
UNIVERSITY OF CAPE TOWN

EVALUATING VIRAL LOAD MONITORING IN ANTIRETROVIRAL-EXPERIENCED HIV- POSITIVE PREGNANT WOMEN ACCESSING ANTENATAL CARE IN KHAYELITSHA, CAPE TOWN.

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LIST OF ABBREVIATIONS

ART	Antiretroviral Therapy
DOH	Department of Health
HCT	HIV Counselling and Testing
MOU	Midwife Obstetric Unit
MTCT	Mother to Child Transmission
NHLS	National Health Laboratory Service
PCR	Polymerase Chain Reaction
PGWC	Provincial Government of the Western Cape
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	(HIV) Viral Load
VLM	Viral Load Monitoring
VNS	Virologically non-suppressed
VS	Virologically suppressed
WHO	World Health Organisation

DEFINITIONS

'to book'	to present for antenatal care
booking visit	the first antenatal visit
booking VL	VL taken at first antenatal visit
Virologically suppressed	VL \leq 400 copies/ml

ABSTRACT

BACKGROUND

A viral load monitoring algorithm in the 2013 Western Cape Department of Health PMTCT guidelines include VL measurement in women who are antiretroviral (ART)-experienced at presentation for antenatal care, the timing of subsequent VL measurements and criteria for regimen change. The study evaluates the implementation of the algorithm in women who are virologically nonsuppressed and determines the outcomes of virological resuppression and infant PCR status.

METHODS

This retrospective cohort study focused on all ART-experienced women who presented for antenatal care at one of two primary level Maternity Obstetric Units (MOUs) in Khayelitsha, Cape Town between July 2013 and June 2014. The study used routine data from facility registers, clinical records and electronic monitoring systems at the MOU, and referral ART sites and hospitals.. Data collected included age, ART clinic, start date and regimen, and maternal VL and infant PCR results.

RESULTS

Forty percent of the 1412 HIV-positive pregnant women, were ART-experienced, of whom 14.1% were VNS. Predictors of being VNS included a duration on ART of more than 4 years ($p=0.04$), attending an ART clinic other than that in the facility ($p=0.02$), being on a second-line ART regimen ($p=0.07$) and being younger than 25 years ($p=0.05$). The algorithm was correctly followed in up to 87.5% of women identified as VNS. The rate of virological resuppression by three months postpartum was 70.0% to 82.3%. Excluding three neonates who died, all of the 82.2% of infants tested were PCR negative.

CONCLUSIONS

Nearly 15% of ART-experienced women were virologically nonsuppressed on presentation for antenatal care.

Levels of adherence to the guideline, and virological resuppression rates of up to 82.3% are encouraging.

The implementation of the VLM algorithm could be improved by the integration of obstetric and ART care, the adoption of a single electronic monitoring system and the use of standardised integrated clinical stationery. (300 words)

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PART 1: STUDY PROTOCOL

INTRODUCTION

Over the past two decades, great progress has been made globally in programmes aimed at the prevention of transmission of HIV from mother-to-child (PMTCT). In the days preceding any form of PMTCT intervention, mother-to-child transmission (MTCT) of HIV was estimated to be 15-30% by the time of delivery, with subsequent breastfeeding adding a further 20% risk (Newell, 2005). By the late 2000's, in well-resourced countries, transmission rates of less than 2% were achieved through the combined approach of antiretroviral prophylaxis, elective caesarean section and the avoidance of breastfeeding (Newell, 2005). By December 2009, the global coverage of PMTCT services reached 53%, while many low-and-middle income countries had achieved at least 80% coverage. These include high HIV-burden countries such as Botswana, Namibia, Swaziland and South Africa (UNAIDS, 2011). However, developing countries face enormous challenges in implementation of optimal PMTCT programmes due to various factors, including limited resources, struggling health systems, high HIV prevalence, and socio-behavioural practices.

The risk of MTCT is influenced by a number of factors, including the woman's viral load (VL) and immune status, as well as obstetric practices (Kourtis, 2010). Of these factors, the VL is the strongest predictor of transmission (Thorne et al, 2004). A higher baseline VL in the mother is associated with vertical transmission to the infant (Garcia, 1999). It is also associated with a longer duration to virological suppression on antiretroviral treatment (ART) (European Collaboration, 2007) and suboptimal virological suppression at the time of delivery (Louis, 2005). Evidence from Cape Town, South Africa suggests that almost half the ART-naïve women in this setting presented with VLs that could be considered high (greater than 10 000 copies/ml) (Myer et al, abstract CROI 2014).

Suboptimal adherence to ART is the strongest predictor of poor viral suppression in PMTCT, as is the case in general ART programmes (Louis, 2005). There are numerous barriers to good ART adherence; these include those related to health services access and organisation, the complexity of the regimen, pill burden and adverse events associated with the medication, an individual's lack of education,

forgetfulness, depression or other illness, and community attitudes of stigma, discrimination with consequent lack of disclosure (World Health Organisation Consolidated Guidelines, 2013). Lack of partner involvement and suboptimal or fewer antenatal care visits have also been identified as risk factors for poor adherence in PMTCT programmes (Columbini et al., 2014).

Late antenatal presentation results in a shorter duration on ART and consequently poorer virological suppression by the time of delivery (Louis, 2005). Women who present for antenatal care late in pregnancy or arrive in labour having had no antenatal care at all, are thus at highest risk of transmission. This scenario is particularly prevalent in resource-poor countries, but even in well-resourced settings, approximately one third of women may not have suppressed at the time of delivery (Louis, 2005; European Collaboration, 2007).

Ideally, frequent VL monitoring during pregnancy could alert clinicians to women whose VLs are detectable, and make it possible to intervene in order to achieve virological suppression. In 2013, the World Health Organisation (WHO) recommended viral load monitoring (VLM) as the preferred approach to diagnose and confirm ART failure (WHO Consolidated Guidelines, 2013). These guidelines propose testing VL at six months post ART initiation. However, no distinction is made between VL monitoring in pregnancy as opposed to in routine ART programmes. Given the generalised nature of these recommendations, and the fact that late entry into antenatal care is so common, the majority of pregnant women would be unlikely to have a six month VL test before delivery.

In many resource-constrained countries, the high costs of VL testing have meant that VLM is not routine in either general ART programmes, or in PMTCT services. Well-resourced countries can afford to test more intensively. The United States of America's National Institute of Health guidelines of May 2014 propose that a VL be measured in all HIV-infected pregnant women at their initial antenatal visit, and several times thereafter during the pregnancy (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2011).

The 2014 British HIV Association guidelines go a step further in proposing HIV resistance testing before initiation of ART in pregnant women. No such VL

monitoring policies could be found in the literature for poorly-resourced countries, suggesting no guidelines exist for monitoring VL in pregnant women in such settings

Where guidelines regarding VL monitoring in pregnancy exist, they have focused on women who initiate ART for the first time in pregnancy. Yet, with improved ART coverage over time, increasing numbers of women enrolling in antenatal care are ART-experienced. A study in Gugulethu, Cape Town, found that nearly 25% of ART-experienced women are not virologically suppressed on presentation to the antenatal services (Myer et al., 2014). Case reports in Khayelitsha, Cape Town, found that several babies testing positive on Polymerase Chain Reaction (PCR) at six weeks had been born to women who had claimed to be taking ART at other sites when entering antenatal care, but had suboptimal adherence or had in fact defaulted treatment (Giddy, personal communication, May 2014). Hence there is a missed opportunity for PMTCT through neglecting to actively ascertain the viral status of ART-experienced women, and manage them accordingly.

One of the objectives of South Africa's National Strategic Plan for HIV/AIDS/STIs for 2011-2016 is to reduce the transmission of HIV from mother-to-child to less than 2% at six weeks by 2011 and less than 5% by 18 months of age by 2016. As a strategy to achieve this, in March 2013, the South African Department of Health adopted the Option B of the WHO Consolidated Guidelines (2013), whereby all HIV-positive pregnant and breastfeeding women are eligible for ART; after cessation of breastfeeding, those women who do not qualify for ART under standard criteria stop this treatment.

The Western Cape Health Department decided to implement Option B+ whereby all of these women would remain on lifelong ART. Included in these guidelines is a VL monitoring algorithm that had been drafted by concerned Khayelitsha clinicians in conjunction with local HIV experts. To address the missed opportunities for the optimal management of HIV-infected pregnant women who are not virologically suppressed, the guidelines recommend more frequent testing of VL in pregnancy, including a baseline VL in ART-experienced women (Appendix 1). The algorithm was implemented in Khayelitsha antenatal services in May 2013.

As discussed above, while policies for VL monitoring in pregnancy exist in some well-resourced countries, no evidence of similar policies in resource-poor countries

could be found in the literature. There is thus a gap in what is known about VL monitoring in pregnancy in resource-constrained settings such as South Africa.

The aim of this research is to describe the implementation of the Western Cape VLM algorithm and to evaluate its effectiveness in identifying ART-experienced pregnant women with detectable viral loads and achieving improved outcomes in their virological suppression antenatally and up to 12 weeks postnatally. In addition, the PCR status of their infants at six weeks will be assessed.

AIM

The aim of the study is to evaluate the implementation of viral load monitoring guidelines in ART-experienced HIV-positive pregnant women and determine the outcomes of these interventions on the virological status of the women and PCR status of their infants.

OBJECTIVES:

The objectives of the study are for the cohort of ART-experienced HIV-positive women presenting for PMTCT antenatal care at Site B Midwife Obstetric Unit (MOU) in Khayelitsha, during the 12 month period from July 2013 to June 2014:

1. To describe the implementation of the Western Cape HIV viral load monitoring algorithm as regards VL testing and actions taken in response to ART-experienced women being found to have a detectable VL on presenting for antenatal care;
2. For those ART-experienced women who had a detectable VL on presenting for antenatal care : to determine the virological outcomes at their last monitoring visit;
3. To determine whether there are factors associated with non-suppression of VL in these women; and
4. To determine the proportion of exposed infants born to ART-experienced women who had a detectable VL on presenting for antenatal care, who are diagnosed HIV-positive by a PCR test at six weeks.

RESEARCH QUESTIONS:

The research questions are:

1. What are the socio-demographic characteristics and clinical features of ART-experienced HIV-positive pregnant women presenting for PMTCT antenatal care?
2. What is the virological status of ART-experienced HIV-positive women accessing PMTCT antenatal care?
3. To what extent are the guidelines implemented in the management of ART-experienced woman having a detectable VL on presenting for antenatal care?
4. What are the virological outcomes of ART-experienced women who have a detectable VL on presenting for antenatal care, at their last monitoring visit (antenatally or up to 12 weeks postpartum)?
5. Are there significant risk factors associated with a detectable VL in this cohort of ART-experienced HIV positive women accessing antenatal PMTCT care?
6. What are the outcomes of PCR testing at six weeks of the infants of ART-experienced women who had a detectable VL on presenting for antenatal care?

METHODS

SETTING:

Khayelitsha is a peri-urban settlement 40kms from the Cape Town city centre, which is home to approximately 450 000 people (Statistics South Africa, 2012). There are high levels of poverty in the population, with an unemployment rate approaching 40% in 2011. Over half of the population live in informal housing.

The population of Khayelitsha experiences a triple burden of disease: infectious diseases (predominantly HIV and tuberculosis), chronic diseases of lifestyle and trauma. The antenatal HIV positivity rate rose from 19.3% in 2000 to 37% in 2011 (Provincial Government of the Western Cape, 2012). By the end of March 2014, routine statistics report that 28738 clients were receiving ART in Khayelitsha health facilities.

PMTCT services have been provided in Khayelitsha since 1999. Over time, regimens have become more efficacious, progressing from AZT-only (1999), ART for eligible women (2004) to the current ART for life for all pregnant and breastfeeding women (Option B+) (Stinson et al., 2014)

The Khayelitsha Site B MOU is one of two facilities providing primary level antenatal and delivery services to women in Khayelitsha. Routine data estimate that an average of 350 women present for antenatal care at Site B MOU monthly, of whom a third are HIV-positive. Up to 40% of HIV-positive women report being on ART at their first antenatal visit. Since the introduction of Option B+ in July 2013, the number of pregnant women initiating ART at the facility has doubled: from an average of 40 (January to June 2013) to an average of 80 per month (July 2013 to February 2014). These women are initiated on ART almost exclusively by professional nurses.

Half of these women who present are obstetrically 'low risk' and deliver at the facility. Those who have obstetric risk factors or complications during delivery are referred antenatally or during labour to either the Khayelitsha District hospital four kms away, or to the tertiary-level Tygerberg hospital almost 30 kms away, depending on the degree of risk. Approximately 50 of the HIV-exposed infants are followed up at the adjacent Site B Community Health Centre (CHC) while the remainder present at other clinics in Khayelitsha or further afield. The majority of the Site B CHC babies are PCR-tested at six weeks. Routine service data shows that in the seven months since the introduction of Option B+ in July 2013, only one of the more than 250 babies tested at the facility tested PCR positive.

STUDY POPULATION

The study population will be the cohort of all ART-experienced HIV-positive pregnant women presenting for antenatal PMTCT care at the Site B Midwife Obstetric unit (MOU) in Khayelitsha during the period July 1 2013 to June 30 2014. Parts of the analysis focused on a sub-sample of ART-experienced women who have a detectable viral load when presenting for antenatal care. All of the latter cohort are included in the sample, regardless of whether they only had one antenatal visit, their pregnancy was terminated or they were lost to follow-up.

STUDY DESIGN

This will be a quantitative study that focuses on a retrospective cohort. The characteristics of the cohort and their virological outcomes will be described. Actions taken by health care providers in response to women with a detectable VL at enrolment into antenatal care will be presented, and an assessment will be made as to whether these actions were consistent with the those specified in the VL monitoring algorithm. An analytic component will consider a detectable viral load on testing at enrolment into antenatal care as an outcome of interest, and determine whether there are associated significant risk factors for a detectable viral load, and predictors of virological non-suppression.

DATA MANAGEMENT AND ANALYSIS

Data will be extracted from the following sources:

1. Paper registers: the Site B MOU HIV Counselling and Testing (HCT) and labour ward registers (including the PMTCT labour ward register); PMTCT Baby registers in Khayeltisha clinics.
2. Electronic ART registers: eKapa (Site B MOU and 3 other Khayelitsha facilities) and TIER.Net (remainder of Khayelitsha facilities), with linkage to laboratory results.
3. Patient folders at Site B MOU and other Khayelitsha facilities, where data are found to be incomplete on the electronic record.

Extracted data will be recorded in hard copy extraction forms (Appendix 2) by the researcher and/or assistant before being captured into an Access data-base for analysis. Data will be independently checked for errors of transcription or translation. Statistical analysis will be performed using Stata version 12 (StataCorp, Texas, USA, 2012).

PROTECTION OF PRIVACY OF DATA

Hard copies of extracted data will be kept, using codes to link patient identifiers to patient-specific information. The codes will be accessible to only the researcher and research assistant.

The software data-base will be encrypted and stored on the researcher's laptop, which is also password-protected.

SITE PREPARATION PLAN

The researcher is an employee of the Provincial Government of the Western Cape (PGWC) Health Department with responsibility for monitoring of HIV services in the Khayelitsha subdistrict, and therefore has an existing relationship with the facility and its management. Once ethical approval and health authority permission has been granted, the researcher will meet with substructure and facility staff to present the proposed study. A brief pilot will be undertaken to gain insight into the service structure and to determine potential challenges to data collection.

ETHICAL CONSIDERATION AND HIGH LEVEL APPROVAL

Ethical approval has been sought from the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town, under an existing protocol which covers routine cohort monitoring and research in the HIV care services within Khayelitsha (HREC Ref: 2005/395: 'Enhanced routine surveillance of an HIV clinic population in Khayelitsha'). While this protocol has existing approval from local authorities, study-specific approval will be sought from both the Health Department of PGWC, and the City of Cape Town Health Department.

The proposed study will be guided by the ethical principles stated in the Declaration of Helsinki which was developed by the World Medical Association (World Medical Association, 2012).

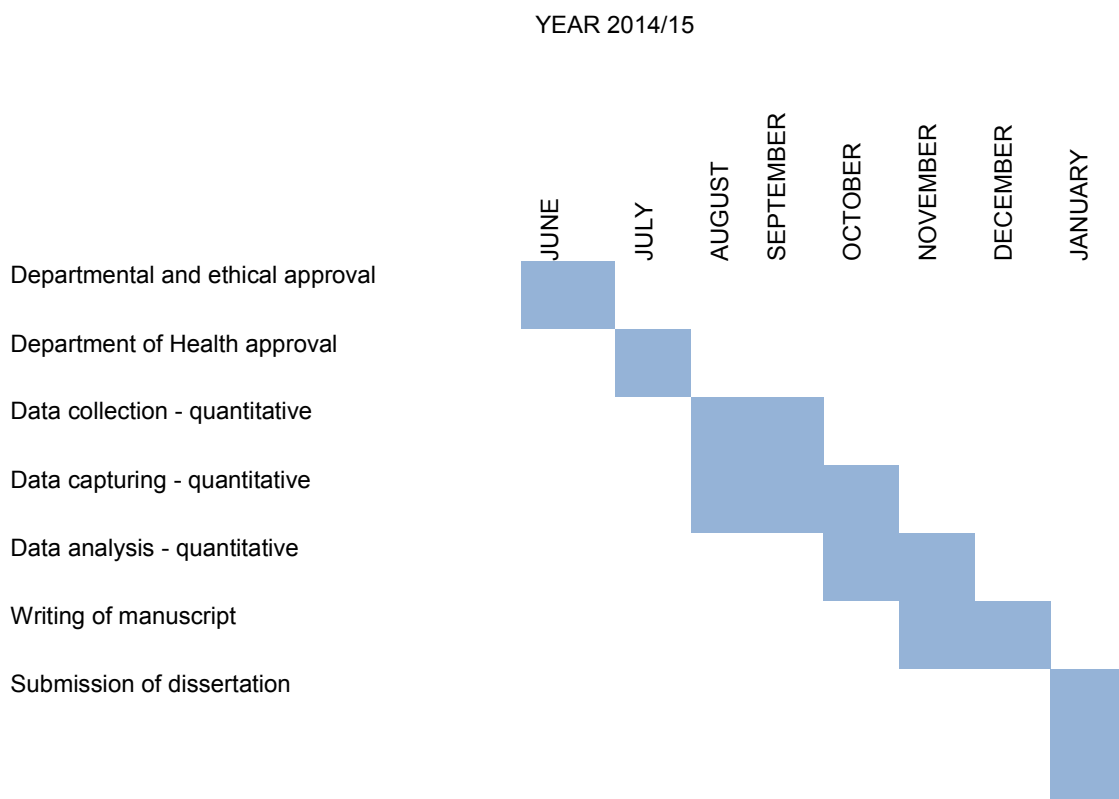
There is a potential risk of breach of confidentiality due to the accessing of patient identifiers while seeking eligible women for the study from the routine data sources. However, given the complexity of working across paper and electronic platforms, the cross-checking of data using names and folder numbers is unavoidable in order to ensure data quality. The researcher acknowledges that this procedure may have ethical implications in terms of protecting patient confidentiality through the use of data collection which is not anonymous. However, it is argued that using patient names in programme research is not a new phenomenon. Once extracted, confidentiality of patient information will be maintained by the use of codes for personal identifiers, and password-protection of computers used. Records with personal identifiers will be destroyed once data cleaning is complete. No other potential harm to the patient cohort is envisaged.

The study results will be communicated to the health management of both the PGWC and City of Cape Town, as well as to staff of the facilities involved in the study. While no direct benefit to the patients in the cohort is anticipated, it is hoped that the study results will contribute to optimising the VL monitoring algorithm which can be operationalised through appropriate standard operating procedures, thus providing benefit to pregnant women going forward. Training of staff in the implementation of the algorithm could be conducted. It is anticipated that the findings of this research may have wider applicability, and publication of findings in journals or presentation at conferences will be sought.

BUDGET

Costs of travel, stationery, printing and photocopying will be paid for by the researcher. The research assistant will be paid for related work by the Centre for Infectious Diseases Epidemiology and Research at the University of Cape Town. There will be no other funding sources.

TIME FRAME



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PART 2: LITERATURE REVIEW

BACKGROUND TO PMTCT: PROGRESS, ACHIEVEMENTS AND CHALLENGES:

Over the past two decades, significant progress has been made globally in programmes for the prevention of mother-to-child transmission (PMTCT) of HIV. In the absence of any preventive interventions, transmission rates of 15-20% occur by delivery, with prolonged breastfeeding potentially doubling this transmission risk (Newell, 2005). Over this period, our knowledge and understanding of the transmission of HIV from mother-to-child (MTCT) has increased significantly, which has enabled the development of increasingly effective policy and prevention guidelines for PMTCT programmes globally. This has been accompanied by efforts to expand and strengthen maternal and HIV services in developing country settings.

There has been impressive programme implementation scale-up in many countries. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that by December 2009, global coverage of PMTCT services had reached 53%, while many low-and-middle income countries had achieved at least 80% coverage (UNAIDS, 2011). While coverage in Africa has been variable, several high HIV-burden countries, such as Botswana, Namibia, Swaziland and South Africa are amongst those having achieved this target (Govender & Coovadia, 2014). Due to these combined strategies, transmission rates of 14-42% (Kourtis & Bulterys, 2014) have been reduced to 1-2% in developed countries, and even in some resource-limited settings (Ramkissoon & Coovadia, 2014).

In 2011, UNAIDS released 'Countdown to Zero: a Global Plan for the elimination of new HIV infections among children by 2015 and keeping their mothers alive'. The plan advocates a comprehensive four-pronged approach to eliminating MTCT. In addition to conventional PMTCT interventions, there should be a focus on primary prevention of HIV in women, prevention of unwanted pregnancies in HIV-infected women, and care and support for the HIV positive mother, her partner and children (UNAIDS, 2011). This strategy is in keeping with the Millenium Development Goals (MDG) four and five, which aim to reduce maternal and child mortality (MDG Africa Steering Group, 2008).

In 2013, the World Health Organisation (WHO, 2013) issued Consolidated Guidelines that recommended the adoption of Option B for PMTCT whereby all HIV-positive pregnant women qualify for antiretroviral therapy (ART) for the duration of pregnancy and breastfeeding, and Option B+, which recommended lifelong ART for these women.

Given these progressive guidelines and successes, recent UNAIDS and WHO plans set elimination of MTCT (eMTCT) targets of a 90% reduction in new paediatric infections, a transmission rate of less than 5%, and a 50% reduction in HIV-related maternal deaths. The case of the Mississippi baby who was started on ART within hours of her birth in 2010, and in whom no HIV virus was detected after cessation of ART, made eMTCT look within reach (Persuad et al., 2013). Unfortunately, the Mississippi baby experienced HIV viral rebound in 2014 (McNeil, 2014). Other interventions to test eMTCT are currently being explored.

The first public sector PMTCT programme in South Africa was started in 1999 by the Western Cape Department of Health (DOH) in partnership with Medecins Sans Frontieres (MSF) (Stinson et al., 2014). Following this, South Africa's National PMTCT programme was launched in a phased approach from the early 2000s. By 2010, 95% of South Africa's health facilities were providing PMTCT services, more than 98% of women were tested, and 91.7% were receiving either ART or dual prophylaxis (Ramkissoo & Coovadia, 2014). The percentage of pregnant women on triple ART rose from 33.1% to 46.2% between 2010 and 2011 (Bhardwaj et al., 2014), before the adoption of WHO PMTCT Option B in 2013. The increasing PMTCT programme coverage in South Africa is reflected in the impressive decrease in MTCT rates. Transmission rates of 32% were reported in the early 1990's (Ramkissoo & Coovadia, 2014). A review of South African national laboratory data revealed that HIV infection rates in infants tested fell from 16.4% in 2006 to 2.4% in 2012, after the adoption of more comprehensive PMTCT interventions (Sherman et al., 2014). By 2012, 73% of exposed infants were estimated to have had a Polymerase Chain Reaction (PCR) test at six weeks. Between 2008 and 2012, the number of infants diagnosed with HIV dropped from 8405 to 4557 (Sherman et al., 2014).

However, developing countries continue to face enormous challenges in the implementation of optimal PMTCT programmes, due to a number of factors, including limited resources and struggling health systems, often in the context of high HIV prevalence. The UNAIDS Global Plan (UNAIDS, 2011) identifies and prioritises many of these challenges, arguing for strong leadership, sufficient financial investment, up-to-date strategic planning at a national level, greater allocation of human resources for health and strengthening of access to essential supplies. It acknowledges the need to address broad socio-cultural impediments.

Even in well-functioning programmes, achieving eMTCT would require the closing of numerous programme gaps. Chief amongst these is the attrition cascade, which sees significant losses to care at every step from initial HIV testing of the mother to ART initiation of an infected infant, and ongoing ART care for both mother and child (Pennazzato et al., 2014). There are several significant missed opportunities for PMTCT. These include the failure to identify HIV-positive pregnant women who enter antenatal care and who should initiate ART (Bhardwaj et al., 2014) and the identification and management of poor ART adherence in women who either initiate ART in pregnancy or are ART-experienced when enrolling for antenatal care. These poorly adherent or defaulting women are at high risk of MTCT, yet there is a dearth of appropriate interventions to mitigate this risk. The targeted use of viral load testing would assist in identifying these women in need of increased adherence support and specific clinical management.

RISK FACTORS FOR MTCT

HIV MTCT can occur during pregnancy, labour and delivery or postpartum during breastfeeding through transfer of virus in maternal blood, breastmilk and other maternal bodily fluids (Newell, 1998). It has been estimated that in a non-breastfeeding population, approximately two thirds of vertical transmission occurs during labour and delivery (Newell, 1998). Breastfeeding can increase the transmission rate by 15% to 14-42% depending on the duration (Kourtis, 2010).

Numerous risk factors for MTCT have been identified, of which maternal HIV viral load (VL) is the strongest (Newell, 2005) Transmission risk is associated with the level of the viral load (Garcia, 1999; Kourtis, 2010), as well as the stage of disease and immunological compromise (Newell, 2005). Other risk factors include invasive

obstetric procedures, such as foetal scalp monitoring and artificial rupture of membranes (Kourtis, 2010; Garcia, 1999). Lower infant birthweight and prematurity have been postulated as risk factors for MTCT (Newell, 2005).

INTERVENTIONS TO REDUCE MTCT

Interventions to reduce MTCT have addressed the identified risk factors, and have included the mother's use of ART to reduce maternal VL, ART as post-exposure prophylaxis (PEP) for infants, and obstetric procedures that minimise opportunities for MTCT.

The PACTG 076 trial of 1991-1993 established the principles of reducing vertical transmission of HIV to infants through the use of ART antenatally to pregnant women and postnatally to infants (Connor et al., 1994). The trial demonstrated a relative reduction of 67.5% in MTCT at six weeks in non-breastfeeding women through the use of Zidovudine (AZT) from 14 weeks of pregnancy through delivery, and AZT as PEP to the infant. Many subsequent studies have evaluated the administration of ART in various drug combinations and for differing durations, provided to the mother and/or the infant in breastfeeding and non-breastfeeding women; these trials are summarised in the 2011 Cochrane review (Siegfried et al., 2011). In breastfeeding populations, MTCT could be reduced to less than 5% by extended use of maternal ART and the adoption of safer breastfeeding practices, including exclusive breastfeeding (Kuhn et al., 2013; Tsague & Abrahams, 2014).

Based on the findings of these trials, PMTCT protocols progressed from the use of a single dose of one antiretroviral drug to mother and infant, to progressively more complex and efficacious regimens whereby triple therapy was provided for those women with more serious disease, and dual therapy for others. The current WHO 2013 Consolidated HIV guidelines recommend ART for all pregnant and breastfeeding women (Option B or B+) and prophylaxis for infants based on transmission risk and feeding method.

The risk of MTCT is related to the level of the maternal viral load (Garcia et al., 1999). PMTCT outcomes are thus optimised by achieving viral suppression as early as possible before birth, which is the time of the highest transmission risk (Mnyani et al., 2014). Time to virological suppression is influenced by a number of factors, the

strongest being the efficacy of the specific ART regimen adopted (The European Collaborative study, 2007). The Collaboration (2007) found that the median time to viral suppression in a subgroup of women on a specific regimen could be as short as five weeks. Louis (2005) demonstrated the positive association between the baseline viral load of the pregnant or breastfeeding woman and time to viral suppression. Women who were more immunologically compromised took longer to suppress their viral load (Garcia et al., 1999). Duration on ART is an independent predictor of transmission risk (Fitzgerald et al., 2014). The lowest rates (0.5% and 0.16%) are achieved in those women taking ART before pregnancy and who are adherent (Cooper et al., 2002). Fitzgerald et al. (2014) found that transmission risk was reduced by 20% for each additional week of ART. However, Hoffman et al. (2010) found only an 8% reduction per week. In a recent study in Zambia, Chibwasha et al. (2011) concluded that at least 13 weeks of ART pre-delivery was required for maximal efficacy.

While the earliest possible initiation of ART in pregnancy would maximise the likelihood of achieving viral suppression, public policy has been challenged by factors including resource constraints and concerns about the teratogenicity of certain antiretroviral drugs, such as Efavirenz (Ford et al., 2011), in the first trimester. In recent years, the recommended time of ART initiation in pregnancy has become progressively earlier.

Evidence accumulated from the abovementioned studies culminated in the WHO 2013 Consolidated HIV Guidelines recommending either Option B or B+ for PMTCT. This policy was adopted by Malawi in 2011. A number of other resource-constrained countries have subsequently followed suit, including South Africa, in 2013 (Kieffer et al., 2014). It is estimated that with implementation of WHO Option B/B+, peripartum MTCT rates of 2% can be achieved, with breastfeeding adding 0.2% per month to this transmission rate (Ramkissoon & Coovadia, 2014).

The implementation of guidelines is compromised by the reality of patients' health seeking behaviours and existing health systems. In many countries, including South Africa, significant numbers of women present for care at advanced stages of gestation, or attend few antenatal visits, or do not access antenatal care at all and attend in labour for the first time. System delays in, or failure to initiate ART

commonly occur (Fitzgerald et al., 2014). Such realities have a deleterious effect on maternal and child outcomes by reducing the duration of maternal ART received.

ADHERENCE TO TREATMENT AND CARE

Adherence to ART is essential to achieve virological suppression. Barriers to adherence in PMTCT programmes in Sub-Saharan Africa have been well summarised in two recent literature reviews (Gourlay et al., 2013; Columbini et al., 2014) and in the WHO 2013 Consolidated Guidelines.

Adherence can be compromised by factors relating to the medication itself: unpleasant or serious drug toxicities, complexity of regimens, pill burden and dietary restrictions (WHO, 2013). The increasing use of drug formulations with better side-effect profiles, and once-daily fixed dose combination of ART are attempts to address these barriers.

Adherence risk factors at the level of the individual woman include young age (Gourlay et al., 2013; Columbini et al., 2014), substance abuse, depression and other illness (WHO, 2013). At a societal level, adherence is negatively affected by ongoing stigma towards and discrimination against HIV-infected individuals. The resultant fear of disclosure and its possible consequences deprives many women of the support of partners and family, factors that improve adherence (Gourlay et al., 2013; Columbini et al., 2014).

The health system itself poses numerous barriers to health care visits and medication-related challenges to adherence. These include the accessibility of the service and the related direct and indirect costs of clinic attendance (Columbini et al., 2014; WHO, 2013), system challenges, such as staff and equipment shortages (Gourlay et al., 2014), drug stock-outs, and the necessity for frequent visits and long waiting times (WHO, 2013). Sub-optimal staff-client interactions can have a negative effect on adherence (Columbini et al., 2014). These include negative staff attitudes in general, as well as a lack of trust in staff, fears of breaches of confidentiality, and discrimination by staff. The uptake of PMTCT interventions and adherence is negatively affected by poor quality of counselling and too little emphasis on the importance of adherence (Gourlay et al., 2013). Continuity of care, and linkages

between antenatal and other primary care services are important in promoting adherence.

Much has been written recently regarding the benefits to PMTCT uptake and adherence of the involvement of a male partner in antenatal and postnatal care. Such involvement can be promoted by supporting disclosure, providing couples' counselling and testing, and encouraging male partners to accompany women on visits to the clinic (Peltzer et al., 2011; Osofi et al., 2014; van den Berg et al., 2015)

VIRAL LOAD MONITORING

While routine monitoring of HIV VL has been a key component of ART programmes in developed countries from the outset (United States of America Public Health Service Task Force, 2004; de Ruiter et al., 2008), until recently this has not been the case in many resource-constrained countries. A Ugandan study (Essajee & Kumarasamy, 2014) concluded that VL monitoring was less cost-effective than other forms of monitoring because of relatively low clinical benefit and relatively high cost. Essajee and Kumarasamy (2014) argue that these constraints have resulted in the prioritisation of rapid scale up of ART initiation. In such contexts, VL monitoring has been regarded as optional, but not a prerequisite for the rollout of treatment programmes.

The purpose of VL monitoring of patients on ART is important at both the individual and public health level. For the individual patient, the purpose is to improve clinical outcomes. In a systematic review, Tucker et al. (2014) make the case that VL monitoring has the potential to assess early response and adherence to ART, and to create the opportunity for interventions to achieve viral suppression through adherence support. This view is supported by a study in Swaziland in which Jobanputra et al. (2014) found that the main impact of VL monitoring was on reinforcing adherence. Essajee and Kumarasamy (2014) argued that the absence of VL monitoring results in a delayed diagnosis of treatment failure and the accumulation of resistant mutations which result from delays in switching ART, while Tucker et al. (2014) add that viral load monitoring reduces the likelihood of unwarranted switching, thus preserving future treatment options for the patient.

In the absence of virological testing, reliance has been placed on defined clinical and/or immunological (CD4 count) monitoring. A number of studies have, however, highlighted that criteria such as these have a poor positive predictive value. Tucker et al. (2014) conclude that the combination of clinical and immunological monitoring has significant benefit in morbidity and mortality endpoints compared with clinical monitoring alone. However, a survival benefit of VL over CD4 count monitoring was not consistently demonstrated; an observational study by Keiser showed benefit, while a randomised control trial by Merriman did not (Tucker et al., 2014).

From a public health perspective, monitoring allows for programme surveillance. However, it is particularly important in the preservation of first line regimens by avoiding the accumulation of resistant mutations at the population level. In 2007 Boule and Ford suggested that at the start of programme roll-out in developing countries, viral load monitoring was not initially necessary; virological outcomes were likely to be good, given the low levels of transmitted resistance in these countries and the strong focus on the promotion of adherence. However, the authors proceeded to argue that this situation had changed as the programmes had expanded, and high-level genotypic resistance was being demonstrated.

For all these reasons, pressure has mounted for the implementation of virological monitoring even in resource-constrained settings. In 2009, the WHO made a recommendation for the use of VL monitoring in ART programmes to confirm treatment failure (WHO, 2009). In 2010 it was recommended that VL be assessed routinely at six monthly intervals, with a VL greater than 5000 being defined as failure and an indication to switch to a second line regimen (Nelson et al., 2014). Finally, in June 2013, the WHO issued a strong recommendation that VL monitoring be adopted as 'the preferred monitoring approach to diagnosis, and confirming ART failure' (WHO, 2013). VL should be measured after six months on treatment and annually thereafter; the threshold for the diagnosis of treatment failure was lowered to 1000. CD4 count and clinical monitoring could be maintained in situations where this gold standard was not available. The WHO conceded that there was only weak evidence to support the recommendation, as Tucker et al. (2014) demonstrated in their systematic review.

Nelson (2014) reports that when the 2013 guidelines were issued, 54% of 69 Low and Middle Income Countries indicated that they had already adopted routine VL monitoring, a further 40% monitored in a targeted fashion, while in only 6% of these countries, VL monitoring was not available at all. South Africa included routine VL monitoring from inception of the ART programme in 2004.

There are significant challenges to the implementation of WHO guidelines. In many resource-constrained countries, financial resources have to be available, laboratory infrastructure and equipment secured, adequate and appropriately skilled staff available, supply chain management improved, and health systems strengthened in several other respects.

A number of strategies are proposed to finance virological monitoring. The decrease in drug costs, especially that of second line drugs has the potential to allow the reallocation of resources to virological monitoring. Stevens and Ford (2014) propose the use of CD4 testing at baseline for initial clinical management, and the reduction of CD4 count monitoring thereafter in those who demonstrate VL suppression. These authors argue that resources should be channelled to both VL and drug resistance testing. Other options include batching of testing and negotiating reduced rates for high volumes of testing: these strategies have been adopted in South Africa. The decentralisation and simplification of virological testing, as has been done for infant Dried Blood Spot PCR testing, has the potential to decrease costs and reduce the dependence on laboratories and highly skilled staff. As Essajee and Kumaramsany (2014) argue, there is an urgent need for newer more sensitive, consistent and reliable Point of Care viral load assays; such techniques are under development (Stevens et al., 2014; Scott et al., 2015)

VIRAL LOAD MONITORING IN PREGNANCY

Given that VL is the greatest risk factor for MTCT, a strong argument is made for more frequent VL monitoring during pregnancy and breastfeeding. In well-resourced countries, frequent VL monitoring during pregnancy has been standard practice for more than ten years (British HIV Association, 2012; Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2014).

However, the 2013 WHO guidelines do not make a distinction between VL monitoring in pregnancy as opposed to routine ART programmes. Given that many women in developing countries, enrol late for antenatal care and thus many HIV positive women initiate ART in advanced pregnancy, following routine guidelines, a significant number of these women would deliver before their first VL test at six months. Similarly, pregnant women who conceive while on ART might not qualify for their annual VL test screening during their pregnancy.

As ART coverage increases, a greater proportion of women enrolling in antenatal care are ART-experienced. In a Cape Town study, 35% of women enrolling in antenatal care were already on ART (Myer et al., 2014). ART-experienced pregnant women have previously been assumed to be virally suppressed during their pregnancy. However, Myer et al. (2014) reported that 24% of ART-experienced women in a public sector clinic were not virologically suppressed at the time of presenting for antenatal care; 13% of these women had a VL>1000. These women may have defaulted ART entirely, have been poorly adherent to ART, or have experienced virological failure due to transmitted or acquired resistance to ART. Case reports in Khayelitsha, Cape Town, found that several babies testing HIV positive at six weeks had mothers who had claimed to be taking ART at other sites when entering antenatal care, but had in fact either defaulted treatment, or had suboptimal adherence (Ibeto et al., 2014). These authors conclude that 'the absence of routine viral load monitoring at antenatal booking and subsequently through pregnancy and breastfeeding, resulted in a failure to detect women who had defaulted ART prior to or during pregnancy' (Ibeto et al., 2014:108).

There is no clear international policy for VL monitoring in pregnancy. As there is limited time during pregnancy in which to achieve viral suppression and prevent MTCT, it is extremely important to timeously identify high VLs in women newly initiated on ART, as well as those who are ART-experienced. This provides an opportunity to achieve virological suppression before delivery through intensified adherence support, restarting ART in those who have defaulted, and switching of ART regimens in cases of failure. In addition, virological monitoring facilitates the identification of infants at high risk of in-utero transmission. The South African National Consolidated HIV guidelines (National Department of Health, 2014) recommend that these 'high risk' infants are tested for HIV at birth, and that those

testing positive should be initiated on ART immediately. Maternal virological monitoring also has the potential to influence decisions regarding infant feeding and prophylaxis.

POLICIES FOR THE MONITORING OF HIV VIRAL LOAD DURING PREGNANCY

In well-resourced countries, intensive VL monitoring of HIV positive pregnant women on ART is promoted. The 2014 guidelines of the USA National Institute of Health (NIH) recommend that VL is measured in all HIV-infected pregnant women at their initial antenatal visit, and if it is high, monthly until they are suppressed, and three-monthly thereafter (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2014). The 2014 guidelines of the British HIV Association go a step further in proposing HIV resistance testing before initiation of ART in pregnant women (BHIVA, 2014). Given that until recently, VL monitoring has not been routine in general ART or PMTCT programmes in most resource-constrained countries, it is not surprising that VL monitoring policies and guidelines for these countries could not be found in the literature. Where VL monitoring has occurred in pregnancy, it has followed the VL monitoring policies of general ART programmes, and thus mainly focused on women initiating ART in pregnancy. There are thus missed opportunities for preventing transmission by not ascertaining the virological status of women initiated on ART during pregnancy, as well as ART-experienced women, and to intervene if necessary to achieve viral suppression.

In 2011 the South African National Department of Health (DOH) produced a National Strategic Plan for HIV/AIDS/STIs (NSP) for 2012-2016 (National Department of Health, 2011). One of the Plan's objectives is by 2016 to reduce MTCT to less than 2% at six weeks postpartum and to less than 5% by 18 months of age. As a strategy to achieve this, in March 2013, the National DOH adopted the WHO's PMTCT Option B.

The Western Cape DOH implemented Option B+ in July 2013. These guidelines for the first time in South Africa made specific recommendations for VL monitoring during pregnancy and breastfeeding (Department of Health Western Cape, 2013). The VL monitoring guidelines were presented in the form of an algorithm (Appendix A). More frequent VL measurement in pregnancy and breastfeeding was recommended. It was advised that women initiated on ART should have a VL test at

four months, or earlier (36 weeks) if they were likely to deliver before four months on ART. ART-experienced women should be tested at first antenatal visit if no recent result were available. In women who were virologically suppressed, VL monitoring should be done six-monthly for the duration of pregnancy and breastfeeding; thereafter monitoring should revert to the standard annual VL monitoring of the general ART programme. Where women were not virologically suppressed, further interventions (retesting or switching of regimen) were guided by the number of VLs that were unsuppressed, and whether the gestational age of the pregnancy was before or after the third trimester. This algorithm was implemented in Khayelitsha antenatal services on 1 July 2013, with initial support by local MSF clinicians. The Western Cape DOH modified the algorithm in 2014, and a 2015 update is awaited. The National DOH has for the first time included a VL monitoring algorithm in their 2015 guidelines (National Department of Health, 2014).

NEED FOR THIS RESEARCH

There has finally been an acceptance in the South African public health sector of the need for a policy on VL monitoring during pregnancy and breastfeeding. The implementation of the 2013 Western Cape VL monitoring guideline has not yet been evaluated. There is a need to establish whether the guideline was successfully implemented and what implementation challenges there were. It is important to establish whether the guideline was effective in ensuring that pregnant women with high VLs were identified timeously and were provided with the appropriate adherence support, care and treatment to maximise their chance of viral resuppression, and hence minimise the risk of MTCT.

This research aims to fill this gap as far as the antenatal period is concerned. The research focuses on women who are ART-experienced at the time of their first antenatal visit. Currently little is known about these women in the South African public health system.

The findings of this study will improve understanding of the challenges in the implementation of the guidelines, and enhance efforts to improve this. It will provide a profile of pregnant women with previous ART experience, particularly those who are not virologically suppressed when entering into antenatal care.

The results of the study could contribute to the future refinement of VL monitoring guidelines for pregnant and breastfeeding HIV positive women in South Africa.

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PART 3: MANUSCRIPT

INTRODUCTION

BACKGROUND

Great progress has been made globally over the past two decades in reducing vertical transmission of HIV. This is the result of implementing evidence-based Prevention of Mother-to-Child Transmission (PMTCT) programmes. The most recent recommendations are the World Health Organization (WHO)'s Option B/B+ [1] which advise antiretroviral therapy (ART) for all HIV-positive pregnant and breastfeeding women. In addition, global coverage and scale-up of PMTCT programmes reached 53% by 2010 [2], with several low and middle-income countries, including South Africa, having reached the target of 80%. PMTCT interventions have resulted in the reduction of mother-to-child transmission (MTCT) rates of 14-42% [3] without any form of intervention, to 1-2% in developed countries, and even in some resource-limited settings [4]. The Joint United Nations Programme (UNAIDS) report [2] refers to the elimination of MTCT, setting targets of transmission rates of less than 5%, and a 90% reduction in paediatric HIV infections by 2015, and it reiterates that programme gaps need to be addressed in order to achieve these targets.

HIV viral load (VL) is the strongest predictor of MTCT [5]. Frequent VL monitoring (VLM) in pregnancy facilitates the early detection of poor adherence to ART [6], creating the opportunity for interventions to urgently support adherence in order to achieve viral suppression. VLM further enables the timely detection of treatment failure, and consequent regimen change [7].

In a context of increasing levels of resistance to ART medication [7], in its 2013 guidelines [1], the WHO recommends routine annual VLM as 'the preferred approach for the detection of treatment failure'. Until recently, VLM has not been widely implemented in resource-constrained settings, even in general ART programmes [8]. Many health systems are struggling and under-resourced: VL monitoring may thus not be implemented due to the high costs of VL testing, shortages of technically skilled staff, and poor infrastructure, transport and supply chain management to support this intervention. [9]

A number of strategies are being employed to overcome the challenges faced by these countries. These include the freeing up of resources for VLM by decreases in the cost of drugs, especially second line ARVs [9] and the phasing out of long-term CD4 testing [10]. The challenges of poor infrastructure and transport, and inadequate numbers of technically-skilled staff could be addressed by the decentralisation of testing, which will be possible in the near future by simplification of the technical process of VL testing, including point of care testing [10].

Given the urgency of achieving viral suppression in pregnancy, VL should be monitored more frequently than annually, which is the guideline followed in most ART programmes. While PMTCT guidelines for enhanced VLM have existed in developed countries for many years [11, 12] no such guidelines could be identified for resource-constrained settings at the time of this study. In June 2013, the Western Cape Department of Health issued PMTCT guidelines [13] based on WHO Option B+ [1]. These guidelines include a VLM algorithm for both ART-naïve and ART-experienced pregnant women which appears in Appendix A. The aim of the algorithm was to reduce MTCT by more frequent monitoring of pregnant and breastfeeding women on ART, in order to identify those who are not virologically suppressed, and to achieve virological re-suppression as soon as possible, through increased adherence support and clinical interventions. Little is known of the effectiveness of the implementation of these guidelines, nor is there descriptive evidence regarding the profile of women who could benefit from their implementation.

This study focused on the cohort of women who were ART-experienced but virologically non-suppressed when presenting for antenatal care. The purpose of the study was to evaluate to what extent the VLM algorithm was followed in these women, and determine their virological status at their last monitoring visit, as well as the PCR status of their infants. The study also aimed to describe the sociodemographic characteristics and clinical features of the cohort, and to determine whether there were factors associated with viral non-suppression in these women.

SETTING

Khayelitsha, a township 30 km from the Cape Town city centre, is home to approximately 450 000 people [14], the majority of whom live in poverty and are unemployed. In 2011, the HIV prevalence in Khayelitsha in 2012 was 34.3% [15]. Antenatal and delivery services for low-risk pregnancies are provided at two primary-level nurse-managed Midwife Obstetric Units (MOUs). Routine data estimates that 50% of women who access antenatal care in Khayelitsha deliver at these two facilities. Women with obstetric risk factors or complications are referred to district or tertiary-level hospitals. ART services are provided at all of the 11 primary level clinics and the 2 MOUs in Khayelitsha. Traditionally, most women who became pregnant while attending these ART services, continued to attend these services while attending an MOU for obstetric care. Since the implementation of Option B+ in the Western Cape on 1 July 2013, all HIV-positive ART-naïve women accessing obstetric care at a Khayelitsha MOU initiate ART and receive integrated HIV and obstetric care by professional nurses there. Women identified at either of these MOUs as having a non-suppressed VL have been encouraged to transfer their ART care to the MOU, so that urgent case management could be provided. Post-delivery, all mothers and their infants are referred for ongoing care to a clinic of their choice.

Site B MOU in Khayelitsha was chosen as the site for the study as an existing study on PMTCT Option B+ was already underway at the facility and a degree of overlap in the studies was planned. Routine data for 2013/14 estimate that 320 women enrolled in antenatal care, and 150 delivered per month at this MOU. While the majority of these women reside in Khayelitsha, some live in other parts of Cape Town, while others relocate temporarily from a neighbouring province to access obstetric services in the metropolitan area.

Patient data across the pregnancy and ART service continuum of the Western Cape are recorded on standardised HIV stationery and captured into one of three electronic monitoring platforms in accordance with local data monitoring protocols. Given that the three monitoring platforms are not linked, electronic follow up of patients across obstetric and ART services is limited. Furthermore, electronic ART data is not collected on ART-experienced women in the MOU unless they transfer their ART care to the MOU. Hospitals record patient information by electronically

scanning patient notes. However these records cannot be accessed from clinics. Pregnancy and delivery information is recorded in a patient-held maternity record, which is filed at the delivery site

THE VIRAL LOAD MONITORING ALGORITHM

The elements of the guidelines pertaining to ART-experienced pregnant women stipulated that VL testing be done at the time of presenting for antenatal care ('booking') for all women who had been on ART for more than four months unless a VL result within this time period could be found. In the algorithm women were classified as VS (virologically suppressed, VL \leq 400 copies/ml) or VNS (virologically non-suppressed, VL $>$ 400 copies/ml) based on their VL at the time of booking. All women identified as VNS should have received increased adherence support. Their further clinical management was guided by their gestational age at booking and their ART regimen. Women on a first line ART regimen who booked before the third trimester needed to have their VLs repeated after two months, and be switched to a second line ART regimen should they still be VNS. However, women on first line who booked in the third trimester should have had Alluvia (a protease inhibitor) added to their regimen, and been switched to a second line ART regimen if still VNS after three months: this was likely to be post-delivery. In cases where the woman's VL was non-suppressed for the second consecutive time, she should have been changed to a second line regimen without delay. VNS women already on a second line regimen at booking should have received adherence support and repeat VL testing; infant post-exposure prophylaxis and feeding method would need to be discussed.

In this study, three important pre-delivery elements of the algorithm were traced in each ART-experienced VNS woman: the identification of ART-experienced women through measurement of VL at booking, the repeating of VL testing at two months, and the switching of regimens if indicated. Outcomes of maternal VL and infant's HIV status on Polymerase Chain Reaction (PCR) testing were established.

METHODS

STUDY POPULATION

The study population included all HIV-positive women enrolling for antenatal care at one Khayelitsha MOU over 12 months from the implementation of the Option B+ guidelines on 1 July 2013 to 30 June 2014. Specifically, the study design comprised a retrospective cohort of ART-experienced women; for VNS women follow-up and outcomes data were traced until January 2015. Much of the analysis focused on a sub-sample of ART-experienced women who have a detectable viral load when presenting for antenatal care. Data on all these VNS women was analysed regardless of whether they only had one antenatal visit, their pregnancy miscarried or was terminated, or the women were lost to follow-up.

DATA COLLECTION

The facility staff kept a VL/CD4 register designed specifically to trace HIV-positive women at their first visit and to identify those eligible for management as specified in the VL algorithm. Clinical data included CD4 count and VL testing of ART-experienced pregnant women. The register was used to assist in tracking of VL results and to facilitate the recall of women with high VLs. ART-experienced women were identified from the VL/CD4 register; when the use of this register ceased at the end of May 2014, the relevant column in the HIV testing (HCT) register fulfilled this purpose. For the subset of VNS women, the following data was collected: age, ART regimens at initiation, booking and delivery, duration on ART, ART clinics attended, CD4 and VL results, obstetric details (gravidity, parity, gestational age at booking, pregnancy outcome and delivery site) and maternal virological outcomes and infant PCR results. This information was collected by reviews of their MOU folders, and missing information obtained through electronic data sources, the National Health Laboratory Service (NHLS) patient data-bases, and manual audits of patient records at relevant clinics, district and tertiary hospitals. For VS women, a subset of this data (age, ART regimens, duration on ART, and ART clinics attended), were sought through searches of the NHLS data-base and electronic monitoring systems. All information was recorded on a paper tool.

In addition to support data collection efforts, the MOU folders of 37 of the VNS women were reviewed to document potential gaps in clinical recordkeeping and data regarding the management of these women. Triangulation of data from the HCT, CD4/VL and electronic registers was undertaken in a related study to assess gaps that might exist in the identification of the VNS women.

DATA CAPTURING AND ANALYSIS

Information on the ART-experienced women was electronically captured from the paper tool. The relevant data was analysed using Stata Version 13 (Statacorp, Texas). Continuous data were analysed using a two-sample t-test or Wilcoxon rank-sum. Categorical data were analysed using the χ^2 (chi-square) statistic and logistic regression. Multiple logistic regression was used to model the predictors of being virologically non-suppressed. Forward stepwise procedures were used in model selection, with the Akaike Information Criterion being used to assess best model fit.

These same data was used to construct an ART and obstetric flow-chart history for each of the VNS women. From these histories it was possible to determine whether the key elements of the algorithm for each VNS woman had been followed, and what the maternal virological and infant PCR status outcomes were in each case. By manually collating the individual compliance and outcomes, overall measures were obtained for the cohort.

ETHICS APPROVAL

Ethics approval was granted by the Human Research Ethics Committee at the University of Cape Town. In addition, the Western Cape Department of Health granted permission for access to the site for data collection.

RESULTS

DESCRIPTION OF THE ART-EXPERIENCED COHORT

A total of 1412 pregnant HIV-positive women were identified as having enrolled in antenatal care during the study period (Figure 1). Of these 848 (60.0%) initiated ART at the MOU according to Option B+ guidelines and 564 (40.0%) were ART-

experienced. Of the ART-experienced women, VL results were not found for 82 (14.5%). Of the remaining 482 women, 414 (85.9%) were found to be VS and 68 (14.1%) were VNS.

Twelve women disclosed at first antenatal visit that they had stopped taking ART; their VL was thus not measured and they were thus not initially identified from the VL/CD4 register as they had no VL entered. Data analysis was at an advanced stage when this was discovered; for this reason they were excluded from the 53 VNS women investigated. A further 30 (3 VNS and 27 VS) who did not appear in the VL/CD4 register had been identified in a related study, and were excluded as they too were identified too late in the data collection process. Of those with VL results, data for 93.5% (n=387/414) of VS women and 77.9% (n=53/68) of VNS women were analysed. These 440 women represent 78 % (n= 440) of the full cohort of 564.

CHARACTERISTICS OF VS AND VNS PREGNANT WOMEN

VS and VNS ART-experienced women were compared by age, duration on ART and ART regimen at first antenatal visit, and the most recent ART clinic attended (Table 1). This data was complete for VNS women, while for VS women there was data for age, ART regimen, duration on ART and recent ART clinic in 94.1%, 82.7%, 82.2% and 82.4% respectively. No significant difference was shown in mean age of the VS and VNS women (32 years vs 31 years, p=0.17) or for median duration on ART (31 months (IQR 18, 50) vs 37 months (IQR 19, 63), p=0.23). However, the ART regimen at booking and recent ART clinic attended approached significance (p=0.07 and p=0.06 respectively).

LOGISTIC REGRESSION MODEL OF PREDICTORS OF ART-EXPERIENCED PREGNANT WOMEN BEING VIROLOGICALLY NON-SUPPRESSED

A logistic regression model for predicting VNS was derived; the best model included all four variables (Table 2). Exploratory bivariate data analysis guided the categorisation of the data.

Women attending a clinic other than that in the same facility as the MOU were 2.2 times more likely to be VNS (p=0.02). Women on ART for four or more years were 2.1 times more likely to be VNS than those on treatment for fewer than four years (p=0.04). Women 30 or more years old were 70% less likely to be VNS than women

younger than 25 ($p=0.05$). However, there were only 26 women in the latter group. Women on a second line ART regimen at booking were 2.3 times more likely to be VNS than those on first line but the p value fell just short of significance ($p=0.08$)

ART ADHERENCE

Case histories collated from a number of sources suggest factors that could either put women at risk of poor adherence or reflect poor adherence in the past (Figure 2). Twenty two (42%) of the 53 VNS women had attended more than one ART clinic and/or had attended a clinic outside Khayelitsha. This is consistent with the results of the logistic regression. A history of defaulting and restarting ART was established in 38% ($n=20/53$) of VNS women. While seven of the 53 VNS women (13.2%) were already on a second line regimen at booking, a further 32.1% ($n=17/53$) had previously had an indication to switch regimens but this switch had not occurred. Forty two percent ($n=22/53$) of the VNS women could not be traced postpartum, either electronically or through the NHLS.

CLINICAL CHARACTERISTICS OF VNS PREGNANT WOMEN

Clinical

The results of the most recent pre-booking CD4 counts were retrieved for 92.5% ($n=49/53$) of the VNS women, and ranged between 34 - 641 cells/ μ L, with a median of 252 cells/ μ L (IQR 170, 338 cells/ μ L) (Table 3a).

The median VL of the 53 women at first antenatal visit was 3929 (log 3) (IQR 898, 49119). Fourteen of the 53 women (26.4%) had VLs < log 3, which could have constituted a transient elevation of VL ('viral blip'). Nineteen of the 53 women (35.8%) with VLs log 4 or greater were likely to have defaulted ART entirely, while 20 (37.7%) with intermediate VLs could have either had poor adherence, or have been failing ART due to viral resistance; the remaining 14 (26.4%) may have experienced a transient 'viral blip'. By adding the 12 declared defaulters to the 19 presumed defaulters, 45.6% of the women known to be VNS ($n=31/68$) could be estimated to have defaulted ART entirely: this gives a default rate of 6.4% ($n=31/482$) of the ART-experienced women. When presented with their booking VL result, nine of the 53 women were recorded as having admitted to defaulting from or adhering poorly to their ART.

Comparing recent CD4 counts with booking VL results, 16.3% (n=8/49) of the women with CD4 count results had a CD4 count less than 100 cells/ μ L, five of whom had VLs \geq log 5 (Table 3b). Again, it is likely that these women had completely defaulted their ART, but did not report this at their first antenatal visit. Five of the 49 women (10.2%) had CD4 counts \geq 500, three of whom had a VL less than 1000 (log 3).

Obstetric characteristics

The gestational age at first antenatal visit was established for 49 (92.5%) of the VNS women. The median gestational age at booking was 19 weeks (IQR 16, 27; range 6, 35). While 14.3% (n=7/49) booked before 12 weeks, the majority (71.4%, n=35/49) of women booked in the second trimester (Table 4). Of the seven who booked in the third trimester, two were already 35 weeks pregnant.

Of the 49 VNS women for whom there was gravidity data, (22.4%, n=11/49) were primigravid. Almost half the women (48.9%, n=24/49) had a gravidity of two or three while 28.5% (n=14/49) were gravida four or five.

Excluding the five pregnancies that either miscarried or were terminated, the delivery site for 93.8% (n=45/48) of the women was identified. Thirty three percent (n=15/45) of VNS women delivered at the MOU. The remainder delivered at the district hospital (28.9%, n=13/45) or the tertiary hospital (33.3%, n=15/45).

IMPLEMENTATION OF THE VL MONITORING ALGORITHM

Of the 564 women identified as ART-experienced, 482 (84.5%) could be classified as virologically suppressed (VS) / non-suppressed (VNS) based on a VL measured at first antenatal visit.

Of the 53 VNS pregnant women, repeat predelivery VLs were indicated in 40 (75.5%), of which 34 (85%) were measured. On the basis of these results, a change to a second line regimen was indicated for 15 women: 73.3% (n=11/15) had their regimen changed. Thus 40% of the VNS women (n=18/53) were on a 2nd line regimen by delivery.

Of the 53 women identified as VNS who were included in the study, the guidelines were followed in 79.2% (n=42/53) of cases. Excluding those who lost their pregnancies, this increases to 87.5% (n=42/48).

Compliance with the algorithm could also be estimated through modelling scenarios using the gaps in the care cascade demonstrated in this study. For example, were 100 VNS women to present for antenatal care before 28 weeks and remain in care, and those identified as VNS all required a regimen change after a second non-suppressed VL, only 53 of the women would have been managed according to the VLM algorithm.

OUTCOMES OF IMPLEMENTING THE VL MONITORING ALGORITHM

Nineteen women (55.9%, n=19/34) were VS on repeat predelivery VL testing; a further four achieved viral resuppression before delivery after a regimen change (Figure 3). Thus 67.6% (n=23/34) of the women were known to be VS predelivery. A further five women became VS within three months of delivery. Hence a total of 82.3% (n=28/34) of the women were known to have virologically resuppressed by three months postpartum. If, however, one calculates the results using as a denominator the 40 women for whom predelivery VLs were indicated, and assuming a worst case scenario in which those six women who did not have a repeat VL did not virologically resuppress, these figures fall to 47.5% (n=19/40) pre regimen change, 57.5% (n=23/40) pre-delivery and 70% (n=28/41) by 3 months postpartum.

Of the six women who were not retested, two were not suppressed when they booked for their next pregnancy less than a year later

Of the five women who should have had regimen changes, four were still VNS by two months

In summary, depending on assumptions made, predelivery virological resuppression rates could range from 57.5% to 67.6% and rates at 3 months postpartum from 70% to 82.3%.

There were 48 live births (Table 4). Four infants had birth PCRs measured as specified in the 2013 Western Cape PMTCT guidelines [13]; all these tests were negative. Of the 45 infants who survived beyond the neonatal period, 82.2%

(n=37/45) had PCRs performed at approximately six weeks, and a further 6.7% (n=3/45) between four and six months. All these PCRs were negative. Six week PCR results could not be found for three of the four babies who had birth PCRs.

A REVIEW OF FILING, DATA MONITORING SYSTEMS AND CLINICAL RECORDKEEPING

A number of challenges were encountered in data collection for this study; these are reported as they are likely to have negatively impacted on the implementation of the VLM algorithm.

Despite there having been recent efforts to reorganise the filing system, 14.3% (n=9/63) of the folders originally sought for the study could not be found.

There were challenges in accessing patient data electronically for this study due to the use in Cape Town of multiple electronic monitoring systems, which limit the sharing of clinical information between the MOU and ART services in feeder clinics and hospitals. Staff at the MOU are unable to access ART records for women who receive ART care at services using a different electronic monitoring platform. Unless women transfer their care to the MOU, their clinical details are not electronically captured at the MOU, and cannot be entered onto other monitoring systems. Thus other sites cannot determine electronically details of test results and other management ART-experienced women receive at the MOU.

A comparison of the different manual and electronic registers used for HIV positive women revealed a number of inconsistencies, which compromised identification of the study cohort. In several cases, incorrect HIV status was recorded in the HCT (HIV Counselling and Testing) register: women recorded as HIV negative, HIV positive (newly diagnosed) or HIV positive 'not on ART' were found to either be/have been on ART at another clinic, or to have been initiated on ART at the MOU. There were also inconsistencies between the HCT and CD4/VL registers: some women recorded as HIV positive in the HCT register did not appear in the VL/CD4 register, while others recorded as HIV negative in the HCT register did.

Thirty five ART-experienced women were misclassified as ART-naive in the VL/CD4 register, while 20 were not entered at all. In the last months of the study period, few results were entered in the VL/CD4 register. The results of 27 women appearing in the register could not be found on the NHLS data-base. Use of the register ceased in the last six weeks of the study period.

As a check of other electronic monitoring systems in the Cape Town area could not be done at the time, these findings might underestimate the extent to which ART-experienced women are not identified for care.

Limited clinical data could be obtained from many of the patients' folders. A manual review of 37 folders of VNS women (Table 5) found ten (27%) with maternal case records filed. Fifteen (40.5%) folders had no VL result filed or recorded in clinical notes. Only 15 (40.5%) of clinical notes made reference to adherence support. A minority of folders had clinical notes recording the need to repeat a VL or to change regimen; most of these notes were written by the medical officer from Medecins Sans Frontiers (MSF) who was supporting the implementation of the VLM guidelines.

DISCUSSION

This study evaluated the extent and outcomes of the implementation of an algorithm for the monitoring of viral loads in 1412 HIV positive pregnant women at a primary care antenatal and delivery site in Khayelitsha, Cape Town, with a specific focus on 53 ART-experienced women who were virologically non-suppressed (VNS) at presentation for antenatal care. Forty percent of the HIV positive cohort (n=564/1412) were ART-experienced, of whom 14.1% (n=68/482) were virologically non-suppressed at their first antenatal visit. Many women were severely immunocompromised. There were high rates of hospital delivery and poor pregnancy outcomes.

Significant predictors of virological non-suppression included a younger age (< 25 years), a longer duration since ART initiation (> 4 years) and attending an ART clinic other than that in the same facility as the antenatal and delivery service, while being on a second-line ART regimen at presentation approached significance. While the virological status of nearly 13% of women could not be determined, the guidelines were correctly followed in 79.2%-87.5% of women classified as virologically non-

suppressed. Predelivery and 3 month postpartum virological resuppression rates ranged from 57.5% to 67.6% and 70.0% to 82.3% respectively. Excluding three early neonatal deaths, 82% of the infants had PCR tests at approximately 6 weeks, all of which were negative.

THE COHORT OF ART-EXPERIENCED PREGNANT WOMEN

A large proportion (40%) of HIV positive women have ART-experience when presenting for antenatal care at the study site: this is very similar to the 35% found in a study by Myer et al in an adjacent township [16]. This may reflect the comparatively good ART coverage in the Khayelitsha subdistrict, the increasing numbers of women qualifying for ART under the general or PMTCT programme and/or an active desire of ART-experienced women to start or add to their family. It would be instructive to determine what proportion of these pregnancies were unplanned.

ADHERENCE AND DEFAULTING IN THE ART-EXPERIENCED PREGNANT WOMEN

The proportion of ART-experienced women who were VNS at presentation for antenatal care (14.1%) is very similar to the 13% found in the same Myer study [16]. The estimated defaulter rate of 6.4% (n=31/482) in this cohort of ART-experienced pregnant women cannot be directly compared to that of the general ART population in Khayelitsha as the loss-to-follow up rates in the latter programme are reported by year of initiation, and include unreported deaths and 'silent' transfers out.

These high rates of defaulting, poor ART adherence and possible treatment failure amongst these ART-experienced women are of grave concern, particularly given that risks of perinatal transmission of HIV – even a resistant virus – to their infants, and the threat to their own health. It is imperative that the reasons for these behaviours in the local context be explored and understood, so that appropriate and effective interventions can be implemented.

Systematic reviews by Colombini [18] and Gourlay [19] report a wide range of factors that could contribute to poor adherence and retention in care: the factors may relate

to the individual client, the society in which they live, the health system and the ART medication prescribed.

The predictors of virological non-suppression derived in this study are all plausible as factors that could affect adherence or retention in care, and concur with the findings of many studies reported in the latter reviews. The lower levels of virological suppression in women younger than 25 years compared to those 30 years or older is consistent with several studies that report youth as a risk factor for poor adherence [18,19].

The significantly inferior virological suppression in women who initiated ART more than four years previously could reflect the increasing risk of developing viral resistance over time, especially in those with suboptimal adherence. It may also result from treatment fatigue [20], leading to poor adherence or defaulting from ART entirely.

Being on a second line ART regimen at booking as a predictor of being VNS could be explained by a poor adherence history prior to this pregnancy that resulted in a regimen change: such poor adherence may have continued on the second line regimen. It may also be related to the high pill burden and intolerability of the second line ART regimen: these factors could be additive.

The study showed that women who received prepregnancy ART at the ART clinic in the same facility as the antenatal service were less likely to be virologically non-suppressed than those attending any other ART clinic. There could be several reasons for this. The clinic is regarded by many as a centre of excellence; MSF initiated ART services in the facility in 2001 and have made an ongoing contribution to the development of clinical skills and health systems strengthening in the Khayelitsha district, particularly at this clinic. Several innovations aimed at improving adherence and virological resuppression have been piloted at this facility with good outcomes. In addition, the HIV activist organisation, the Treatment Action Campaign, has a strong presence at the clinic: the treatment literacy delivered by their peer educators could have contributed to better rates of virological suppression in the patients attending the clinic.

This finding may also reflect the fact that women who received their pre-pregnancy ART elsewhere are in some respect different. It is possible that these women had defaulted ART at their original clinic due to various challenges, but were reluctant to return to the same facility for antenatal care as they feared the reaction of clinic staff: poor staff attitude has been reported as a risk factor for poor adherence [18]. These could be women who have relocated to Khayelitsha and not transferred their care to a local clinic. There may be women whose adherence had been compromised by leading unsettled lives involving relocation or movement within Cape Town, or between Cape Town and other regions or provinces, notably the Eastern Cape. This is suggested by the case histories obtained which found that almost half the VNS women had attended more than one clinic and/or had attended a clinic outside Khayelitsha. According to a Khayelitsha clinician [21], patients report that, especially in the rural areas of the Eastern Cape, they struggle to access due to factors such as limited ART services, difficulty in accessing ART clinics due to long distance and limited transport, a reluctance of clinic staff to accept patients from other areas without referral, and ART stock-outs.

Other commonly reported challenges to adherence [18, 19] could apply in the local context: these include social stigma and discrimination, and denial or non-disclosure of status. The latter may account for the incorrect information given to staff by some women in this study. Poor knowledge of HIV/ART and the importance of PMTCT could also contribute. According to the same clinician [21] there are increasing anecdotal reports of ART patients stopping ART treatment for a variety of reasons, including the belief that they are well and no longer require ART, or are cured of HIV.

OBSTETRIC CHARACTERISTICS OF THE VIROLOGICALLY NON-SUPPRESSED PREGNANT WOMEN

Routine delivery data at the study site [17] reports that 50% of women who enrol for antenatal care at the facility deliver there. In contrast, fewer than 40% of the VNS women delivered at this facility, and a third of them at tertiary level. This is likely to reflect complications due to the severe immunosuppression reported for many of the women. Certainly the mother who is thought to have died had been admitted to the tertiary hospital with septicaemia and related complications.

IMPLEMENTATION OF THE VLM ALGORITHM

For the 53 VNS women in the study, there appears to have been an encouraging level of compliance (79.2% to 87.5%) with an algorithm that required both a depth of understanding by the clinical staff and new systems to be put in place. However, a modelled scenario was more disappointing: by taking into account the failure to classify 14.5% of women as VS or VNS, it estimated that only 53% of women would be managed according to the VLM algorithm. However, such gaps in the care cascade are common and have been documented in many studies such as that of Bhardwaj et al. [22].

The initial support given by the MSF team is likely to have contributed positively to these results; the study did not explore whether performance outcomes were sustained after the withdrawal of this support before the end of the study period.

OUTCOMES OF IMPLEMENTATION OF THE VLM ALGORITHM

Although there is no baseline for comparison, virological resuppression rates of up to 57.5% to 67.6% pre-delivery and 70.0% to 82.3% by three months postpartum suggest that, despite suboptimal adherence to the guidelines, the algorithm is at least partially achieving its purpose. The lower success rates calculated under different assumptions may appear disappointing; however, prior to the implementation of the algorithm, many of the 53 VNS women may not even have been identified, let alone managed appropriately.

Given that routine data reports a PMTCT rate of 1.2% for Khayelitsha for the period of the study [17], it is remarkable that none of the babies tested at birth or at six weeks were HIV positive. Once again, the outcome may not have been as good as these results suggest. It is possible that the three infants who died within days of birth may have been infected in-utero. The possibility also exists that some of these results were false-negative, as in cases reported in the literature where negative PCR results were obtained in babies whose mothers were on ART, or were on prophylaxis themselves [23]. No results were found for five of the babies: some of these infants may have died before being tested.

CHALLENGES IN IMPLEMENTATION OF THE VLM ALGORITHM

In the process of data collection, several challenges were identified in the filing of patient folders and results, the accuracy of registers, clinical recordkeeping and

electronic monitoring systems, all of which are likely to have compromised the implementation of the VLM algorithm and resulted in gaps in care..

Several factors could have resulted in a failure to identify VNS women. Errors occurred in the classification of HIV positive women in the HCT register: some of these are a result of transcription errors, while others result from women deliberately not disclosing their HIV status and/or ART experience. These and further errors and oversights could have resulted in women not being entered into the VL/CD4 register or being incorrectly classified: such women would not have had a VL measured and thus not have been classified as VNS. As many results were not entered into the CD4/VL register, and use of the register ceased towards the end of the study period, it is likely that the system of timeous identification and recall of VNS women would have been more difficult.

Suboptimal filing of patient folders and results and limited clinical record-keeping in MOU-retained records would have challenged the quality and continuity of care and compromised the implementation of elements of the algorithm such as repeating the measurement of VL, and changing ART regimen. It is hoped that clinical recordkeeping will improve with the introduction of stationery currently being designed at provincial level that will document both pregnancy and HIV information in an integrated facility-retained record; this will be captured into the electronic monitoring system. Innovative ways of improving access to, and filing and capturing of laboratory results are being piloted in some Khayelitsha facilities.

Good communication and the sharing of clinical information is essential particularly when various components of care are provided at different sites. It was, however, impossible to share such information between the MOU, clinics and hospitals electronically due to the existence of different monitoring systems: in some cases, VLs had been repeated unnecessarily at another service, and there had been failures to change an ART regimen because clinicians were not aware of the results of a VL test performed at another site. While a search of the NHLS data base could have revealed this information, it would have been impractical do this routinely.

From case histories, it was clear that implementation of the algorithm was sometimes compromised by situations in which the management of other patient conditions was more urgent: this was particularly evident in cases of women

delivering at the tertiary hospital where severe obstetric, medical and/or HIV-related complications took priority over management of a non-suppressed VL.

LIMITATIONS OF STUDY

The number of VNS women in the study was limited by errors in and omissions from the HCT and VL/CD4 registers and the exclusion of 12 'confessed' defaulters who were identified late in the data collection process.. The small number of VNS women may have accounted for some of the variables not achieving significance as predictors of virological non-suppression.

As this was not a formal prospective research cohort, it was necessary to use routine data sources. This proved challenging and time-consuming as data sought from registers, clinical records and electronic monitoring systems was often limited, incorrect, missing, or difficult to access, particularly where sites used different electronic monitoring systems. In some cases, it was necessary to rely to a considerable extent on NHLS results to construct a clinical case history. As a result, the data collected is incomplete and could contain inaccuracies.

Given the challenges and time involved in data collection, it was decided to restrict the evaluation of the VLM algorithm to those sections that guide the antenatal management of those ART-experienced women, who were identified as being virologically non-suppressed at first antenatal visit.. The restricted data available on VS women limited many comparisons with VNS women.

This study was conducted at one antenatal site only, in a peri-urban area of high HIV prevalence and good ART service coverage. MSF contributes to innovations and health systems strengthening in the ART clinic in the facility and at the study site, and provided additional support for the implementation of the algorithm. The results may thus not be generalisable to other contexts.

CONCLUSIONS

A high proportion (40%) of HIV positive pregnant women were ART-experienced at presentation for antenatal care. It is of concern that over 14% of these women were virologically non-suppressed at presentation for antenatal care as a result of poor

adherence to ART, the development of viral resistance, or having defaulted from ART entirely. It is imperative that clinicians and managers become informed of and understand the factors responsible for poor adherence and retention in care of women of reproductive age. The results of this study suggest a profile of women at high risk of poor adherence and/or defaulting: young women, women who have been on ART for more than a few years, women who move residence often or transfer care from one clinic to another, or who regularly migrate temporarily from one part of the country to another. Such women should be identified and received targeted and appropriate enhanced adherence support.

Regardless of HIV status, all women of reproductive age should be regularly educated and counselled about HIV/ART and PMTCT. High prevalence of unplanned pregnancy in this context is well established, and therefore fertility intentions should be proactively discussed and provision of contraception integrated into ART care, as the backbone of PMTCT policy. There should be ongoing efforts to overcome denial of positive HIV status and to encourage disclosure.

Given the many systems and human challenges faced in the implementation of the VLM algorithm, adherence to the guideline was encouraging, and the maternal VL resuppression and infant PCR outcomes reassuring. However, there are several interventions at both local and provincial level that could improve the implementation of the VLM algorithm. These same interventions should positively impact on antenatal and ART care in general.

It is likely that integration of antenatal and obstetric care would lead to improvements in adherence to the VLM guidelines. In fact, the Western Cape 2014 PMTCT guidelines [24] recommend that women receive integrated care (both antenatal and ART care) at the same facility, preferably from the same clinician. Women on ART could choose to receive this care at their ART site if it also offers antenatal care, or transfer their ART care to the MOU. For a variety of reasons, to date, few women have chosen this option. Obstacles to the implementation of this aspect of the guidelines should be identified and addressed.

The adoption of a single networked electronic monitoring system would be ideal as it would allow for a more coordinated approach in clinical care.

The integrated HIV/obstetric stationery under development in the Western Cape should be fast-tracked; it should facilitate integrated care and improve clinical recordkeeping.

Consideration should be given to the introduction of a register, preferably electronic, that could track the management of pregnant women on ART: such a longitudinal record could facilitate the identification of gaps in care, where women had not been managed according to guidelines, or had defaulted from care.

A concerted effort should be made to improve systems for the filing of patient folders, the filing and electronic capture of laboratory results, the accurate completion of registers and improved clinical record-keeping.

The introduction of new guidelines needs to be strongly supported by ongoing focused training, the design of systems, mentoring and monitoring by appropriate staff.

Similar evaluations could be conducted of the implementation of more recent VLM guidelines. There is a need for research looking specifically at adherence and retention in care challenges of women of reproductive age initiated on ART, whether in the routine ART services or during pregnancy. This has become particularly important since the implementation of PMTCT Option B+ [25].

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TABLES AND FIGURES

Table 1: Characteristics of virologically suppressed and virologically non-suppressed antiretroviral-experienced pregnant women (n=440)

	Virologically suppressed, n=387, (88.0%)	Virologically non-suppressed, n=53	P-value	Total, n (%)	Test Type
Characteristics, n (%)	387, (88.0)	53, (12.0)			
Age (years), mean (SD)	32 (4.8)	31 (5.4)	0.17		1
Age (years), n (%)	364, (94.1)	53 (12.0)			
15-24	19 (5.2)	7, (13.2)	0.20	26 (9.2)	2
25-29	85 (23.4)	15, (28.3)		100 (25.8)	25.8
30-34	138 (37.9)	15 (28.3)		153 (33.1)	33.1
35-39	95 (26.1)	14, (26.4)		109 (26.3)	26.3
≥ 40	27 (7.4)	2, (3.8)		29 (5.6)	5.6
Duration on ART at booking (months), median (IQR)	31 (18-50)	37 (19-63)			3
Duration on ART at booking (months), n (%)	318, (82.2)	53, (100)	0.23	371, (84.3)	2
≤11	51, (16.0)	8, (15.1)	0.40	59	15.6
12-23	69, (21.7)	9, (17.0)		78	19.3
24-35	64, (20.1)	8, (15.1)		72	17.6
36-59	79, (24.8)	13, (24.5)		92	24.7
≥60	55, (17.3)	15, (28.3)		70	22.8
ART regimen at 1st antenatal visit, n (%)	320, (82.7)	53, (100.0)		373	84.8
1st line	298, (93.1)	46, (86.8)	0.07	344	90.0
2nd line	22 (6.9)	7, (13.2)		29	10.0
Most recent ART clinic, n (%)	319, (82.4)	53, (100.0)		372	89.2
Closest clinic	185,(58.0)	21, (39.6)	0.06	206	55.4
Other Khayelitsha sites	86, (27.0)	20, (37.7)		106	28.5
Other sites	48 (15.0)	12, (22.6)		60	16.1

SD - Standard Deviation; IQR - Inter Quartile Range; Test Type: 1. 2 Sample t-test; 2. Chi-square test; 3. Wilcoxon Rank-Sum test

Table 2: Logistic regression model of predictors of being virologically non-suppressed

Variable	Virologically suppressed(n=387)	Virologically non-suppressed (n=53)	Odds ratio Unadjusted/adjusted	p-value Unadjusted/adjusted	95% CI Unadjusted/adjusted
Regimen, n (%)	320 (82.7)	53 (100.0)			
1st line			(reference)		
2nd line			2.3/2.3	0.08/0.08	0.9-5.7/0.9-6.2
Clinic, n (%)	319 (82.4)	53 (100.0)			
closest clinic			(reference)		
all other clinics			2.0/2.2	0.02/0.02	1.1-3.7/1.2- 4.3
Duration on ART (years), n (%)	318 (82.2)	53 (100.0)			
< 4			(reference)		
≥4			1.8/2.1	0.05/0.04	1.0-3.3/1.1-4.3
Age (years), n (%)	364 (94.1)	53 (100.0)			
< 25			(reference)		
25-29			0.5/0.5	0.13/0.30	0.2-1.3/0.2-1.3
≥35			0.3/0.3	0.02/0.05	0.1-0.9/0.01-1
Constant			0.2	0.01	0.1-0.7

Table 3a: Clinical characteristics of virologically non-suppressed antiretroviral-experienced pregnant women (n=53)

Characteristic	Virologically non-suppressed (n=53)
CD4 (value), Median (IQR)	252 (170-338)
Last CD4 (value) before first antenatal visit, n (%)	49 (92.5)
<100	8 (16.3)
100-199	11 (22.4)
200-350	18 (36.7)
350-499	7 (14.3)
≥500	5 (10.2)
Viral Load (value), Median (IQR)	3929 (898-49119)
Booking Viral Load, n (%)	53 (100)
401 - 999	14 (26.4)
Log 3 < 4	20 (37.7)
Log 4 < 5	12 (22.6)
Log 5 < 6	7 (13.2)

Table 3b: CD4 count compared to booking viral load in virologically non-suppressed antiretroviral-experienced pregnant women (N=49)

Viral Load	CD4 < 100	CD4=100-199	CD4=200-349	CD4=350-499	CD4 ≥ 500	Total N
Viral Load (log), n (%)	8 (16.3)	11(22.5)	18 (36.7)	7 (14.3)	5 (10.2)	49 (100)
< log 3	1 (8.3)	3 (25.0)	3 (25.0)	2 (16.7)	3 (25.0)	12 (24.5)
log3 <log4	2 (10.5)	3 (15.8)	9 (47.4)	3 (15.8)	2 (10.5)	19 (38.8)
log4 < log 5	0	4 (36.3)	5 (45.5)	2 (18.2)	0	11 (22.4)
≥ log5	5 (71.4)	1 (14.3)	1 (14.3)	0	0	7 (14.3)

Table 4: Obstetric characteristics of virologically non-suppressed antiretroviral-experienced pregnant women (n=53)

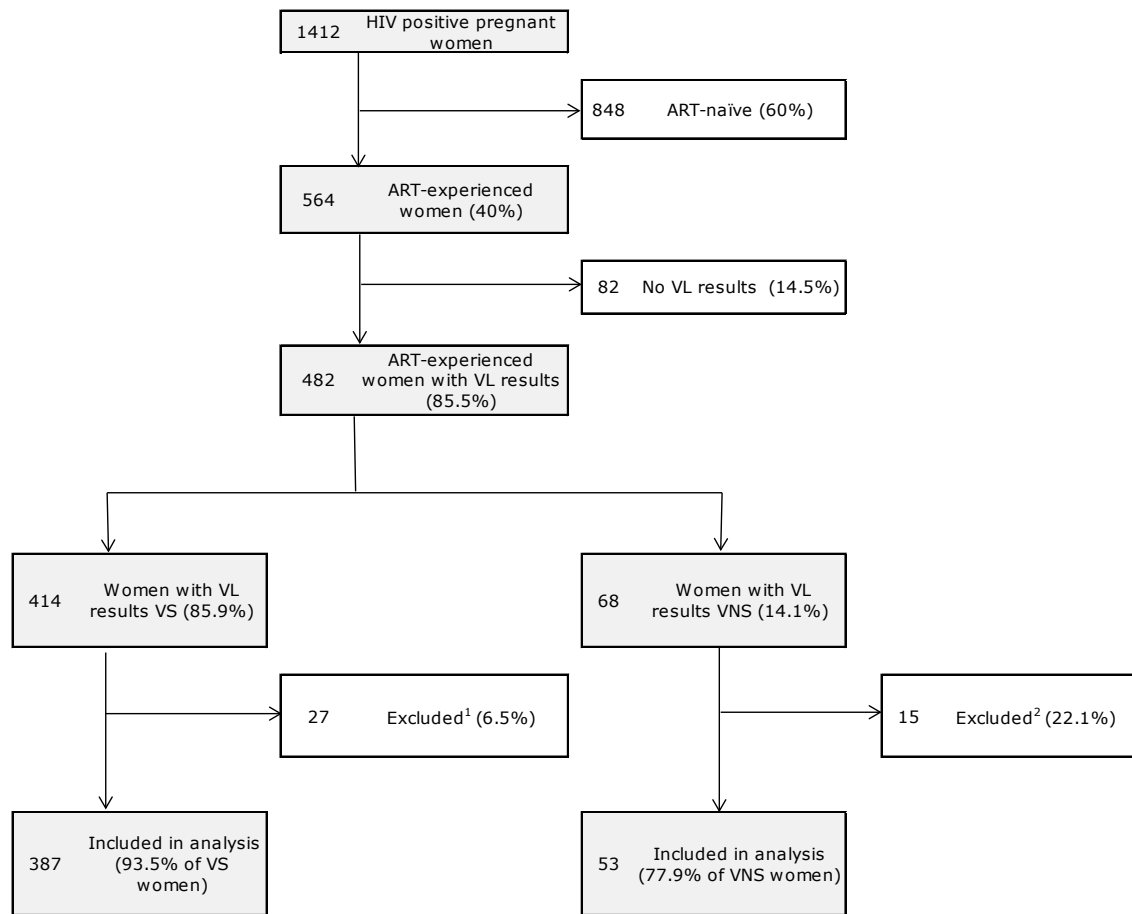
Characteristic	VNS women (n=53)
Gestational age at 1st antenatal visit (weeks), median (IQR)	19 (16-27)
Gestational age at 1st antenatal visit (weeks), n, (%)	49 (92.5)
≤12 weeks	7 (14.3)
13 –20 weeks	21 (42.9)
21-28 weeks	14 (28.6)
29 - 32 weeks	4 (8.2)
>32 weeks	3 (6.1)
Gravidity, mean (SD)	2.6 (1.2)
Gravidity, n (%)	49 (92.5)
G1	11 (22.4)
G2	13 (26.5)
G3	11 (22.4)
G4	11 (22.4)
G5	3 (6.1)
Pregnancy outcomes	53(100)
Confirmed miscarriage	3 (5.6)
Probable miscarriage ¹	1 (1.9)
Probable TOP ²	1 (1.9)
Live deliveries	48(90.6)
Delivery site, n (%)	45 (84.9)
Study site MOU	15 (33.2)
Khayelitsha District Hospital	13 (28.9)
Tygerberg hospital	15 (33.3)
Other	2 (4.4)
Delivery outcome, n (%)	48 (90.6)
Alive at 6 weeks	45 (85.0)
Early neonatal deaths ³	3 (5.6)
Foetal abnormalities on ultrasound	
30 yr women offered TOP for Trisomy 21	
43 yr women suspected Trisomy 21, neonatal death	
35 yr women : foetus with major cardiac abnormalities	
39 year women; unspecified abnormalities; 2 previous IUDs and NND	
* NND : neonatal death	
* IUD : intrauterine death	
* TOP : termination of pregnancy	
¹ No birth record	
² Offered TOP for Trisomy 21 foetus	
³ Infant with Serratia sepsis	
Infant delivered by emergency C/S; mother with postpartum sepsis, unconfirmed maternal death	
Infant with Trisomy 21 on Ultrasound	

Table 5: Audit of clinical record-keeping supporting the VLM algorithm

Characteristic, n (%)	Folders Audited (N=37)
Maternal case records in folder	10 (27.0)
VL result hard copy in folder	12 (32.4)
VL result in clinical notes	13 (35.1)
No VL result in folder	15 (40.5)
Record in folder of reasons for poor adherence	8 (21.6)
Record in folder of receiving adherence support	15 (40.5)
Formal letter for transfer of ART care to MOU	1 (2.7)
Transfer of ART care to MOU assumed from clinical notes	12 (32.4)

**VLM-Viral Load Monitoring; VL-Viral Load; ART-Anti-retroviral; MOU-Maternal & Obstetric Unit*

Figure 1: Cohort of HIV positive pregnant women (n=1412)



* VS : virologically suppressed

* VNS : virologically non-suppressed

1. Women identified as being VS from sources other than the VL/CD4 register

2. Defaulters (12) and women identified as being VNS (3) from sources other than the VL/CD4 register

Figure 2: Adherence characteristics of antiretroviral-experienced pregnant women who are virologically non-suppressed (n=53)

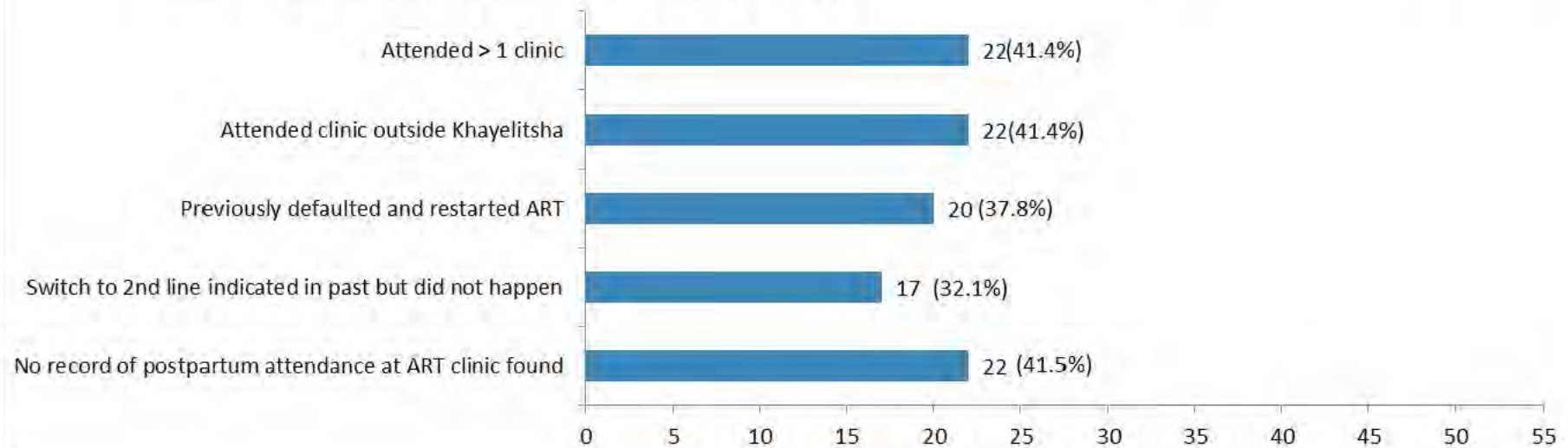
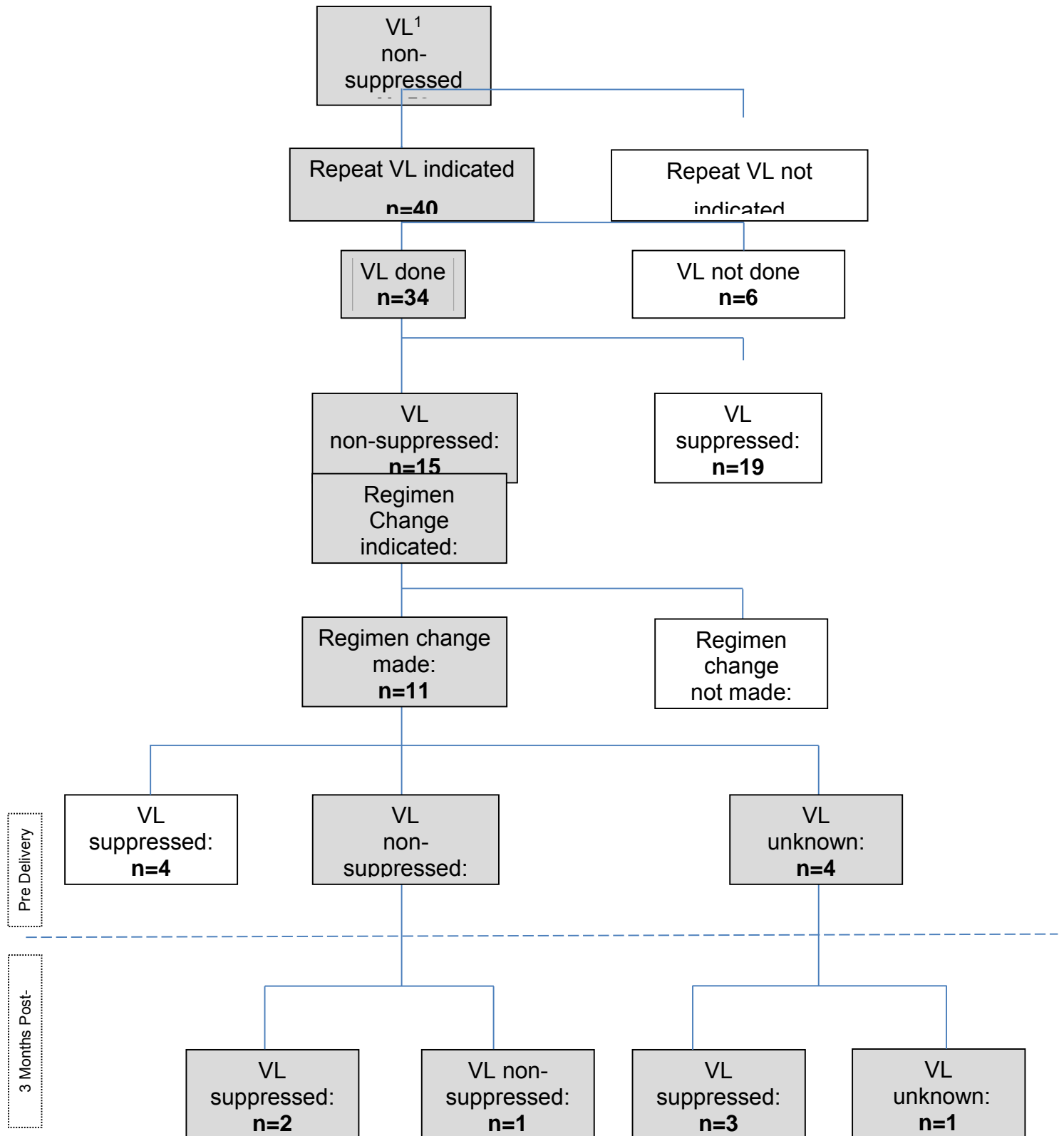


FIGURE 3: VIROLOGICAL OUTCOMES IN VIROLOGICALLY NON-SUPPRESSED ANTI-RETROVIRAL EXPERIENCED PREGNANT WOMEN



APPENDICES

VIRAL LOAD MONITORING AND MANAGEMENT DURING ANTENATAL AND POSTNATAL CARE

- For women on ART for greater than 4 months:**
- At first antenatal appointment – repeat viral load if not done in last 3 months
 - After cessation of breastfeeding, check viral load yearly if all prior viral loads were undetectable

- For women newly initiated on ART or on ART for less than 4 months:**
- Do 1st viral load at month 4 on ART
 - If patient likely to deliver between month 1 and 4 on ART, do 1st viral load at 36 weeks gestation
 - If likely to deliver before month 1 on ART, do 1st viral load at month 4
 - Provide infant PEP until mother virologically suppressed

YES

Is viral load greater than 400 copies/ml?

NO

Before 28 weeks gestation

Give increased adherence support

If this is first viral load greater than 400 copies/ml, continue current ART regimen and repeat viral load in 2 months

If this is second consecutive viral load greater than 400 copies/ml then switch to 2nd line ART and repeat viral load in 3 months

Between 28 weeks gestation and delivery

Give increased adherence support

If this is first viral load greater than 400 copies/ml and patient is on 1st line ART then add Aluvia

If this is second consecutive viral load greater than 400 copies/ml then switch to 2nd line ART

If already on 2nd line ART, prescribe exclusive formula feeding (if AFASS) and discuss with specialist

Provide infant PEP until mother virologically suppressed

Repeat viral load in 3 months

Postpartum

Give increased adherence support

If this is first viral load greater than 400 copies/ml and patient is on 1st line ART then add Aluvia

If this is second consecutive viral load greater than 400 copies/ml then switch to 2nd line ART (or discuss with specialist if patient is already on 2nd line ART)

Repeat or perform infant PCR ASAP

If baby is PCR positive: Manage mother and child as per National ART Guidelines

If baby is PCR negative: Stress importance of exclusive breast feeding

If mother is already on 2nd line ART regimen, prescribe exclusive formula feeding (if AFASS)

Provide infant PEP until mother virologically suppressed

Repeat viral load in 3 months

Continue current ART regimen

Exclusive breastfeeding

Repeat viral load in 6 months if patient is pregnant or breastfeeding

If patient is postpartum and not breastfeeding, repeat viral load in 1 year

YES

Is viral load greater than 400 copies/ml?

NO

Increase adherence support

Switch to second line ART (AZT if no contraindications, 3TC, Aluvia)

If already on 2nd line ART regimen, prescribe exclusive formula feeding (if AFASS) and discuss with specialist

Provide infant PEP until mother virologically suppressed

Repeat viral load 3 months

Continue current ART regimen

Encourage exclusive breastfeeding (if not already formula feeding)

Repeat viral load in 6 months if patient is pregnant or breastfeeding

If patient is postpartum and not breastfeeding, repeat viral load in 1 year

If Aluvia had been added to 1st line ART, continue this combination until cessation of breastfeeding; if viral load is suppressed on this combination, then stop Aluvia, continue 1st line ART and repeat viral load after 3 months. If viral load is still suppressed, continue 1st line ART alone

TIPS FOR PROVIDING INCREASED ADHERENCE SUPPORT

- Ensure patient understands what a viral load is
- Provide reasons for acquiring a high viral load
- Allow patient to conclude the cause of their high viral load
- Discuss possible solutions to their adherence problem:
- Choose an appropriate time to take your ARVs
- Always take a missed dose as soon as you remember
- Carry a few days extra supply of ARVs in your handbag at all times
- Use reminders like your cell phone alarm, regular TV programs, or family/friends.
- Plan for trips and holidays by asking for extra supply of ARVs from your clinic

On Mother's appointment card- document:

- Current ART regimen
 - Last blood results incl: CD4, Viral load, Creatinine, Hep B status
 - Planned date of next viral load
- Encourage mother to remind clinic staff to draw viral load on given date



APPENDIX A: VIRAL LOAD MONITORING ALGORITHM

APPENDIX B:

PLoS ONE: Instruction to Authors (<http://www.plosone.org/static/guidelines>)
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PLOS ONE considers manuscripts of any length. There are no explicit restrictions for the number of words, figures, or the length of the supporting information, although we encourage a concise and accessible writing style. We will **not** consider monographs.

All manuscripts should be double-spaced and include line numbers and page numbers. Manuscripts should begin with the ordered sections:

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- Abstract
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and end with the sections of:

- Acknowledgments
- References
- Figure Legends
- Tables

Figures should not be included in the main manuscript file. Each figure must be prepared and submitted as an individual file. Find more information about preparing figures here.

The title, authors, and affiliations should all be included on a title page as the first page of the manuscript file.

There are no explicit requirements for section organization between these beginning and ending sections. Articles may be organized in different ways and with different section titles, according to the authors' preference. In most cases, internal sections include:

- Materials and Methods
- Results
- Discussion
- Conclusions (optional)

PLOS ONE has no specific requirements for the order of these sections, and in some cases it may be appropriate to combine sections. Guidelines for individual sections can be found below.

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Standardized nomenclature should be used as appropriate, including appropriate usage of species names and SI units.

Guidelines for Standard Sections

Title

Manuscripts must be submitted with both a full title and a short title, which will appear at the top of the PDF upon publication if accepted. Only the full title should be included in the manuscript file; the short title will be entered during the online submission process.

The full title must be 250 characters or fewer. It should be specific, descriptive, concise, and comprehensible to readers outside the subject field. Avoid abbreviations if possible. Where appropriate, authors should include the species or model system used (for biological papers) or type of study design (for clinical papers).

Examples:

- Impact of Cigarette Smoke Exposure on Innate Immunity: A *Caenorhabditis elegans* Model
- Solar Drinking Water Disinfection (SODIS) to Reduce Childhood Diarrhoea in Rural Bolivia: A Cluster-Randomized, Controlled Trial

The short title must be 50 characters or fewer and should state the topic of the paper.

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Authors and Affiliations

All author names should be listed in the following order:

- First names (or initials, if used),
- Middle names (or initials, if used), and
- Last names (surname, family name)

Each author should list an associated department, university, or organizational affiliation and its location, including city, state/province (if applicable), and country. If the article has been submitted on behalf of a consortium, all author names and affiliations should be listed at the end of the article.

This information cannot be changed after initial submission, so please ensure that it is correct.

To qualify for authorship, a researcher should contribute to **all** of the following:

1. Conception and design of the work, acquisition of data, or analysis and interpretation of data
2. Drafting the article or revising it critically for important intellectual content
3. Final approval of the version to be published

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- **Databases and repositories. Examples: figshare, archive.com.** Roberts SB (2013) QPX Genome Browser Feature Tracks. Database: figshare. http://figshare.com/articles/QPX_Genome_Browser_Feature_Tracks/701214. Accessed 17 March 2014.

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