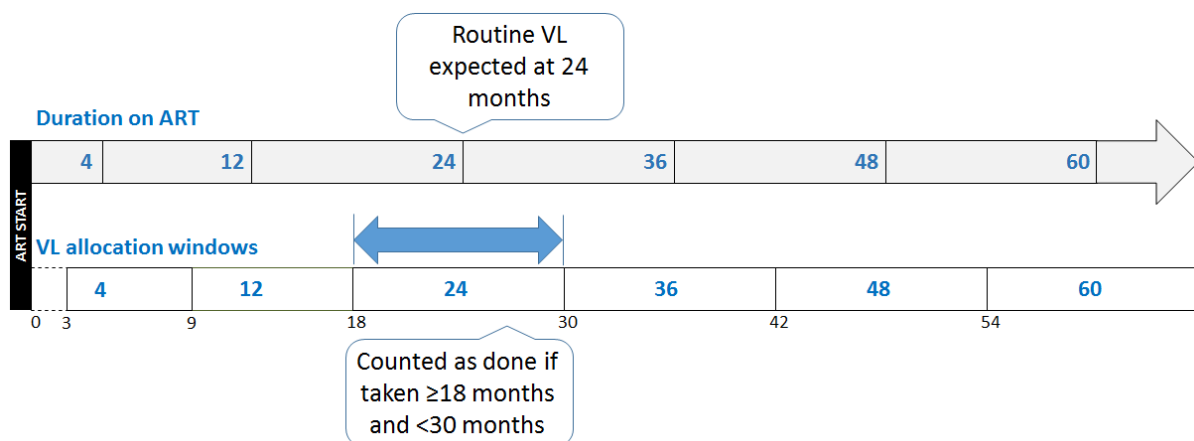


Figure 1: Viral load allocation – using 24 month due date as example

It is therefore impossible to say if VL results are missing systematically or at random, and whether or not the reported suppression proportion accurately reflects suppression in the population on ART. Furthermore, without a better understanding of the challenges to completion, it is difficult to know if results from these routine VL tests are available to the clinician to inform clinical assessment, and impossible to initiate targeted, evidence-based interventions to improve the completion proportion.

Objectives

The primary objective of this study is:

1. To determine how accurately the VL suppression proportion reported in the routine ART programme data reflects the suppression proportion in the population on ART, given the low reported completion proportions.

The secondary objective of this study is:

2. To identify the steps in the VL cascade that impact negatively on completion proportions and quantify their impact, in order to inform future interventions to improve the completion proportion.

Primary objective: the suppression proportion

Each quarter the provincial DoH reports a VL suppression proportion to the National DoH. The numerator is the number of patients with a VL < 400 copies/ml. The denominator is the total number of patients with VL results captured electronically and included in the report. If more than one VL is captured for a patient within an allocation window, only the VL taken closest to the due date is used when calculating the suppression proportion. For example, a patient with an unsuppressed VL at 12 months and a suppressed VL at 15 months is counted as unsuppressed.

Quarterly reports are facility-specific, and the numerator and denominator include only ART-naïve patients who initiated and remain in care at the reporting facility. Patients with prior ART experience and patients who transferred in to their current facility after initiation elsewhere are excluded. From preliminary analysis it is known that this may exclude as many as 25% of patients on ART and in care. Patients with no VL result captured electronically are excluded from the numerator and denominator of the calculated proportion. This may exclude as many as 45% of patients on ART and in care.(12)

It is not known whether these exclusions impact on the validity of the reported VL suppression proportion and, in the context of 90-90-90, how accurately the reported VL suppression proportion for naïve cohorts reflects progress towards suppression in 90% of the total population on ART. This study aims to compare the suppression proportion for naïve cohorts in Khayelitsha reported in the quarterly reports produced by PHCIS to the suppression proportion for all patients on ART in Khayelitsha calculated using all laboratory data available in the Provincial Health Data Centre (PHDC).

The PHDC has been described in detail elsewhere.(13) Briefly, the various health information systems used in PGWC health services use a single unique patient identifier, allowing for data imported from these systems to the central repository to be linked to create meaningful longitudinal patient records using data from across these various sources, including the laboratory systems. As such the PHDC data provides the most comprehensive and accurate view of viral load suppression for the population on ART in the Khayelitsha Cohort during the study period, and constitutes the best available standard against which to compare the suppression proportion reported using PHCIS.

Secondary objective: the viral load cascade

Routine VL results are expected for all patients on ART and in care at four months on ART, again at 12 months and every 12 months thereafter. As indicated in the provincial treatment guidelines, patients may have VLs taken more frequently following a high VL, due to 2nd and 3rd line regimens, comorbidities, in infancy, during pregnancy and while breastfeeding, but at a minimum routine VLs would still be expected.(11) The required steps that must be completed for an expected VL to be reported as done and counted in the VL completion proportion can be broken down as follows (Figure 2):

0. expected: using routine clinical data and treatment Guidelines, PHCIS can produce a list of patients on ART and in care with a VL expected in a specified timeframe.
1. taken: a blood sample must be taken within the timeframe around the due date and sent to the laboratory.
2. done: the VL test must be done by the laboratory and the result imported into the PHDC and linked to the patient.
3. filed: the test result sheet must be delivered to the facility or printed at the facility and filed by a clerk in the patient folder, available for the clinician.
4. noted: at the next visit, the clinician assessing the patient must write the result into the visit summary (clinical notes) that are filed in the patient folder.
5. captured: the result must be captured electronically by a clerk into PHCIS along with other routine clinical data.

It is possible for an expected VL to fail to successfully progress through any of the steps in this cascade. In general, failures higher up the cascade have the most negative impact on the completion proportion, because earlier steps are a prerequisite for steps further along the cascade.

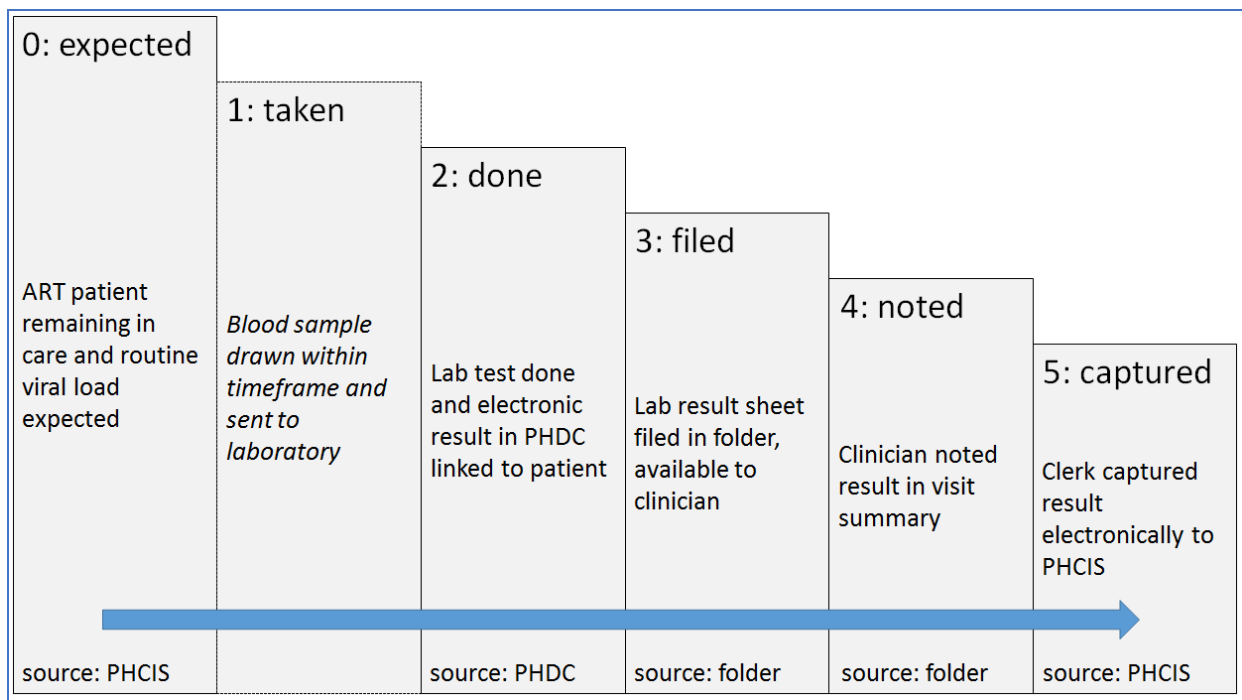


Figure 2: Viral load cascade - from expected to captured

The most concerning failure is at step 1: if the expected viral load is not taken then none of the patient or programme level benefits of routine VL monitoring highlighted above can be realised. However, there is no feasible way to assess step 1 directly (which would involve implementing a parallel monitoring system at the laboratory), so failure at step 2 will be assumed to imply failure at step 1, i.e. the absence of a result in the laboratory data in the PHDC will be assumed to imply a failure to take the blood sample within the timeframe with this limitation of indirect observation noted. This is justified because if a blood sample is taken but a test result is not produced (e.g. due to a contaminated/expired sample) then the patient should be recalled and a second sample should be taken.

Failure at step 3, where the results sheet is not filed in the folder, suggests that the result was unavailable to the clinician at the time of clinical assessment, i.e. in the patient's presence. This is almost as bad as the first failure in its impact on clinical care and perhaps worse at a programme level insofar as the public health system has paid for a test that is, in effect, wasted. Conversely, successful progress to step 3 implies that the VL was done and the result was available to the clinician at the next clinical assessment of the patient. So, from a clinical care perspective, this is the most important step in the cascade.

There is a caveat to this last concern in some facilities where clinicians can access VL test results stored electronically in the laboratory database via a web browser interface when connectivity is available. However, this is still a problem from both a medico-legal perspective (the physical result is

required to be available in the folder for audits and investigations) and because it adds a further technological and infrastructural dependency at provincial facilities that are experiencing many challenges in these areas.

Failure to progress to step 4 may only indicate a failure in clinical record keeping, which may still have a negative impact on a patient's continuity of care when other clinicians attempt in the future to quickly assess a patient's history using the visit summary (in large public healthcare facilities in South Africa, patients are unlikely to see the same clinician consistently, and so the presence of a consistently maintained clinical record is especially important for continuity of care). There is also an issue of potentially wasted resources here because, in the absence of clinically noted results, tests may be repeated unnecessarily.

Finally, failure to electronically capture results compromises the accuracy of potentially useful patient management and programme monitoring reports produced by the electronic system, PHCIS. Such reports are used to identify patients due for their routine VL test, facilitate follow-up of virally unsuppressed patients and report on viral suppression for programme evaluation.

This study aims to "follow" a sample of expected VLs through the cascade to identify the furthest step along the cascade that each VL successfully reached, and quantify the proportion of failure to progress at each step.

Methods

Study design

This study will consist of two parts. In the first part data from two electronic sources, PHCIS and the PHDC, will be merged to allow for a comparison of the suppression proportion for naïve cohorts in Khayelitsha reported in the quarterly data using PHCIS to the suppression proportion for all patients on ART in Khayelitsha calculated using all laboratory data available for these patients in the PHDC. As discussed above, PHCIS can produce the beginning of the cascade (step 0, Figure 2) consisting of all routine VLs expected in the year from 1 July 2015 to 30 June 2016 for patients on ART and in care at provincial primary healthcare facilities in Khayelitsha. It can also indicate which patients with expected VLs are included in reported suppression proportions and will include some common patient characteristics like age, sex and duration on ART. The PHDC will provide the laboratory data consisting of VLs done (step 2), including the actual test result values to allow for categorising VLs into suppressed and unsuppressed.

A logistic regression or log binomial model (depending on the distribution of the data) will be performed on this merged cross-sectional dataset to test for an association between reporting and

suppression, i.e. is a suppressed VL result more or less likely than an unsuppressed VL result to be included in the reported suppression proportion? This bears directly on the question of how accurately routinely reported VL suppression proportions reflect progress towards the 90-90-90 target of 90% suppression in this population.

In the second part of this study, the merged dataset from PHCIS and the PHDC will allow for the identification of all routine VLs that were done (step 2) but were not electronically captured (step 5). From this list, a facility-clustered random sample will be drawn for a folder audit. The folder audit will consist of visiting the facility, drawing the physical patient folder and examining whether the laboratory test result sheet was filed by the clerk in the folder and whether the result was noted by the clinician in the visit summary. From the folder audit, completion proportions for each step in the VL cascade will be estimated.

Setting

The Khayelitsha cohort has been described in detail elsewhere.⁽¹⁴⁾ Briefly, Khayelitsha is the largest township in Cape Town, and the second largest township in South Africa. No published up-to-date population estimates exist, with the last official census from 2011 putting the estimate at just under 400 000, and community-based organisations reporting close to 2 million by 2016.⁽¹⁵⁾ The area is crowded and poor, with an estimated 7 748 inhabitants per square kilometre and employment rate of about 53% in 2011.⁽¹⁶⁾ HIV prevalence is high: 34.3% of pregnant women in 2012 were HIV-positive.⁽¹⁷⁾ Government HIV services were first offered to pregnant women in Khayelitsha in 1999, and the ART programme was started in 2001.⁽¹⁴⁾ Provincial ART services in Khayelitsha are offered at three large primary healthcare facilities, all of which will be included in this study.

Population and sampling

In the study period, there were about 22 000 patients accessing ART services at provincial primary healthcare facilities in Khayelitsha and therefore eligible for selection into the study. For selection into the study patients must be on ART and remaining in care in the study period at one of the three provincial ART facilities and have a routine VL expected during the study period. The guidelines for routine VL testing have been described above. For this study, the definitions of “on ART” and “remaining in care” are taken from the National guidelines:

- Patients are on ART if they have commenced treatment on three or more antiretroviral drugs at any time.
- Patients are remaining in care on a particular date if they have no manually captured or calculated outcome before or on that date. Outcomes that may be captured are death,

transfer out and confirmed loss to follow-up. The only calculated outcome is unconfirmed loss to follow-up, where a patient on ART has not been clinically stopped and has not had drugs in hand for 90 days or more.(18)

The study period is from 1 July 2015 to 30 June 2016. PHCIS will be used to produce the list of patients as it has the relevant routine patient-level ART data and reporting algorithms aligned with the guidelines referred to above in its database. For comparing the reported completion proportions in the first part of this study, all required data exist in the PHDC and PHCIS databases, so all eligible patients will be included and sampling is not required. For the second part of the study, proportions at steps 2 (done) and 5 (captured) can be calculated using all patients. For steps 3 (filed) and 4 (noted) data abstraction from folders is required, which is time consuming and necessitates sampling. A subset of about 1 000 such folders will be randomly sampled for physical audit, clustered by facility.

Data access

Access to patient-level ART programme data written on the patient stationery, captured electronically and stored in the PHCIS and PHDC databases as part of routine monitoring and evaluation will be requested from the DoH in the PGWC. Requests to use patient-level data for research purposes are handled by the Provincial Health Research Committee (PHRC) in the PGWC.

Access to physical patient folders will be facilitated by the HIV/AIDS, STI and TB (HAST) Medical Officer for the Khayelitsha and Eastern Substructure (KESS) in the PGWC working with the Facility Managers and every effort will be made to minimise the impact on the routine operations of the facilities involved. Folders will be reviewed by provincial DoH staff and UCT data support staff seconded to the Substructure office with approved access to these data as part of delivering and supporting routine services. All data will be anonymised prior to analysis.

Data management

Patient-level data are routinely collected by provincially-employed healthcare workers into standardised provincially-approved paper and electronic monitoring and evaluation tools. Data collected using these tools are imported into the PHDC. Patient linkage (de-duplication) is performed as part of the import process into the PHDC. Only data linked to patients in the Khayelitsha cohort will be requested. Data will be stored on an encrypted drive and only the principle investigator and supervisors will be granted access. Folder audit data will be captured directly to an encrypted, password-protected Microsoft Access 2016 database and stored electronically only. No paper records will be generated or kept. Data will be anonymised prior to extraction from this secure

database for analysis by excluding identifying data from the extract process. The identifying data here consists only of the PGWC unique health patient identifier.

The data elements requested will be limited to the routine ART programme data and laboratory VL data as detailed below. No additional data beyond the routine elements will be collected or stored.

Limitations

Several issues may complicate this study. The quality of routine data cannot be guaranteed. For example, the dates on which routine VLs are expected are calculated based on other data collected routinely by the ART programme, specifically baselines and outcomes. Errors in the capture of these data could lead to errors in the calculated due dates for routine viral loads or the incorrect expectation of VLs for patients no longer in care.

Some patients may have had a VL taken elsewhere than at their routine treatment facility. In this case, it would be unreasonable to expect that VL to have been written in the visit summary, electronically captured or reported at the routine treatment facility. However, in the apparent absence of this VL result at the facility, the clinician should have ordered another VL, so the absence of a result at the routine facility is still counted as a failure.

Despite every effort it will not be possible to locate every physical folder sampled. Folders not found will be assumed to be missing completely at random and treated as missing data in the analysis. Based on an unpublished pilot study conducted by the health services, we expect less than 10% of folders to be missing.

Folders that have gone missing are usually replaced, and so it is possible that a new (“duplicate”) folder will have been opened for a patient between the time the VL was taken and the folder audit. Where folders are found with no clinical notes from the study period, these folders will be treated as missing, as above.

Similarly, a results sheet may have been filed (step 3) but subsequently lost, i.e. it may have been in the folder at the time of the clinical assessment but it may no longer be in the folder at the time of the folder audit. This is unfortunately a risk that must be accepted, but previous work has shown many results sheets present in folders from more than 10 years earlier, and hopefully the chosen study period’s recentness mitigates against this risk.

Finally, if a VL is captured electronically with the incorrect date, this may lead to it falling outside of the period during which it can be counted. But, where this has happened, it still reflects a failure of electronic capture and will be counted as not captured (i.e. failing at step 5).

Data analysis

Data from PHCIS, PHDC and results from the folder review will be merged and a dataset will be prepared for separate analysis. The data elements are described in Table 1. The data will be explored using univariate and bivariate statistics. The distribution of continuous covariates will determine whether medians and inter-quartile ranges or means and confidence intervals are reported.

Frequency tables will be populated for categorical and binary covariates.

For the first objective, the overall suppression proportion using all VL done will be compared to the suppression proportion using only VL included in routine reports (*reported*). Suppression proportions will also be compared at various commonly used suppression thresholds, i.e. at 50, 200, 400 and 1 000 copies/mL. This will fulfil the primary purpose of this study and give an estimate of how accurately reported VL suppression reflects suppression in the population on ART in Khayelitsha.

For the second objective, the proportion of expected VL successfully reaching each step of the VL cascade will be estimated. A logistic regression will be performed to determine factors associated with two important steps along the cascade: a) VL test done (step 1) and b) VL test completed the VL cascade to be included in routine reports (*reported*), representing “actual completion” and “reported completion” respectively.

Note that in the encrypted database the folder number is required in order to complete the folder audit, but it is not required – and will be removed prior to export – for the subsequent analysis. All analysis will be performed in STATA 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Table 1: Data elements

Variable	Type	Comment
patientid	integer	unique, anonymous patient identifier for study
facility	integer	unique, anonymous facility identifier
age	number	age at VL due date
sex	integer	sex (0=male, 1=female, 2=other)
pregnant	integer	pregnancy status at VL due date (1=pregnant)
timeslot	integer	duration on ART at VL due date
opendate	date	start of VL allocation window
closedate	date	end of VL allocation window
duedate	date	due date for expected VL
labval	integer	lab test result value (“LDL”=0) from PHDC
labdate	date	lab test date from PHDC

capval	integer	captured test result value ("LDL"=0) from PHCIS
capdate	date	captured test date from PHCIS
done	binary	lab/captured date within VL allocation window
*filed	binary	VL result sheet filed
*noted	binary	VL result noted in visit summary
captured	binary	result captured to the electronic system
reported	binary	result reported in the naïve cohort quarterly reports
suppressed50	binary	result < 50 copies/ml
suppressed200	binary	result < 200 copies/ml
suppressed400	binary	result < 400 copies/ml
suppressed1000	binary	result < 1000 copies/ml
*reviewed	Binary	physical folder manually reviewed (1=yes)
*reviewer	text	name of person who reviewed folder
*reviewdate	date	date on which folder was reviewed

* These elements will be captured by the reviewer during the physical folder audit

Ethics

Ethical review

Ongoing collection of routine data is performed by the DoH in the PGWC. Research use of this routine data for the Khayelitsha Cohort has already been approved by the University of Cape Town Human Research Ethics Committee (HREC REF Number 395/2005, updated annually). No additional data elements will be collected. The review of folders for missing viral load results not captured electronically constitutes a data cleaning exercise as these results should have been captured as part of routine DoH data collection to PHCIS anyway. Missing results found during folder review will be imported into PHCIS. Only staff with existing approved access to these data will work on this study; no new data access will be granted.

Risks and benefits

This research will make use of existing data collected as part of routine monitoring and evaluation, including data collected electronically and manually to the patient folder. No folders or other documentation will be removed from the facility. Data abstracted from folders will be captured directly to an encrypted database. The primary risk of this study is to patient privacy and confidentiality, and every effort to mitigate this risk will be taken. Other than concerns around privacy and confidentiality addressed explicitly below there is no risk to the health or wellbeing of

patients as there will be no contact with patients and no changes to the care already received. As such, we are requesting a waiver of the requirement for informed consent.

There is no direct benefit to patients anticipated, but this research seeks to inform the interpretation of routinely reported data, and inform future interventions to improve the handling and capture of VL test results, to make it more likely that a VL test is performed, that the result is available to the clinician at the time of assessment and that the result is used in routine reporting. As such it is hoped that this research may have an indirect benefit to patients by improving the understanding of the ART programme and by guiding interventions to improve the health system. As such it is intended to provide improved insight for programme managers and direction to those working on health systems strengthening.

Privacy and confidentiality

The review of physical folders would not be possible without the availability of the folder number to link the data from the electronic systems to the offline data in the physical folder at the facility. This folder number is an integer, eight or nine digits long, that contains no personally identifiable information, and no other personally identifiable information will be captured or stored in this study. However, those with approved access to provincial electronic health information systems, and access to physical folders in facilities, could identify the patient using this number, hence it is not truly anonymous.

As stated above, the folder reviewers involved in this study are employed by or seconded to the DoH in the PGWC and already have access to this data, so no new access will be granted for the purposes of this study. Datasets containing the folder number will only be stored electronically and always encrypted and password protected. Following the folder review, the data will be truly anonymised by removal of the folder number prior to export for analysis. Furthermore, this study will be conducted with direct oversight from the substructure Medical Officer who will monitor study activities closely. As such, the risk to patient privacy and confidentiality is perceived to be minimal.

Timeframe

The timeframes for this research are heavily dependent on approval from the University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee (HREC) and data access from the DoH in the PGWC. However, the intention is to submit the manuscript in the fourth quarter of 2017. The proposed timeline is detailed below (Table 2):

Table 2: Proposed timeline

Month	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Literature review												
Stakeholder engagement												
Data collection												
Data cleaning												
Data management												
Data analysis												
Results												
Write-up												

Dissemination of research findings

A summary of research findings will be presented to Facility Managers, the Director of the Khayelitsha and Eastern Substructure and their staff, the Director of HAST in PGWC, and investigators will avail themselves to respond to any questions about the research and findings.

The Centre for Infectious Disease Epidemiology and Research (CIDER) at the University of Cape Town will be approached with an offer to present a summary of the research findings at the regular Academic Lunch events held within the Centre. A journal-ready manuscript will be produced in partial fulfilment of the requirements for the degree of Master of Public Health (Epidemiology and Biostatistics). This manuscript will be further worked on before being submitted to journals, hopefully resulting in a journal publication.

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Part B: Literature Review

Introduction

The Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the 90-90-90 strategy in 2013 with the goal to end the AIDS epidemic by 2030.⁽¹⁾ HIV treatment can be viewed as a cascade from diagnosis to viral suppression. The 90-90-90 strategy identified targets to reach by 2020 at three steps along this cascade:

1. 90% of people living with HIV (PLWH) will know their status;
2. 90% of people diagnosed with HIV will receive sustained antiretroviral therapy (ART); and
3. 90% of people receiving ART will have viral suppression.

Due to the cascading nature of the target proportions, the second and third 90s can also be stated as “81% of PLWH will receive sustained ART” and “73% of PLWH will be virally suppressed” respectively.

The targets are self-consciously ambitious and simplified, intended to “drive progress..., promote accountability and unite diverse stakeholders in a common effort.”⁽¹⁾ The strategy has been widely adopted, with many publications reporting on progress towards the targets in different populations and settings. However, there is a diversity of interpretation of these targets and there is also diversity in the approaches to measure progress against the targets and the types of data sources used.

This literature review focuses on the third 90: viral suppression in the population on ART in the context of the 90-90-90 strategy. It aims to describe and synthesise the currently published literature on progress towards the third 90 and identify where further research is needed.

Objectives

The aim of this literature review is to systematically synthesise English-language literature published before 1 December 2017 reporting on viral suppression in the context of the UNAIDS 90-90-90 strategy. The review will describe the study designs, populations, definitions, data sources and analytical methods used. It will highlight similarities and differences between approaches, and draw attention to ambiguities and missing information and the limitations these place on appropriate comparison and interpretation of reported results. The focus here is methodological; the reported suppression proportions are summarised in Table 1 but will not be discussed. Note that technical

details about storage times and temperatures and assay methods for laboratory measurement of viral load and discussion thereof are beyond the scope of this review.

There is more than one legitimate approach to measure progress against the third 90 in the 90-90-90 targets. Different settings provide different opportunities for analysis. In some settings, rich routine datasets are available, but access to viral load testing in most resource-limited settings has been scarce and routine viral load monitoring has not been implemented until recently. In some of these contexts, population-based surveys have produced broadly representative datasets while elsewhere it has been necessary to produce modelled estimates based on minimal data. Following similar approaches in different settings can lead to better comparability, but can also have the effect of introducing a “lowest common denominator” effect in which more valid measurements based on richer datasets are ignored in favour of estimates derived using a common approach.

Search strategy

PubMed was searched using the terms 90-90-90[Title/Abstract] AND (HIV[Title/Abstract] OR ART[Title/Abstract] OR antiretroviral[Title/Abstract]) to identify publications reporting on progress towards the 90-90-90 targets. The search returned 167 publications, which were examined to determine if they reported against the third 90: viral suppression in the population on ART. No exclusion criteria were applied on the basis of geography, study population or year of publication. However, the 90-90-90 strategy was only proposed by UNAIDS in 2013 and this search was performed in December 2017, with the result that all studies included were published between these dates.

The inclusion of 90-90-90 in the search terms had a significant effect on the number of results returned; removing this term returned 347 837 results. This significant restriction was helpful as it focused the review on publications reporting on progress towards the 90-90-90 targets, which is the focus of this research. Furthermore, the 90-90-90 targets have been so widely adopted that few authors reporting on the HIV treatment cascade at a population level (including key populations) fail to place their research in the context of the 90-90-90 targets since their inception.

Reference lists of included publications were also reviewed. Results from the Population-based HIV impact assessments (PHIAs) were not included as results are preliminary and not yet published in a peer-reviewed manuscript at the time of writing.

Summary and interpretation

The search yielded 167 publications, 25 of which reported on viral suppression. One publication was added from references. Table 1 summarises the study design, geographical context, study population and ART experience inclusion criteria for each of the reviewed studies. These features are discussed in more detail below.

Study design

All studies reviewed used either a cohort (including cohorts from trials) or cross-sectional design (Table 1). In practice, the study design and data sources largely determine the study population: a retrospective cohort study using routine data collected at a single facility can only include HIV patients currently or previously in care at that facility, while a population-based survey can include both those who have linked to care and those who have not but, due to non-responses, may miss some of the patients in care that the cohort study would have included.

Many of the studies reviewed also reported on progress against the first 90 (testing) and second 90 (linkage to care). Population-based surveys are the most commonly used method to assess progress against the first and second 90s because they seek to include those in the community who have not tested or who have tested and not linked to care. When assessing the third 90 – viral suppression among people receiving ART – the denominator as defined by UNAIDS includes only those who are in care.

There is room for confusion in the classification of these studies as either cohort or cross-sectional. In some cases the confusion is due to a combination of data collected using different methods. For example, survey data and longitudinal patient-level programme data were combined by Billieux et al. to allow for estimates of progress towards all three 90-90-90 targets.⁽²⁾ For the purposes of classification in Table 1, the study design is indicated as specified by the authors unless it clearly did not apply to the method used to measure progress against the third 90 specifically.

While the surveys fit neatly into the cross-sectional classification, a retrospective cohort study using the latest viral load for all patients in care at a particular timepoint may in fact be more like a cross-sectional study. For example, Ndahimana et al. conducted a nationwide retrospective cohort study in Rwanda in which data were collected for a sample of patients still on ART at their initiation facility at 11-13 months who were invited to provide a blood sample for viral load testing and resistance genotyping.⁽³⁾ In practice this amounts to a cross-sectional estimate of viral suppression among patients in care at the facility at a particular timepoint.

Table 1: Summary table of reviewed studies

Publication	Study design	Last year of data included	Geography	Population (age in years, key pop)	ART experience	Duration on ART (months)	VL threshold (copies/ml)	Suppressed (%)
Billioux, 2017(2)	Cohort	2015	Uganda (Rakai)	15-49	Naïve	12	1000	92
Boullé, 2016(4)	Cross-sectional	2014	Cameroon (Mfou)	≥15	Naïve	≥6	1000	76
Bowman, 2017(5)	Cohort	2015	Dominican Republic	“adult”	Naïve	12	20	57
Chkhartishvili, 2016(6)	Cohort	2015	Georgia	All?	All?		1000	85
Chkhartishvili, 2017(7)	Cohort	2014	Georgia	≥18	Naïve		1000	89
Drew, 2017(8)	Mixed	2014	Europe, Central Asia	All	All		Mixed	73
Gaolathe, 2016(9)	Cross-sectional	2015	Botswana	16-64, citizens	All		400	97
Gisslén, 2017(10)	Cross-sectional	2015	Sweden	All	All	≥6	50, 200	95, 99
Gourlay, 2017(11)	Cohort	2013	Europe, Central Asia	≥15	All		200	85
Grobler, 2017(12)	Cross-sectional	2015	South Africa (KZN)	15-49	All		1000	88
Iwamoto, 2017(13)	Cross-sectional	2015	Japan	All	All	≥6	20, 400	94,99
Jiamsakul, 2017(14)	Cohort	2017	Global	<18 ≥18	Naïve	12, 24, 36	1000	80 (child) 90 (adult)
Johnson, 2017(15)	Modelling	2015	South Africa	All	All	48	400	78
Kerrigan, 2017(16)	Cohort	2016	Tanzania (Iringa)	≥18, FSW	Naïve		400	70
Kim, 2016(17)	Cross-sectional	2013	Kenya (Ndhiwa)	18-64	All		1000	79
Kwarisiima, 2017(18)	Cohort	2015	Uganda, Kenya	CD4 ≥350	Naïve	12	500	93
Labhardt, 2017(19)	Cohort	2014	Lesotho	≥16, VL ≥80	Naïve	≥24	80	91
Maman, 2016(20)	Cross-sectional	2013	Malawi	15-59	All		1000	90
Maman, 2015(21)s	Cross-sectional	2012	Kenya	15-59	All		1000	84
Maskew, 2016(22)	Cohort	2015	South Africa	12-20	Naïve		400	69
Naidoo, 2017(23)	Cohort	2017	South Africa (KZN)	≥14	Naïve	12, 24, 36, 48, 60, 72	400	90 (male) 96 (female)
Ndahimana, 2016(24)	Cohort	2011	Rwanda	≥15	Naïve	12	400, 1000	86, 88
Raymond, 2016(25)	Cross-sectional	2014	USA (SF)	≥18, MSM	All		200	89
Takuva, 2017(26)	Cohort	2012	South Africa	All	All		400	74
Xia, 2016(27)	Cross-sectional	2014	USA (NYC)	All	All		200	86
Zhang, 2016(28)	Cross-sectional	2014	China (Shandong)	≥18 months	All		50	60

Key: KZN=KwaZulu Natal; SF=San Francisco; NYC=New York City; FSW=Female Sex Workers; MSM=Men who have Sex with Men; Duration on ART blank if not explicitly selected/stated; VL=Viral Load

It complicates matters still further when the viral load test result is also used as the signal for being in care.(26) Takuva et al. assessed progress against the third 90 using only laboratory data and therefore relied on laboratory results alone to determine both the numerator and denominator of the viral suppression proportion. The issue with this approach is that the gaps in the data cannot be seen: patients in care without virological outcomes cannot be identified and patterns in their characteristics cannot be assessed. This is concerning because guidelines recommend viral load testing at different frequencies for different groups of patients, so it should be expected that certain groups will be over-represented such as patients who are sick or where there are concerns about non-adherence. Jiamsakul et al. excluded patients with no viral load tests results available after initiation, which would raise similar concerns but to a lesser extent as they did not rely entirely on the presence of viral load test results.(14)

Population

Geography

The study populations of the studies reviewed ranged in geographical coverage from a single facility(29) through the city(25,27), provincial(12,23) and national(15) levels, up to the global level.(14) As discussed above, the choices of study design and availability of data largely determine the study population. Similarly, though, the choice of study population may inform the choice of study design and data sources, depending on data availability for that population.

In many cases different facilities within the same district collect different data in different ways, let alone across countries. Only two of the reviewed studies reported suppression across multiple countries. Gourlay et al. reported on countries in Europe and Central Asia, whereas Jiamsakul et al. reported on countries in the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration including 16 countries in North America, the Caribbean, Central and South America, Asia-Pacific and Africa.(11,14) Both studies faced significant challenges with data availability, standardisation and comparability, as discussed under the relevant headings below. For example, due to the relatively recent introduction of routine viral load monitoring in most of sub-Saharan Africa, the only country in the region with enough data to be included by Jiamsakul et al. was South Africa.(14)

Age

Age categories were inconsistently defined across studies and no reasons were given for the chosen categorisations. The World Health Organisation (WHO) ART Guidelines define the following age categories: (30)

- An adult is a person older than 19 years of age.
- An adolescent is a person 10–19 years of age inclusive.
- A child is a person 1 to younger than 10 years of age.
- An infant is a child younger than 1 year of age.

These age categories are useful because they facilitate focus on infants, children and adolescents, vulnerable sub-populations that may face quite different challenges. However, these cut-offs do not align with those used more broadly across health programmes in different countries, and even studies focused on these sub-populations are not consistent. The single paediatric-focused study reviewed included all participants aged <16 years, and the single adolescent-focused study reviewed included participants aged 12-20 years.(22)

Most studies reviewed used 15 years as the binary cut-off between children (<15) and adults (≥15), and most of these included only adults (≥15), but ages 12, 16 and 18 years were also used as cut-offs (see Table 1). At the other end of the spectrum, studies used various upper bounds of between 49 and 64 years with no reasons given. It cannot be assumed that viral suppression in those older than these thresholds is the same as in those younger, and the utility of explicitly excluding older patients is not obvious. In fact, there is a growing body of evidence that ageing cohorts play an important role in the HIV epidemic.(31)

Key populations

Studies reporting exclusively on progress towards the third 90 in children, adolescents, men who have sex with men (MSM) and female sex workers (FSW), and studies that included (and highlighted) results for these groups within the broader population, were included in the review (see Table 1). Comparing progress against the 90-90-90 targets across key populations and the broader population provides a useful way to identify barriers to care or where current models of care may be failing some sub-populations. No studies reported on progress towards the third 90 in people in prisons, people who inject drugs and transgendered people were reviewed, and this may indicate gaps in the current literature.

Inconsistency in the categorisation of age-based vulnerable populations has been addressed above.

ART experience

Most of the cohort studies reviewed – including retrospective cohorts derived from existing routine data – included only ART-naïve patients initiating at the study sites of interest, explicitly excluding patients with prior treatment experience. Population-based surveys by their very nature include not only those with prior treatment experience but also those with no treatment experience, i.e. those

that have no past or current link to HIV care, but almost all relied on self-report to determine whether or not participants were on ART.

Definitions and measurements

Definition of suppression: the numerator

In the seminal 90-90-90 document from UNAIDS, there is only one mention of a viral load suppression threshold: the y-axis in Figure 16, which reports on the “Proportion Of People On Art With Viral Suppression In Latin America And The Caribbean, 2013”, is labelled “Percent suppressed viral load (<1,000 copies)”.(1)

The use of different absolute value thresholds for viral suppression makes comparison across studies and settings difficult. In the publications reviewed, thresholds ranged from 20 copies/ml to 1 000 copies/ml (Table 1). Reporting suppression at more than one threshold is helpful to enable comparability between studies. However, in the studies reviewed only two reported at more than one threshold, and coincidentally there was no threshold in common between the two, thus direct comparison was still not possible. (3,10)

What makes comparison even more difficult is failure to report thresholds along with suppression proportions. In a study using a country-based questionnaire, Drew et al. reported, “Of the 25 countries reporting data, 44% reported the threshold they used.” (8) If the suppression threshold is known to be different and the difference is known then it can perhaps be accounted for. If it is unknown, it is not possible to make any reasonable comparison.

As defined by UNAIDS, the second 90 says people “will receive *sustained* ART” but the third 90 says only “will have viral suppression”.(1) Some authors like Gisslén et al. define the third 90 as “should have durable virological (*sic*) suppression”, yet report suppression based on most recent VL.(10) They have even reported this as a limitation: “Using a single VL measurement may also overestimate durable viral suppression”, but this is not strictly a limitation on validity as per the UNAIDS target.

Chkhartishvili et al. reported separately on viral suppression using each of two interpretations of viral suppression: “Ever Suppressed” and “Maintained Suppression”.(7) Of 1 044 patients who were virally suppressed during the study period (Ever Suppressed), only 792 (88%) were virally suppressed throughout the study period (Maintained Suppression). The authors also reported that 902 (89%) of 1011 patients on ART at the end of the study period were virally suppressed, which is how most of the reviewed studies (cohort and cross-sectional) interpreted the third 90.

This raises a concern: preventing transmission is an important corollary of suppression and one of the main goals of the 90-90-90 strategy, but can be realised only with sustained viral suppression. As

it is currently defined by UNAIDS, the third 90 target does not require viral suppression to be sustained, and reporting on sustained viral suppression may be too onerous in many settings. Nonetheless, Chkhartishvili et al. are right to draw our attention to this as another important consideration towards preventing transmission and thereby realising the main goal of 90-90-90: ending the AIDS epidemic.

Definition of suppression: the denominator

All survey studies reviewed relied on self-report to determine current ART status and estimate the number of participants receiving ART, used as the numerator of the second 90 and the denominator of the third 90. Self-report may lead to overestimation of the second 90, and underestimation of the suppression proportion in the third 90 (due to overestimation of the denominator). In an effort to limit overestimation, one survey required participants to produce some evidence of receiving ART.⁽⁹⁾ Another study was more concerned with underestimation of ART coverage, accepting either self-report or record of an ART start date in routine data.⁽²⁾

Estimation of the denominator is also complicated by confusion about what constitutes “sustained antiretroviral therapy”. While active transfer out and mortality are relatively well defined (even if not well ascertained), different studies have used very different definitions of “remaining in care” (RIC) and “loss to follow-up” (LTF). For example, in the absence of a recorded outcome, Jiamsakul et al. defined a patient as LTF if no visit was recorded within six months of the closing date, compared to Zang et al.’s RIC criterion of “ ≥ 2 CD4 count or VL test results separated by ≥ 90 days”.^(14,28)

In South Africa, the National Guidelines define LTF as 90 days with no medication in hand.⁽³²⁾ At each visit, ART patients are given a next appointment date and enough medication to last until shortly after that appointment date, so a patient would usually be classified as LTF at roughly 90 days after a missed appointment. However, there is not inherently any longitudinal nature to this definition. At any chosen timepoint, patients are classified as RIC if they fulfil the relevant criterion at that timepoint, not if they have consistently fulfilled that criterion for a period of time prior to that timepoint. Thus a patient who returns to care just before the time point after significant interruptions in care will be counted as RIC.

Counting these patients in this way has the effect of shifting the burden from the second to the third 90, because they are counted in the numerator of the second 90 and the denominator of the third 90. In other words, it may be unreasonable to expect these patients to have achieved viral suppression (the third 90) because they have not received sustained ART (the second 90), and interventions to address this should be aimed at improving retention, not at improving viral suppression itself.

Indeed, it might be argued that there are two distinct 90s hidden in the second 90 – linkage to care and retention in care. Population-based surveys tend to provide a more thorough approach to measuring the first 90 (testing) and the first part of the second 90 (linkage to care), while the use of routine clinical records in retrospective cohort studies tends to provide a more thorough approach to measuring the second part of the second 90 (retention) and the third 90 (suppression among those retained in care).

Data sources

Data sources used in the studies reviewed ranged from computer-assisted personal interviews (combined with study-specific laboratory test results) for population-based surveys to questionnaires for country-based surveys, from small study laboratories to national laboratory data warehouses, and from surveillance systems to patient-specific electronic medical records. As discussed above, choices of study population, design and data sources are closely interlinked and interdependent. In some settings, rich routine data sources are available for use but, even then, population-based surveys may extend the reach of the study to populations not otherwise included. In other settings where there is a paucity of data, such surveys may be the only immediately feasible method to assess progress towards to the 90-90-90 targets.

Completeness

As discussed above, the numerator of the third 90 is the number of those with a viral load less than a threshold and the denominator is those receiving sustained ART (i.e. the numerator in the second 90). Alternatively, the third step in the cascade can be defined as 73% of PLWH (i.e. the numerator of the first 90). However, viral load results are not usually available for each and every one of those included in either of these denominators, and it can be surprisingly difficult to ascertain the completeness of data used to report against the third 90.

It is easiest to report on completeness (and mitigate incompleteness) in studies that perform study-specific HIV and viral load tests. For example, Gaolathe et al. performed HIV testing on all participants without a documented HIV-positive status, and performed viral load testing on all HIV-positive participants (known positive and newly tested). Of 2617 participants on ART, the study was able to include viral load results for 2609 (99.7%).⁽³³⁾ As such, any concerns about missing data in this study are more likely to stem from sampling methods or non-participation in the study rather than missing viral load results for participants.

However, performing study-specific viral load tests does not necessarily overcome challenges with completeness. In their cohort study, Ndahimana et al. found 837 patients who met their study inclusion criteria, but nine patients were excluded due to missing patient folders.⁽³⁾ Of the 828

remaining, 711 were still active at the time of data collection and invited for blood collection, of whom only 597 (84% of active patients) presented on data collection day.

Working with routine data in the absence of study-specific viral load tests can present greater challenges with completeness. Johnson et al., looking at viral load test results at 48 months on ART and working with national routine data from the District Health Information System in South Africa, reported 55% completeness, which varied from 68% in one province to 85% in another.(15)

In comparison, others working with routine data reported high completion. Naidoo et al. reported on 3547 (88%) of 4043 patients with viral load results available and Maskew et al. reported on 103 (82%) of 126 participants with viral load results available.(22,23)

Whether completion is high or low, it is helpful when authors report on it explicitly, as the authors did in each of the three studies just discussed. By contrast, Bowman et al. reported that of 88 patients RIC at 12 months on ART, 51 (58%) had achieved viral suppression.(5) It is not clear whether viral load results were available for all 88 patients or missing results were counted as unsuppressed.

Identification of gaps in research

In order to report consistently and comparably on progress towards the target of 90% viral suppression in the population on ART in the context of 90-90-90, a proportion is not enough. The population reported on as well as the methods, definitions, thresholds, data sources used and completion must be explicitly reported. Where possible, multiple definitions and thresholds should be reported against to facilitate more direct comparisons. Different methods may be more appropriate in different settings and for reporting on different targets within the cascade. It would also be helpful to have some evidence base that would allow for correction when comparing results reported using different methods, and for designing interventions to improve completion in routine settings.

Another facet to reporting on the third 90 target that has not been discussed is feasibility. While a once-off measure is useful, regularly reported measurements are required to track progress against the third 90. Designing and deploying regular population-based surveys is unlikely to be feasible and may be an unnecessary expenditure of limited resources in settings where adequate routine data are available. Furthermore, while surveys can provide helpful guidance to programmes, e.g. by identifying sub-populations that experience barriers to accessing care, they generally do not strengthen existing clinical or monitoring and evaluation health information systems.

Conclusion

Published literature reporting on progress towards the third 90 reveals a number of different approaches to measuring viral load suppression in the population on ART. Different study designs, study populations, definitions, data sources and levels of completion may impact on the validity and comparability of results.

In South Africa, each level of healthcare from facility through district and up to province reports to the national government on progress towards the third 90 using routine clinical data that is digitised on-site at facilities and then reported to higher levels in the Department of Health. Data are reported quarterly in the form of facility-based naïve cohort datasets. Viral load suppression is reported as the number of viral loads <400 copies/ml out of the number of viral loads done. Viral load completion is reported separately, and is often very low.

It is not known whether low reported viral load completion is due to low adherence to virological testing guidelines or missing data on viral load tests done, and in the latter case it is not known what the cause of missing data or its impact on the validity of reported viral load suppression proportions might be. The effect of using a viral load threshold of 400 copies/ml rather than 1 000 copies/ml is not known, nor is the effect of reporting on only naïve facility-based cohorts, excluding experienced and transferred-in patients.

This study aims to answer these questions by examining viral load suppression and completion in a high-prevalence routine care setting in South Africa.

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PART C: Journal-ready Manuscript

Title

How accurately do routinely reported HIV viral load suppression proportions reflect progress towards the 90-90-90 target in the population on ART in Khayelitsha, South Africa?

Abstract

Background: The third 90-90-90 target requires 90% of patients on antiretroviral therapy (ART) to be virally suppressed <1000 copies/mL. Khayelitsha reported viral load (VL) suppression <400 copies/mL as 89% in 2016, but only 56% of patients had a result recorded in routine data. We conceived a “VL cascade” to represent the steps required for an expected VL to be reported as complete in routine data and thus contribute to reported VL suppression: among those for whom a VL is “expected”, a sample must be collected and tested (“done”), a result must be “filed” in the patient folder, “noted” by a clinician and electronically “captured”. The low reported completion suggested gaps along the VL cascade and cast doubt on the validity of reported suppression.

Objectives: To assess the validity of routinely reported VL suppression and identify barriers to VL completion.

Methods: A retrospective cohort study including all patients on ART in Khayelitsha with a routine VL expected between 1 July 2015 and 30 June 2016 was conducted. We obtained data routinely captured on-site and VL data from the laboratory system. A sample of 1 035 physical patient folders were also reviewed. VL suppression was calculated using laboratory data including all tests done and compared to reported suppression based on on-site electronic data capture. Successful progression through each step on the VL cascade was estimated. We used logistic regression to identify factors associated with laboratory and reported VL testing.

Results: Of 22 991 patients with a routine VL due, 84% were done, 79% filed, 76% noted, and 55% captured. Using all laboratory data, VL suppression was estimated to be 82%, 87%, 89% and 91% at the 50, 200, 400 and 1 000 copies/mL thresholds respectively, but reported suppression using captured results was 80%, 86%, 88% and 89% at those thresholds. Routine VL were more likely to be done among children <15 years old (aOR 1.89, 95%CI 1.45–2.48) and pregnant women (aOR 1.90, 95%CI 1.28–2.81) compared to men, adjusted for facility.

Conclusion: Despite low reported completion, VL testing completion was high. Reported suppression using captured data was similar to suppression calculated using all laboratory data, providing an accurate measure of progress towards the 90-90-90 target. More work is needed to reach the 16% of patients missed by routine testing.

Introduction

The 90-90-90 strategy ambitiously aspires to have 90% of all people living with HIV (PLWH) know their status, 90% of those to receive sustained antiretroviral treatment (ART), and 90% of those to achieve viral load (VL) suppression by 2020.(1) Many studies have assessed progress against these targets in different settings, with significant heterogeneity in data sources, outcome definitions, methods and results.(2)

The Khayelitsha Cohort in Cape Town is one of the oldest and largest HIV cohorts in South Africa. Free public-sector ART was initially rolled out here in 2001 in partnership with Médecins Sans Frontières.(3) VL testing is the gold standard in HIV treatment monitoring.(4,5) Unusually for a low-resource setting, VL monitoring has been widely used in Khayelitsha since programme inception in 2001. With approximately 22 000 patients on ART and in care at Provincial facilities in 2016, Khayelitsha reported almost 89% suppression on quarterly reports, but also reported only 56% completion of routine VL tests indicated by national guidelines.(6) This low reported completion does not necessarily imply low actual completion, as it may be the result of incompleteness in routine data capture.

For this study, the concept of a “VL cascade” was introduced to represent the steps required for an expected VL to be reported as complete in routine data and thus contribute to reported VL suppression on routine quarterly reports (Figure 1). At the first step, among patients from whom a routine VL is expected, a blood sample must be taken (step 1). The VL blood sample must then be processed by the laboratory (step 2), the test result printed, couriered to the facility, sorted and distributed to the appropriate registry and filed by a clerk in the patient folder (step 3), the result noted by a clinician in the visit summary paper stationery at the next clinical assessment (step 4) and electronically captured by a clerk into the Primary Healthcare Information System (PHCIS) (step 5). Finally, routine quarterly ART data report on facility-based ART-naïve cohorts, so VL results for patients who initiated outside of the facility at which they are now in care will not be included in reports (step 6).

The low reported completion for Khayelitsha in 2016 therefore raised two important questions: was the high reported suppression proportion a valid measure of progress towards the third 90, and what were the barriers to VL testing and recording of VL results in the context of widely available laboratory testing? This study aimed to answer these questions by describing a VL cascade from ‘expected’ to ‘reported’ and estimating success and failure at each step on the cascade.

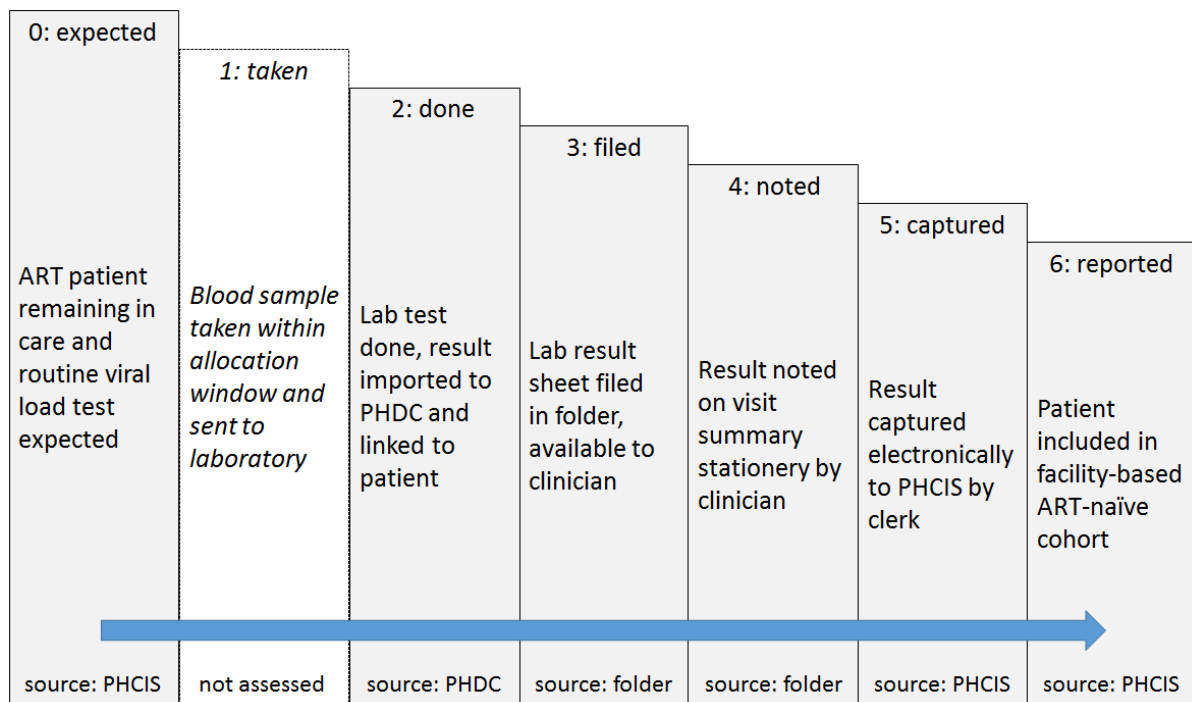


Figure 1: Viral load cascade - from expected to reported

Methods

Setting

The Khayelitsha Cohort has been described in detail elsewhere.(7) Briefly, Khayelitsha is the largest township in Cape Town, South Africa, with a high burden of HIV. The provincial government has provided free ART services at primary healthcare facilities starting in 2001.(3) Eligibility criteria have evolved in response to World Health Organisation (WHO) recommendations, with Universal Test and Treat adopted nationally in September 2016.(8)

Study design

A retrospective cohort was constructed including all patients on ART and in care at provincial healthcare facilities in Khayelitsha with a routine VL expected in the year from 1 July 2015 to 30 June 2016. Ethics approval for this study was granted by the University of Cape Town Human Research Ethics Committee.

Population

In the South African ART programme, routine quarterly reports follow naïve cohorts while in care at their initiating facility. Patients who die, transfer out or are lost to follow-up (defined as 90 days without medication in hand) exit the cohort. Even if they return to care elsewhere they are no longer included in the reported suppression proportion. By contrast, the intended denominator for the “third 90” includes all patients receiving ART regardless of where they access care. This study included all patients receiving ART in Khayelitsha in the study period irrespective of where they initiated ART but distinguishes between patients who are part of the reporting cohort (the naïve cohort at the reporting facility) and those who are not.

Outcomes

Suppression

National guidelines define VL suppression as <400 copies/mL. While the UNAIDS 90-90-90 document does not explicitly define a threshold, it is generally taken to be 1 000 copies/mL, although various thresholds have been used in different settings.(9) To assess the effect of using different thresholds and facilitate comparability across studies, multiple thresholds are reported against here.

Completion

Provincial guidelines recommend routine VL testing for all patients at four months on ART, again at 12 months and annually thereafter.(10) More frequent testing is recommended after an unsuppressed VL or regimen switch, in HIV-exposed infants, HIV positive children <5 years of age and pregnant and breastfeeding women. To calculate routine VL completion, we calculated patient-specific time windows around each expected VL due date based on the patient’s ART initiation date, using the same algorithms as routine reports (Figure 2). This algorithm is the same for all patients despite the different clinical guidelines alluded to above. According to this algorithm, where more than one VL was taken within an allocation window, the VL on the date closest to the due date is used and others are excluded from reports.

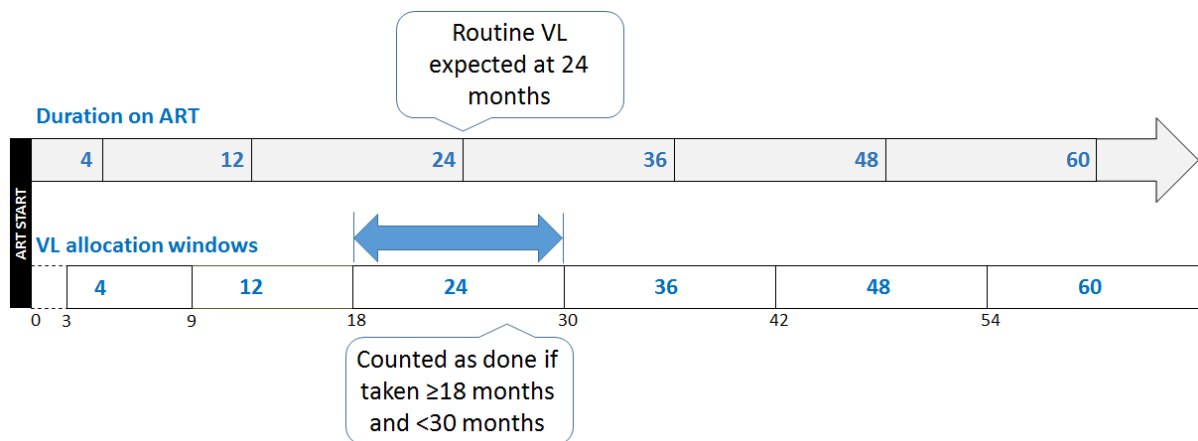


Figure 2: Viral load allocation – using a 24-month due date as an example

Data collection

We used 3 data sources to assess completion at each step in the cascade: PHCIS, the Provincial Health Data Centre (PHDC) and the physical patient folder containing all paper records at the facility (Figure 1). To assess completion at steps 0, 2 and 5 on the cascade, data were requested from PHCIS and PHDC. PHCIS contains routine data digitised by clerks on site at the healthcare facility. The PHDC contains all data from the National Health Laboratory Services (NHLS), which performs all VL testing for patients in care at Provincial facilities in Khayelitsha. All VL testing during the study period was performed by the NHLS using a Roche COBAS Ampliprep/TaqMan HIV-1 test v2. Step 1 could not be directly assessed: for example, if a test was not registered by the laboratory system due to incorrect or illegible request forms, it would not be counted as “done” at step 2, despite a blood sample having been taken within the timeframe and sent to the laboratory. Completion at steps 3 and 4 was assessed by physical folder review, for which folders were drawn on-site at facilities and some data captured directly to a standalone encrypted electronic database. Routine patient data in all sources (physical folder, PHCIS, NHLS and PHDC) are captured and linked using the unique patient identifier used across the public health platform in the Western Cape Province.(11)

Data analysis

The VL cascade is simplified insofar as it reports the furthest step a VL reached on the cascade and assumes that the VL successfully reached all previous steps on the cascade. Only VLs done (step 2) but not captured (step 5) were sampled for physical folder review. The folder review then generated proportions of the sample that were filed (step 3) and noted

(step 4). These proportions (of the sample) could then be added to the proportion captured (of the total) to generate the proportions filed and noted on the cascade.

Statistical analyses were performed using Stata 14 (StataCorp. 2015, College Station, TX). The sample of folders selected for review was prepared using the Simple Random Sample function in Stata, clustered on healthcare facility.

A logistic regression model was built to investigate the effect of facility, age category and pregnancy status on VL testing completion (“done”) and inclusion in routine reports (“reported”). Healthcare facility was included to account for different operational practices at different facilities. Age category and pregnancy status were included because different models of care are provided for children and pregnant women and different clinical guidelines are followed. Adjusted odds ratios (aOR) with 95% confidence intervals (95%CI) were estimated using this model.

Results

There were 22 991 patients on ART and in care at provincial healthcare facilities in Khayelitsha with a VL expected between 1 July 2015 and 30 June 2016, of whom 18 450 (84%) had a VL done within their window. Of these, 11 100 (60%) were included in the reported suppression proportion in routine data: 1 790 (10%) were excluded because the patients were not part of the naïve cohort at the reporting facility, and 5 560 (30%) were excluded because they were not captured (step 5). Of those not captured, a total of 1 035 physical folders were reviewed, and completion at steps on the cascade was estimated to be 84% done (VL sample taken and tested), 79% filed, 76% noted by clinician, and 55% captured electronically.

Actual completion (“done”) and reported completion (“reported”) varied by facility, age category and pregnancy status (Table 1). Expected VL were less than half as likely to be “done” at Facility C when compared to Facility A (aOR 0.46, 95%CI 0.42–0.51). Expected VL at Facility C were also less likely to be included in the reported suppression proportion (aOR 0.74, 95%CI 0.69–0.78). Children under 15 years of age were more likely than men to have a routine VL done (aOR 1.89, 95%CI 1.45–2.48). Despite pregnant women being almost twice as likely as men to have a VL done within the routine window, their results were 0.60 times as likely to be included in reported suppression proportions (aOR 1.90, 95%CI 1.28–2.81 and aOR 0.60, 95%CI 0.47–0.77, respectively). The inclusion of duration on ART

in the model made no meaningful difference to the effect estimates in the model (Supplementary Table 1).

Suppressed VL <400 copies/mL were slightly less likely to be included in reported suppression proportions (OR 0.70 95%CI 0.63–0.77). Actual VL suppression among all those VL done calculated using laboratory data was 82%, 87%, 89% and 91% at the 50, 200, 400 and 1 000 copies/mL thresholds respectively, but reported suppression would have been 80%, 86%, 88% and 89% at those same thresholds.

Table 1: Patient characteristics, outcomes and adjusted odds ratios

	Expected	Done		Reported	
	n (%)	n (%)	aOR (95%CI)	n (%)	aOR (95%CI)
Facility A	7 129 (32)	6 313 (34)	1.00	3 815 (34)	1.00
Facility B	5 916 (27)	5 130 (28)	0.84 (0.76–0.94)	3 181 (29)	1.01 (0.94–1.08)
Facility C	8 946 (41)	7 007 (38)	0.46 (0.42–0.51)	4 104 (37)	0.74 (0.69–0.78)
Men	6 097 (28)	5 012 (27)	1.00	3 138 (28)	1.00
Non-pregnant women	15 011 (68)	12 649 (69)	1.17 (1.08–1.27)	7 546 (68)	0.96 (0.90–1.01)
Pregnant women	275 (1)	246 (1)	1.90 (1.28–2.81)	107 (1)	0.60 (0.47–0.77)
Children <15 yrs	608 (3)	543 (3)	1.89 (1.45–2.48)	309 (3)	0.99 (0.84–1.17)
Years on ART median (IQR)	4 (2–7)	4 (2–7)	1.09 (1.08–1.11)	4 (2–7)	1.07 (1.06–1.08)

Discussion

The reported VL suppression proportion <400 copies/mL from routine data of 89% differed by only 1% when including all VL results from the laboratory, despite only 60% of these VL contributing to reported suppression. This confirms that Khayelitsha is very close to achieving the third 90 among those with results available. However, taking into consideration the 16% of patients not tested, the proportion of patients with confirmed suppression <400 copies/mL drops to 75% of those on ART and in care. This is worrying because it implies that even as we successfully increase ART coverage, the proportion of patients on ART who may be at risk of transmitting HIV remains between 10% and 25%.

Reported completion proportions were low mostly due to failures to test patients (16%) and failures to capture VL results electronically (21%). The inclusion of electronically imported test results from laboratory systems in routine quarterly reports is currently being trialled in the Western Cape and would obviate the need for manual capturing of the results into PHCIS. However, the advantage of manual capture from the folder was that it allowed for indirect monitoring of other steps in the VL cascade, because the presence of a VL result in routine data implied successful progress through previous steps on the cascade. Specifically, it

implied that the result was available to the clinician at the next clinical assessment, as the clinician had to note it in the stationery for a clerk to capture it electronically. Importing results will improve the completeness of data in routine reports, but it will no longer be possible to make inferences about intermediate steps on the VL cascade from the routine data. Reassuringly, there was relatively little loss on the cascade between VL being done (step 2), filed (step 3) and noted (step 4), implying that results from VL tests that were done were usually available to clinicians at the next clinical assessment.

Our results suggest that if electronic import of test results from laboratory systems is successfully implemented, the reported VL completion proportion will increase substantially but there will be little effect on the reported suppression proportion. Of note, this study only assessed whether clinicians noted the VL results in the folder and did not attempt to assess the effective use of VL results for clinical decision-making and further research in this important area is required.

The variation in actual completion between facilities based on laboratory data suggests facility-specific challenges that require further investigation. The variation by pregnancy status and age category is expected, as clinical guidelines recommend more frequent testing for pregnant women and children.

The underrepresentation of pregnant women in the reported suppression proportion may be due to increased mobility during pregnancy due to movement between integrated maternal-ART clinics and routine ART clinics.⁽¹²⁾ As discussed above, routine reports include only facility-specific naïve ART cohorts. However, this deserves further investigation as pregnant and breastfeeding women are vulnerable groups and viral suppression is critical to prevent vertical transmission.⁽¹³⁾ Since the conclusion of this study, a separate routine quarterly report specifically for pregnant women was mandated by the national government.

Overall, actual completion was relatively high, but more must be done to close the gaps and reach those patients not being tested, especially among men and non-pregnant women. Both suppressed and unsuppressed VL results inform patient management and clinical care. A suppressed VL may be used along with other indications to identify patients for recruitment to differentiated models of care, while an unsuppressed VL alerts a clinician to possible adherence challenges or drug resistance. We noted above that suppressed VL results were slightly less likely to successfully complete the VL cascade than unsuppressed VL results. This may suggest missed opportunities to recruit stable patients to differentiated models of

care, thereby unburdening the health facilities. Furthermore, it suggests that routine data may minimally underestimate the success of the ART programme.

This study has limitations. Firstly, the study could not estimate the small proportion of requested VL that were not successfully processed by the laboratory. Secondly, in this study, in routine quarterly ART reports, and in the third 90 as defined by UNAIDS, the suppression proportion is calculated at a point in time using a single VL. By contrast, sustained suppression over time is required to reap the full benefits of ART and mitigate the risk of transmission. Thirdly, the results of this study may not be generalisable to other settings. Three large provincial facilities were included in this study and, while the main findings are likely to apply to other similar facilities in metropolitan areas of South Africa, some of the results may not be generalisable to settings outside of Khayelitsha.

Strengths of this study include the assessment of routine data on >20 000 patients from multiple facilities including adults, pregnant women and children. This was made possible through close collaboration with the Provincial Department of Health, and the availability of harmonised data from different data sources in the health system provided by the PHDC.

Conclusion

Despite low reported VL completion, actual VL testing completion was high. The study confirmed the high levels of suppression that are routinely reported. More work is needed to reach the 16% of patients missed by routine testing. Most VL results were accessed and noted by clinicians, and further research is needed to assess how effectively these results are used in clinical decision-making.

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Part D: Appendices to the Dissertation

1. Only electronic data capture instruments were used.
2. The requirement for informed patient consent was waived.
3. The letter of approval from the UCT Human Research Ethics Committee is attached following this page.
4. Instructions for Authors from the South African Medical Journal are attached following the letter of approval from the UCT Human Research Ethics Committee.



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 6626
Email: jamees.emiedl@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

05 May 2017

HREC REF: 270/2017

A/Prof M Davles
Public Health & Family Medicine
Falmouth Building
Medical School

Dear A/Prof Davles

PROJECT TITLE: HOW ACCURATELY DO ROUTINELY REPORTED HIV VIRAL LOAD SUPPRESSION PROPORTIONS REFLECT PROGRESS TOWARDS THE 90-90-90 TARGET IN THE POPULATION ON ART IN KHAYELITSHA, SOUTH AFRICA (masters-candidate-J Euvrard)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee. Thank you also for submitting your response to the queries raised dated 18 April 2017.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study subject to updating the annual approval of study 395/2005.

Approval is granted for one year until the 30 May 2018.

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)

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 before the research may occur.

The HREC acknowledges that the following Masters Candidate Mr J Euvrard will also be involved in this study.

Please quote the HREC reference number in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC REF 270/2017

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.

SAMJ manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, **full** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and °C), e.g. '40 kg' and '20 cm' but '50%' and '19°C'.
- Please be sure to insert proper symbols e.g. μ not u for micro, α not a for alpha, β not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

****NB:** Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
 - **Background:** why the study is being done and how it relates to other published work.
 - **Objectives:** what the study intends to find out
 - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
 - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
 - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the \pm symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.