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Routine laboratory and clinical monitoring of HIV-positive pregnant women on antiretroviral therapy

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Routine laboratory and clinical monitoring of HIV-positive pregnant women on antiretroviral therapy

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A submissible research article submitted to the Faculty of Health Sciences at the University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine (M-MED), in the field of Obstetrics and Gynaecology.

Final submission: August 2022

Declaration by Authors

Declaration by Authors

To: The Dean

Faculty of Health Sciences

University of the Witwatersrand

Re: Acknowledgement of major role of Dr KMK Khulu (19111093/ M180331) in the development of the manuscript, titled: Routine laboratory and clinical monitoring of HIV-positive pregnant women on antiretroviral therapy

We, the undersigned author and co-author hereby declare that the submitted manuscript, with the above stated title is the Master of Medicine work of Dr Khulu. She was chiefly responsible for conceptualisation of the study, writing of the literature review, collecting data and performing the statistical analysis. She has also written the final draft of the manuscript. We are happy for her to submit this work for MMED examination.

Signed:



Dr K.M.K. Khulu



Dr C.N. Mnyani

Supervisor & Co-Author

BA (UCT), MBChB (UCT), FCOG (SA), PhD (Wits)

Abbreviations

3TC: lamivudine

AIDS: acquired immune deficiency syndrome

ART: antiretroviral therapy

AZT: zidovudine

CLAT: cryptococcal latex antigen test

CMJAH: Charlotte Maxeke Johannesburg academic hospital

C/S: caesarean section

CrAg: cryptococcal antigen test

d4T: stavudine

EFV: efavirenz

FTC: emtricitabine

FDC: fixed dose combination

Hb: Haemoglobin

HIV: human immune deficiency virus

HBV: hepatitis-b vaccine

IPT/TPT: isoniazid preventative treatment/ TB Preventative treatment

LPV/r: lopinavir/ritonavir

MTCT: mother to child transmission of HIV

NVD: normal vaginal delivery

NVP: nevirapine

PCR: polymerase chain reaction test

PJP: pneumocystis Jirovecii pneumonia

PMTCT: prevention of mother to child transmission of HIV

TDF: tenofovir disoproxil fumarate

TB: tuberculosis

TST: tuberculin skin test

sd: single dose

WHO: World Health Organization

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RESEARCH ARTICLE: FOR SUBMISSION TO SAJHIVMED

Title: Routine laboratory and clinical monitoring of HIV-positive pregnant women on antiretroviral therapy

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Conflict of interests

The Authors have declared there was no conflict of interest.

Authors' contributions

K. Khulu conceptualized the study and conducted all the research as well as capturing data on RedCap and interpreting the findings. C.N. Mnyani contributed as a co-author and revised and edited the manuscript.

Abstract

Background

Developments in South Africa's prevention of mother-to-child transmission of HIV (PMTCT) programme show a decline in AIDS-related paediatric deaths. In 2015, PMTCT guidelines were updated, with revised protocols for clinical and laboratory monitoring for patients on antiretroviral therapy (ART). The aim of this study was to assess adherence to monitoring guidelines for HIV-positive pregnant women on ART.

Methods

This was a clinical audit of 185 HIV-positive pregnant women, on pre-pregnancy ART, or initiated during the index pregnancy and delivered at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in the period January to June 2017. Data were collected on timing of HIV diagnosis and ART initiation, clinical and laboratory monitoring, and initiation of prophylaxis for opportunistic infections.

Results

Of the 185 patients, 64.9% (120/185) were known with HIV infection prior to the index pregnancy, and 85.8% (103/120) were initiated on ART pre-pregnancy, with 64/103 (62.1%) virally suppressed (<50 copies/ml) at baseline. Overall, 179/185 women accessed antenatal care. A total of 82 patients were initiated on ART in the index pregnancy, and of these 60/82 (73.2%) had a 3-month viral load done, and 22/82 (26.8%) were suppressed. A total of 153/185 (82.7%) patients had CD4 counts done, and of these, 63/153 (41.2%) were ≤350 cells/dl, with 7/63 (11.1%) patients receiving cotrimoxazole prophylaxis. Tuberculosis (TB) screening was documented for 35/179 (19.6%) patients, with 6/35 (17.1%) receiving TB preventative therapy. Birth HIV PCR tests were available for 175/185 (94.6%) neonates, and all were negative.

Conclusion

There were gaps identified in laboratory and clinical monitoring. ART initiation was however high, with no cases of MTCT reported.

Keywords: *HIV, antiretroviral treatment, laboratory and clinical monitoring, Pregnant women, PMTCT, HIV-positive*

Background

There have been great strides made in South Africa's prevention of mother-to-child transmission of HIV (PMTCT) programme, and this is reflected in the decline of AIDS-related paediatric deaths and the number of new HIV infections in children by 94% and 84%, respectively (1). The country's PMTCT guidelines have evolved rapidly in line with the World Health Organization (WHO) guidelines, with key updates to improve maternal health in HIV-positive women and decrease mother to child transmission (MTCT). (2) When the first South African PMTCT guidelines were released in 2002, only maternal and infant single dose nevirapine were available for prophylaxis, and no antiretroviral therapy (ART) for lifelong treatment was available (3). In 2015, there were major changes in the guidelines with the introduction and implementation of Option B+, providing triple ART throughout pregnancy and breastfeeding regardless of CD4 count (2). There was also the introduction of an ART fixed dose combination (FDC) in 2013, and in 2016, South Africa adopted universal test-and-treat with provision of lifelong ART for all persons living with HIV (4).

The aim of ART is to achieve viral suppression and subsequently immune reconstitution. For the HIV-positive pregnant woman, this is important for maternal health and decreasing the risk of MTCT, without which it is estimated that 15 – 45% of all children born to women living with HIV will be infected (5). The longer the duration of ART during pregnancy, the higher the chance of an undetectable viral load at the time of delivery, the highest risk period for MTCT (6). There is, therefore, a need for both laboratory and clinical monitoring in individuals on ART, to assess adherence and efficacy of treatment, and identify any adverse effects of treatment. Clinical monitoring is valuable to identify individuals at risk of opportunistic infections such as cryptococcal infections and pneumocystis Jirovecii pneumonia, as HIV infection potentiates the deterioration of the immune system (7). Clinical monitoring is also fundamental in diagnosing infectious diseases and in particular tuberculosis (TB), an important cause of morbidity and mortality for people living with HIV, and one of the leading causes of maternal death in South Africa (8).

Several challenges exist with routine monitoring, especially in resource-constrained settings. Health facilities need to be well resourced, particularly with staff who are knowledgeable and up to date with current PMTCT protocols, and therefore ensuring adequate management strategies and treatment plans that are patient specific as outlined in the PMTCT guidelines (9). Long waiting periods at clinics due to staff shortages and challenges with accessibility to transportation for women living far from antenatal clinics, may lead to poor antenatal attendance (10). A study done in the Eastern Cape showed that knowledge about PMTCT programmes was low among expectant mothers, and this affected the rate of uptake of antenatal services (11). In another study done in Soweto, South Africa, most patients testing HIV-positive during pregnancy felt the counselling and perceived expertise of the counsellors was inadequate, and the women had limited knowledge of current PMTCT interventions that were available to them (12).

Adherence to routine clinical and laboratory monitoring, and appropriate management of any conditions and complications identified, reflects the quality of care in PMTCT programmes. Poor patient satisfaction and understanding for the need for routine antenatal follow-up were also contributing factors to poor adherence to antenatal care and PMTCT programmes (13). A reported 20% of HIV-positive pregnant women, Initiated on ART in pregnancy defaulted ART for at least a month during pregnancy in a study done in the Western Cape, South Africa (14).

There were four key strategies implemented in Sub-Saharan Africa as a response to the 2011 Global plan implemented at the United Nations General Assembly High-level Meeting on HIV/AIDS. Robust monitoring and evaluation systems was one of these key strategies, along with committed political leadership, support structures within the community and innovation in service delivery, but there has been little data available with regards to monitoring PMTCT programmes (15,16). This study aimed to assess routine clinical and laboratory monitoring of HIV-positive pregnant women on ART, in accordance with the 2015 South African PMTCT guidelines (Table 1).

Table 1: Summary of 2015 South African National Consolidated Guidelines for HIV-positive pregnant women[2]

PMTCT Guidelines	ART regimens	Viral load monitoring	CD4 count	Creatinine	TB screening	ART Initiation
	First line - TDF+FTC+EFV given as a fixed dose combination (FDC) Second line - AZT + 3TC + LPV/r - AZT + TDF + 3TC + LPV/r (4 drugs if HBV co-infected) Failing on a d4T or AZT-based first line regimen - TDF + 3TC (or FTC) + LPV/r ART naïve and in labour - sdNVP + sdTruvada and AZT 3-hourly in labour	At baseline for those already on ART and at 3 months on ART for newly initiated. Repeat at 6 months and 6-monthly intervals during pregnancy and breastfeeding.	At baseline to identify eligibility for cotrimoxazole prophylaxis (CD4 ≤350 cells/uL) and screening for cryptococcal infection (CD4 <100 cells/uL)	At 3, 6, and 12 months, and every 12 months if on a TDF-based regimen Threshold for continuing with a TDF-based regimen in pregnancy ≤85µmol/l	Clinical screening at each visit	All HIV-positive pregnant women were eligible for lifelong ART regardless of gestational age and CD4 count. - Patients changed to FDC if on individual first line drugs, virally suppressed and no contraindication to FDC
Infant Prophylaxis	Mother	Infant				

	- On lifelong ART - Mother did not get ART before or during delivery Or ART for <4 weeks before delivery Or Mother newly diagnosed within 72 hours of delivery Or Latest viral load > 1000 copies/ml - Unknown HIV status, including orphans	- Rapid HIV test for infant, initiate NVP until maternal and/or infant HIV status confirmed - NVP for 6 weeks - NVP for 12 weeks - Rapid HIV test for infant, initiate NVP until maternal and/or infant HIV status confirmed				

3TC: lamivudine, ART: antiretroviral therapy, AZT: zidovudine, CD4: , CLAT: cryptococcal latex antigen test, C/S: caesarean section, CrAg: cryptococcal antigen test , d4T: stavudine, EFV: efavirenz, FTC: emtricitabine, FDC: fixed dose combination, Hb: haemoglobin, HBV: hepatitis-b vaccine, IPT: isoniazid

preventative treatment , LPV/r: lopinavir/ritonavir , NVP: nevirapine, TDF: tenofovir disoproxil fumarate , TB: tuberculosis, TST: tuberculin skin test, sd: single dose

Methods

Study setting and population.

The study was done at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), in Johannesburg, South Africa. CMJAH is a tertiary hospital and forms part of the main training and teaching hospitals for the University of the Witwatersrand. The hospital also serves as a referral centre for secondary and district hospitals, and community health centres in the catchment area. The obstetrics department at CMJAH sees high-risk patients, and had at the time of the study, on average 600 live births per month, with approximately 10% (60/600) of these births occurring in HIV-positive women. The study population included HIV-positive pregnant women who had live births and delivered at CMJAH, from 1 January 2017 to 30 June 2017, and were already on ART or initiated on ART during the pregnancy.

At the time of the study, management of HIV-positive pregnant women followed the 2015 South African PMTCT guidelines – Table 1. Viral suppression was defined as a viral load of <50 copies/ml or <20 copies/ml, depending on the instrumentation used at a particular laboratory. If the viral load result was between 400 – 1000 copies/ml, strict adherence counselling was to be done and a repeat viral load test done within six months of the previous test. For patients with a viral load ≥ 1000 copies, a repeat test was to be done one month after the previous test to assess adherence, and a decline of 1 log or more was expected with optimal adherence. Second line ART was initiated if there was evidence of treatment failure to first line treatment, or the development of adverse side effects.

Study design

This was a clinical audit of antenatal and delivery records of HIV-positive women who delivered at CMJAH during the study period, and were already on ART pre-pregnancy, on were initiated on ART during the index pregnancy. On average, there were 600 deliveries at CMJAH per month with 10% (60) being HIV-positive, which translates to approximately 360 deliveries in six months. The intended convenient study sample was 200 participants, which translates to just over a half (55.5%) of HIV-positive women who were expected to have delivered during the study period. Patients were randomly selected by choosing every third entry of a live birth from an HIV-positive woman in the labour ward and caesarean section theatre registers. The objectives of the study were: to evaluate whether baseline and

monitoring blood tests – CD4 count, viral load and creatinine – were done in HIV-positive pregnant women on ART, according to the 2015 PMTCT guidelines; to assess whether appropriate action, e.g. repeat blood tests and ART regimen switch where indicated, was taken in case of abnormal laboratory test results; to assess whether screening for opportunistic infections, including TB, was done and if appropriate prophylaxis was initiated; and lastly, to evaluate whether HIV PCR was done at birth and appropriate prophylaxis initiated according to the guidelines in the HIV-exposed neonates of the women included in the audit.

Data were extracted from maternal antenatal and delivery records using a standardised data sheet, and data on the following variables were collected: demographics, timing of HIV diagnosis and ART initiation, baseline and monitoring bloods done, TB screening, and prophylaxis given for opportunistic infections. Results not documented in patient records were checked on the National Health Laboratory Services (NHLS) TrakCare website using the patient's name, surname, hospital number and/or NHLS specimen barcode if available.

Ethics clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (No. M180331) The project was registered with the South African National Health Research Database and the chief executive officer (CEO) at CMJAH gave approval for the study.

Data analysis

The data was captured on an electronic data capturing system, REDCap® (v10.6.2), and was exported onto STATA analytical software (v.15) for analysis with the help of a statistician (17). Continuous data was assessed for normality and where appropriate, was presented as means and standard deviations, or medians and interquartile ranges (IQR). Categorical data was summarised as frequencies and percentages and the relationships between the categorical data was assessed using Fisher's exact test at a significance level of p=0.05.

Results

There were 185 patients who met the inclusion criteria for the clinical audit. The demographics of the participants and information on timing of HIV diagnosis and ART initiation are presented in Table 2. The mean age of the participants was 30.2 years (standard

deviation (SD) 5.5), and the median parity was 1 (IQR 1-2) and the median gravidity 2 (IQR 2-3). Most patients, 120/185 (64.9%), were diagnosed with HIV infection prior to the current pregnancy, and of these 103/120 (85.8%) were initiated on ART pre-pregnancy. There was a total of six patients who had had no antenatal care during the pregnancy; they were known HIV-positive and three had their initial bloods (CD4, Creatinine and viral load) taken on arrival on the day of delivery. The remaining three had no bloods taken on arrival at delivery although a birth PCR was available in the maternal file. Thus, all baseline blood results (CD4 count, creatinine, and viral load) were assessed for 185 women and infant birth HIV PCR was assessed for 185 HIV-exposed neonates. Of the women included in the audit, 179 had more than one antenatal visit and accessed routine antenatal care and were assessed for routine repeat blood tests and clinical monitoring according to the South African National PMTCT guidelines.

Table 2: Characteristics of the participants at baseline (n=185)

Demographics	**n**	**%**
Age, Mean 30.5 (SD 5.4)		
- **18 – 35**	155	83.9
- **>35**	30	16.2
Booked	179	96.8
2)Timing of HIV Diagnosis		
- **Pre-pregnancy**	120	64.9
- **Antenatal**	65	35.1
3)Timing of ART initiation		
- **Pre-pregnancy**	103	55.7
- **Antenatal**	80	43.2
- **Not documented**	2	1.1
4)ART regimen		
- **1st line***	180	97.3
- **2nd line****	3	1.6
- **Regimen not documented**	2	1.1
4)Baseline CD4 count (cell/dl)		
Median, IQR	408, (250-578)	
- **≤100**	10	5.4
- **101 – 200**	18	9.7
- **201 – 350**	35	18.9
- **> 350**	85	45.9
- **Not documented**	37	20.0

*1st line: TDF + 3TC(FTC) + EFV

**2nd line:(AZT + 3TC + LPV/r) or (AZT + TDF + 3TC + LPV/r (4 drugs if HBV co-infected))

Of the 185 records assessed for baseline bloods (CD4, Creatinine and viral load), 145 (78.4%) had a documented CD4 count, and the median was 408 cells/dl, and IQR 250 – 578 cells/dl, and 34/185 (18.4%) records did not have a CD4 count documented or barcode in the maternity file as proof of the blood test being done. There were 63/185 (34.1%) patients with a CD4 count ≤350 cells/dl, of whom 10/63 (15.9%) received co-trimoxazole prophylaxis during pregnancy. There was a total of 10/185 (5.4%) patients with a CD4 count of ≤100 cells/dl and of these, reflex cryptococcal antigen (CrAg) testing was done for seven (70.0%), with results available for six (60.0%), and all were negative.

Viral load levels were stratified according to those who were already on ART pre-pregnancy and those initiated during the index pregnancy – Table 3. The baseline viral load was done at the first antenatal visit for those already on ART and for those initiated during the pregnancy, the initial test was to be done 12 weeks after ART initiation. For those initiated on ART pre-pregnancy (103/185, 55.7%), 100/103 (97.1%) had a documented viral done at the first antenatal visit, and the median was 20 copies/ml, IQR 0 – 116, with 64/100 virally suppressed (viral load <50 copies/ml). Of the 24/100 (24.0%) that were not virally suppressed and required a repeat viral load test, six (25.0%) had repeat viral loads done to monitor for virologic suppression and treatment failure.

There were 82/185 (44.3%) patients who were initiated on ART in the antenatal period, of whom 21/82 (25.6%) had no documentation of viral loads being done in the antenatal period. There were 27/82 (32.9%) patients within the group initiated on ART during the pregnancy that had a viral load of >1000 copies/ml. Of those with a viral load of >1000 copies/ml after 12 weeks on ART, 8/27 (29.6%) had repeat viral load testing. The majority, 135/179 (75.4%), did not have routine repeat viral load test done in pregnancy at 3 months and 6 months, in accordance with the PMTCT guidelines.

Table 3: Patient viral load levels in relation to the timing of ART initiation (n=185)

Baseline viral load (taken at first visit or at 3 months post ART initiation)	Pre-pregnancy ART initiation (n=103)		ART initiation during pregnancy (n=82)		P-value [α]
	n	%	n	%	
<50	64	62.1	22	26.8	0.001*
50-100	12	11.6	4	4.9	
101-1000	12	11.6	8	9.8	
>1000	12	11.6	27	32.9	
Viral load test not done	3	2.9	21	25.6	0.001*

*P<0.05, [α]Fischer exact test

Baseline creatinine tests were not done for 38/185 (20.5%) at the initial antenatal visit. Routine repeat creatinine at 3 months and 6 months during pregnancy were done for 48 (26.8%) and 13 (7.3%) respectively, of the 179 patients who attended routine antenatal care. However, repeat creatinine testing was also done for other indications in 22/179 (12.3%), such as hypertensive disorders, admission for operative procedures (caesarean section), and other medical conditions. There were four participants with creatinine > 85 µmol/l, all of whom had repeat tests done. One was repeated for hypertensive disorder and another repeat for an unspecified condition. Two out of four participants with creatinine >85 µmol/l had ART changed due to renal side effects and the remainder two continued on the first line regimen.

Clinical screening for TB was documented in 35/179 (19.6%) patients, with 6/35 (17.1%) overall receiving IPT. Of the 63/185 (34.1%) who qualified for cotrimoxazole prophylaxis, with a CD4 count of < 350 cells/dl, 10/63 (15.9%) were documented to be given treatment. There were 175/185 (94.6%) birth PCR tests done and seven (3.8%) were rejected due to electronic gatekeeping from duplication of the test, and 1 (0.5%) PCR test result was indeterminate. There was also no documentation of birth prophylaxis given in 50/185 (27.0%) cases and the majority (98.5%) of babies received NVP as birth prophylaxis as indicated in Table 5.

Table 4. Results of birth PCR and details of Prophylaxis given as a measure of the effects of PMTCT (N = 185)

Mode of Delivery	**n**	**%**
C/S	56	30.3
NVD	**129**	69.7
Birth PCR		
Not recorded	12	6.5
Positive	0	0.0
Negative	**165**	89.2
Indeterminate	1	0.5
Test rejected	7	3.8
Birth Prophylaxis		
NVP	135	73.0
NVP + AZT	2	1.1
Not documented	48	25.9

Discussion

In this study, there were aspects of laboratory and clinical monitoring of HIV-positive pregnant women on ART that were done well, according to the guidelines, and others that were not. Almost two thirds of the patients were diagnosed as HIV-positive pre-pregnancy, and just over a half were initiated on ART prior to the index pregnancy. Viral load monitoring was poor, especially in the patients initiated on ART during pregnancy. Of the patients who were initiated on ART pre-pregnancy and had a documented viral load, just over half were virally suppressed, viral load < 50 copies/ml and 76.7% had a viral load of ≤1000 copies/ml. The median CD4 count was high, and of the patients that were eligible for cotrimoxazole prophylaxis based on the CD4 count (<350 cells/dl), only 15.9% received it. The clinical screening for TB was poorly documented, with no evidence of it being done in most patients, and therefore most patients did not receive IPT.

Baseline viral load monitoring done at the initial presentation, for women already on ART, was done and documented in 97/103 participants, with 28% having a detectable viral load and 15.5% had a viral load of ≥ 1000 copies/ml. An antenatal survey conducted in South Africa regarding viral load suppression in pregnancy, showed the duration of time on ART was inversely proportional to a viral load of < 50 copies/ml. Participants who attended their first antenatal visit in the late second trimester onwards were more likely to have a viral

load > 1000 copies/ml at delivery (18). The duration of ART prior to viral load testing in this group was not well documented and tests may have been done within the first 12 weeks of initiation of therapy, as 92.1% will have a viral load <1000 copies/ml after 25-31 weeks on ART and 79.9% will have a viral load <1000 copies/ml in less than six weeks on ART (19).

A lower than detectable limit, which implies viral suppression, is the ideal end goal of comprehensive PMTCT programmes to eliminate new HIV infections among children and to keep their mothers alive. Repeat viral load testing at 3-monthly intervals were not routinely done in this study. This could be because routine antenatal visits may not have correlated with the timing of repeat viral load testing, and clinicians not being aware of guidelines. In a simulation study comparing different regions in Sub-Saharan Africa, it was found that guidelines may lead to suboptimal recognition of viraemic episodes, from delays in detection of the onset of viraemic episodes and the detection of such during routine monitoring in pregnancy (20). Another study done in Kwa-Zulu Natal showed that the optimal time for viral load testing was at 36 weeks of gestation, with a higher sensitivity and specificity for detecting those with viral load >1000 copies/ml at delivery (21). At the time of the study there was yet to be implementation of a viral load test done at delivery, which is according to the 2019 South African PMTCT guidelines (22). A standard repeat viral load at delivery gives an indication of ART adherence during pregnancy and has implications for the type of neonatal prophylaxis that is appropriate, based on the risk stratification of the mother (23). The delivery viral load also informs the timing of follow-up viral load testing during the postpartum period (24). Increased viral load at delivery is associated with an increased risk of MTCT and is more prevalent in women initiated on treatment in the antenatal period (24). In our study, there were no cases of MTCT even though only 55.7% were on ART prior to the index pregnancy.

Tenofovir Disoproxil fumarate (TDF) is part of the first line ART regimen and is associated with proximal renal tubulopathy and impaired glomerular filtration, the effects of which are reversed with cessation of TDF use. Abnormalities in proximal renal secretion of TDF may lead to accumulation in renal tubular cells causing toxicity, reflected by an increase in creatinine (25). Potential risk factors for toxicity include pre-existing renal disease, diabetes mellitus, hypertension, a baseline CD4 count of <200 cells/dl and administration of ritonavir-

boosted protease inhibitors in combination with TDF (25). In this study, baseline creatinine was well monitored and documented, but routine repeats at three monthly intervals was poor. Only two out of four study participants who had a creatinine >85 µmol/l had a change in ART, based on renal side effects of TDF. There is a possibility that some patients with an increased creatinine were not detected as routine repeat creatine tests were not done in most.

ART is no longer initiated according to the CD4 count; all pregnant women and all HIV-positive people are now eligible for life-long ART. CD4 count does however remain a marker of the immunological status of the patient and a marker for the increased risk of opportunistic infections such as PJP, Toxoplasmosis, malaria, and a range of other bacterial infections, such as Isospora belli diarrhoea (26). Therefore, a CD4 count is an important determinant of when to start co-trimoxazole prophylaxis, and the duration, as well as when to screen for cryptococcal infection. Co-trimoxazole prophylactic is associated with a decrease in malaria and non-serious bacterial infections especially in endemic areas (27). In our study, the median CD4 count was 408 cells/dl, and there were 63/185 participants who had a CD4 ≤ 350 cells/dl and 10/185 who had a baseline CD4 count ≤100 cells/dl. The latter two groups are noteworthy as they required further investigations for opportunistic infections and co-trimoxazole prophylaxis. Most women (103/185) were already on ART before accessing antenatal care. In a larger study conducted in various metropolitan districts in Gauteng, South Africa, women on ART pre-pregnancy were more likely to have a CD4 count >500 cells/dl as opposed to those initiated on ART during the pregnancy (28). In the past 20 years, cryptococcal testing has progressed from culture, which may take days to report, to India Ink, which is quick, but lacks sensitivity. Reflex laboratory India Ink is done for CD4 counts of ≤100 cells/dl and is not dependant on provider-initiated screening. With reflex laboratory screening >95% of eligible persons are screened for cryptococcal meningitis (29). In our study, there were 10 participants who qualified for cryptococcal screening and prophylaxis. It was however not documented whether the results were appropriately interpreted and if further action was taken or not. Only 15.9% patients with a CD4 count ≤350 cells/dl had documentation that they received co-trimoxazole prophylaxis. A possible reason for this is that the information was recorded in the ART clinical stationary, which is stored separate from the maternity case records.

South Africa has a high prevalence of HIV and TB coinfection. According to the 2020 Saving Mothers Report, non-pregnancy related infections such as TB and pneumonia, remain the leading cause of maternal mortality in South Africa (8). TB is responsible for 67% of all HIV related hospital admissions, and pregnant women with active TB infection have poorer outcomes than women without TB especially when anti-tuberculosis treatment was started late (30). In the 2015 guidelines, all pregnant women were eligible for TPT for 12 months if the TST was negative and for 36 months if the TST was positive. TST was not done antenatally and TB screening was exclusively clinical, and symptom based. IPT could be started at any point in pregnancy, provided the patient did not have active TB infection, and had not already completed TPT prior to the pregnancy (2). In this study, only 17.1% of those screened for TB received IPT and monitoring for opportunistic infections was not well documented at each antenatal visit. However, it has been shown that starting IPT in pregnancy is associated with a 1.6 to 1.7-times increase in adverse pregnancy outcomes, indicating a need for alternative preventative treatment (31).

The success of PMTCT programmes is ultimately defined by the number of new neonatal and infant HIV infections that are a result of HIV transmission during pregnancy and the breastfeeding period(32). In this study, only the birth PCR was included as part of the assessment of routine monitoring of the HIV-exposed infant. Overall, 93.5% of infants had results for birth PCR, and all were negative. It is possible that some tests were missed because of neonatal files that were separate from the maternal documentation.

There are several strengths of this study and include the fact that patients were from a wide catchment area of Johannesburg, and included patients seen antenatally in all tiers of the health system even though delivery was at CMJAH, a tertiary institution. This indicated that despite the different levels of availability of resources, the results showed that monitoring was poor at all levels of care. Despite the strengths, there are limitations and include the fact that this was a retrospective study, and it had a small sample size. Another limitation is that neonatal records were not accessed and hence some of the information on infant

testing and prophylaxis may have been missed. Despite these limitations, the study provides important information on the poor adherence to routine monitoring in pregnant women on ART. This has implications on the timeous identification of treatment failure and drug toxicity, which has dire consequences (33).

Conclusion

There is hence a need to strengthen both clinical and laboratory monitoring in HIV-positive pregnant women on ART. There is also a need to align routine monitoring during the antenatal period with the standard antenatal visits. This could improve healthcare worker workload and improve patients' satisfaction without hindering appropriate care of HIV-positive pregnant women. Updates on PMTCT guidelines also need to be well communicated in all tiers of health care for successful results. There are also encouraging changes in the 2019 PMTCT guidelines for the further reduction in MTCT rates, such as the implementation of a viral load test done at delivery.

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Appendix A:Turnitin Report

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ORIGINALITY REPORT

75%	11%	10%	73%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	73%
2	Olumuyiwa Omonaiye, Snezana Kusljic, Pat Nicholson, Elizabeth Manias. "Factors Associated With Success in Reducing HIV Mother-to-child Transmission in Sub-Saharan Africa: Interviews With Key Stakeholders", Clinical Therapeutics, 2019 Publication	<1%
3	open.uct.ac.za Internet Source	<1%
4	Aziz, N, A Sokoloff, J Kornak, NV Leva, ML Mendiola, J Levison, C Feakins, M Shannon, and D Cohan. "Time to viral load suppression in antiretroviral-naive and -experienced HIV-infected pregnant women on highly active antiretroviral therapy: implications for pregnant women presenting late in gestation", BJOG An International Journal of Obstetrics & Gynaecology, 2013. Publication	<1%
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B.Declaration of plagiarism

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Kwano Mahlako Kgwerano Khulu (Student number: 1911093) am a student registered for the degree of Mmed in the academic year 2022.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 23 Aug 2022

C. SAJHIVMED author guidelines

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** forms part of a submission and must be submitted together with all the required **forms.** All forms need to be completed in English.

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Word limit	3500-5500 words (excluding the structured abstract and references)
Structured abstract	250 words to cover a Background, Objectives, Method, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of five paragraphs labelled Background, Objectives, Method, Results and Conclusion.

- Background: *Why do we care about the problem?* State the context and purpose of the study. (What practical, scientific or theoretical gap is your research filling?)
- Objectives: *What problem are you trying to solve*? What is the scope of your work (e.g., is it a generalised approach or for a specific situation)? Be careful not to use too much jargon.
- Method: *How did you go about solving or making progress on the problem*? State how the study was performed, and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- Results: *What is the answer*? Present the main findings (that is, as a result of completing the procedure or study, state what you have learnt, invented or created). Identify trends, relative change or differences on answers to questions.
- Conclusion: *What are the implications of your answer*? Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)

Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.

- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected, and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used, or steps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our policy on competing interests.
- Author contributions: All authors must meet the criteria for authorship as outlined in the authorship policy and author contribution statement policies.

- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

D. Approved research protocol and Data sheet

Introduction

In 2015 there were 36.7 million people living with HIV/AIDS globally, with an estimated 2.1 million new infections that year. Sub-Saharan Africa is home to a mere 12% of the world population but

bears a disproportionate burden and accounts for 70% of the global HIV population, and of the 10 Sub-Saharan countries, South Africa is home to 25% of people living with HIV/AIDs(1) .

The total number estimated living with HIV in South Africa has increased from 4.9 million in 2002 to 7.06 million in 2017. With 3.4 million people on antiretroviral treatment (ART), South Africa has the biggest HIV treatment programme as of 2016. There has been a steady decline in the number of AIDs related deaths since 2007 and this can be attributed to the increase in antiretroviral (ARV) availability due to the national rollout program which started in 2005 and, by 2015, 95% of HIV positive pregnant women were on ART(2). There have been great strides made in South Africa with regard to the efficiency and efficacy of the prevention of mother to child transmission (PMTCT) programme, detailed in the decline of AIDS-related paediatric deaths and a decline in the number of new HIV infections in children. Therefore, success in preventing new infections and also specifically, PMTCT, has the potential to impact globally.

Literature Review

National Guidelines for prevention of MTCT of HIV

In 2010 the World Health Organisation (WHO) released new guidelines with regards to the PMTCT programme(3). Since 2001 until the latest revision in 2016, there have been four revisions to the guidelines. The South African Guidelines are modelled on the WHO guidelines and are specific for the setting in South Africa as a progressive but resource limited setting. There are key updates to the guidelines that are specific to maternal health and decreasing the burden of disease in HIV-positive pregnant women and decreasing MTCT. Firstly, all pregnant women must be tested for HIV at the first antenatal visit using a rapid HIV test. HIV counselling and testing is done routinely at 3,6,9,12,18 and 24 months for the duration of the pregnancy and breastfeeding if the initial test is negative. This is important for identifying the group that is at increased risk for MTCT due to new HIV infections during pregnancy and the postnatal period. HIV-positive pregnant women, as in all individuals diagnosed as HIV-positive, qualify for lifelong ART and are to be initiated on a fixed dose combination (FDC) upon booking, irrespective of CD4 count or WHO disease stage. Women who were previously on other regimens and are virally supressed are also initiated on lifelong ART in the form of FDC (4). This is a significant change as previously pregnant women were offered two options, Option A and Option B. Under option A, pregnant women with a CD4 count of ≥350 cells/µL and WHO clinical stage of 1 and 2 disease, the regimen was as follows: ART prophylaxis with zidovudine (AZT) from 14 weeks gestational age, single dose nevirapine (NVP) and 3 hourly AZT during labour and delivery. Postpartum the women received either a single dose tenofovir (TDF) and emtricitabine (FTC) combination, which is Truvada, or AZT and lamivudine (3TC) until 1 week postpartum. Option B dictated that women with a CD4 <350 cells/µL or WHO disease stage 3 or 4, were started on lifelong triple therapy as soon as possible during pregnancy. Currently under option B+, introduced in South Africa in 2015, all pregnant women receive a FDC (TDF+3TC+EFV) as a first line regimen (5).

Implementation of comprehensive PMTCT programmes has had the greatest impact on reducing child mortality associated with HIV vertical infection. Literature has shown that HIV infected pregnant women have higher rates of still birth, preterm deliveries and low birth weight infants (6). There have been significant improvements in these indices since the implementation of the new guidelines resulting in larger demographic coverage of ART. A randomised control trial of single dose Nevirapine prophylaxis vs triple therapy, has shown that the risk of MTCT was reduced by 43% at 12 months on triple therapy. Also, that the duration of treatment during pregnancy has a strong association with the viral load at the time of delivery. The longer the duration of ART during pregnancy, the higher the chance of an undetectable viral load at the time of delivery (7).

Routine monitoring in HIV-positive pregnant women on ART

In accordance with the new 2015 South African Guidelines, a baseline viral load and CD4 count are to be done at the first antenatal visit if the woman is already on ART, and the results should be followed up in 2 weeks at the same facility. If the woman is newly diagnosed HIV positive and/or ARV naïve, the viral load is done 3 months after initiating ART. CD4 count is no longer used as a marker of disease progression in HIV, but rather viral load testing as a of response to treatment (4).

Viral load monitoring

Viral load testing has been shown to be superior in identifying pregnant women who are virally supressed and those with treatment failure, and those who may need adherence counselling and support. A viral load of >1000 copies/ml is indicative of treatment failure and therefore places the women at high risk for MTCT and a repeat viral load is done after 1 month after adherence counselling. Should the viral load remain > 1000 copies/ml, these women are to be considered high risk and need to be referred to a centre where they can be managed and followed up on second line agents. Therefore, routine viral load monitoring needs to be done upon presentation at the first booking visit if already on treatment and at 3,6,12,18 and 24 months during pregnancy and breastfeeding. This ensures that pregnant women who conceive on ART are virally supressed and to identify those with treatment failure or problems with adherence who require additional clinical attention. The timing of viral load testing is very important as there is evidence to suggest that most women have episodes of detectable viral loads of > 1000 copies/ml during the course of pregnancy despite being on ART. There is also evidence to suggest that there is no correlation between the CD4 count and viral load. A viral load of >10,000 copies/ml was commonly observed in women not initiated on ART who had CD4 of > 350 cells/µL. Likewise, a significant proportion of women who may have already been on ART prior to pregnancy, may have a detectable viral load at the first visit (8). A lower than detectable limit, which implies viral suppression, is the ideal end goal of comprehensive PMTCT programmes in order to eliminate new HIV infections among children and to keep their mothers alive. As discussed, CD4 is no longer used to determine whether women qualify for ART but is used to screen for opportunistic infections and determine the need for prophylaxis to prevent these infections.

CD4 count testing

During the late 1990's HIV treatment was expensive and carries the risk of significant drug toxicities, which meant when starting treatment, the relative benefits would have to outweigh the risks. As treatment options and side effect profiles improved, evidence for starting treatment at higher CD4 count accumulated and the threshold for starting ART was raised in guidelines. Thereafter, studies showed that early initiation of treatment can preserve immune function and prevent early complications associated with HIV, and so, the role of CD4 count testing changed. CD4 count remains the best direct measure of immunologic status, especially in advance clinical stage disease (9). In Sub-Saharan Africa, infectious diseases, in particular tuberculosis (TB) and bacterial infections are the main causes of morbidity and mortality for people living with HIV (10).

The current South African national guidelines recommend baseline CD4 count at the initial visit as part of routine monitoring. Patients with CD4 counts bellow 100 cells/µL are at increased risk of cryptococcal disease and need to be screened for clinical disease by doing a cryptococcal antigen blood test (CrAg) before prophylaxis is given. Pregnant women testing CrAg-positive, indicating disseminated disease and, who are symptomatic, need urgent referral for a lumbar puncture (LP) to

rule out meningitis. Should the LP be positive for meningitis these patients need intravenous antifungal treatment for 2 weeks and ART is started 4-6 weeks after antifungal treatment.

Pregnant women who test CrAg-positive with no symptoms need to be referred for an LP to rule out subclinical meningitis. If no evidence of meningitis is found, oral antifungal treatment is given for 2 weeks, and ART is commenced 2 weeks thereafter. If CrAg is negative, there is no need for antifungal treatment and ART is started as soon as possible (4). It has been found that adherence support and cryptococcal screening in advanced disease has led to a significant reduction in mortality of 30% as compared with groups that did not receive this support (11).

Pregnant women with CD4 counts < 350 cells/µL are at risk for opportunistic infections such as Pneumocystis Jirovecii Pneumonia (PJP), Toxoplasmosis, malaria and a range of other bacterial infections, such as *Isospora belli* diarrhoea (10). Co-trimoxazole prophylaxis is considered safe in pregnancy and can be stopped once the CD4 is ≥ 350 cell/µL (4). Co-trimoxazole is a fixed dose combination of Sulfamethoxazole and Trimethoprim, and prevents morbidity and mortality from numerous bacterial, fungal and protozoal infections. In a systemic review and meta-analysis, of the causes of hospital admission among people living with HIV, AIDs related illnesses and bacterial infections were the main causes for hospitalisation in all geographical regions. Pulmonary TB was responsible for 67% of admissions, PJP 6% and bacterial pneumonia 15% of all bacterial infections (10).

TB/HIV co-infection

South Africa has a high prevalence of TB and HIV co-infection. The HIV positive population provides a unique challenge as they may have diagnostic delay, be infectious for longer and may have poorer treatment outcomes if not properly managed. There is a decrease in mortality due to HIV and TB co-infection of 44 – 70% for individuals who are initiated on ART. Similarly, a CD4 count of <200 cells/µL was associated with increased morbidity and mortality and these patients should be fast-tracked for ART (9). It is therefore essential to exclude and screen for active TB, by asking questions about TB symptoms in all pregnant women who are HIV positive at every antenatal visit. According to the guidelines, all pregnant women who are HIV positive qualify for isoniazid preventative therapy (IP) provided that active TB infection is ruled out as this would result in a single agent being used to treat TB and add to the burden of drug resistance. Any patient who presents with one or more of the symptoms bellow, must be investigated further for active TB.

TB symptoms:

- Current cough of any duration
- Drenching night sweats
- Persistent fever for more than 2 weeks
- Unexplained weight loss or failure to gain weight in pregnancy

IPT should be started at any time during pregnancy/breastfeeding but should be started one month after initiation of ART. Tuberculin Skin Test (TST) is used to determine the duration of IPT. If the TST is negative or unavailable then IPT is given for 12 months duration, and if TST is positive, IPT is given for 36 months. Isoniazid has several undesirable side effects such as peripheral neuropathy, hepatotoxicity, gastrointestinal side-effects, flushing and hypersensitivity reactions that patients should we be made aware of. There are also side effects from the current ART combination needs to

be used with caution or a change in ARV may be necessary in light of certain comorbid conditions. Of particular importance is the need for routine creatinine testing when initiating ART in pregnancy (4).

Creatinine Monitoring

Tenofovir Disoproxil fumarate (TDF) has become part of the first line regimen for ART and in South Africa, the current FDC preparation is TDF- based. TDF is linked with proximal renal tubulopathy and impaired glomerular filtration the effects of which are reversed with cessation of TDF usage. Abnormalities in proximal renal secretion of TDF may lead to accumulation in renal tubular cells causing toxicity. Potential risk factors for toxicity include pre-existing renal disease, diabetes mellitus, hypertension, a baseline CD4 count of < 200 cells/µL and administration of Ritonavir-boosted protease inhibitors in combination with TDF (12). Therefore, because of the impact on renal glomerular and tubular functions it stands to reason that baseline and routine monitoring of renal function is necessary for creatinine levels during pregnancy and glomerular filtration rate is an unreliable marker during pregnancy. According to the 2015 South African Guidelines, creatinine is done at the first visit and repeated at 3, 6, 12 months during pregnancy and the postpartum period. TDF is contraindicated if the creatinine is > 85 µmol/L or if there is evidence of uncontrolled hypertension and diabetes with renal dysfunction, the patient should be initiated on second line drugs (4).

In conclusion, the goal of comprehensive PMTCT programmes is to achieve viral suppression in pregnant and breastfeeding women and hence the risk of MTCT will be significantly reduced. This has far reaching implications for South Africa as a middle-income country and also globally as South Africa bears the majority of the HIV burden in Sub-Saharan Africa. Not only is the PMTCT programme driven towards prevention of HIV transmission during pregnancy and breastfeeding but also the health of women of reproductive age is a key factor in the continuum of care. The success of PMTCT programmes is ultimately defined by the percentage of new neonatal and infant HIV infections that occur during pregnancy and the breastfeeding period. Adherence to routine monitoring and appropriate management reflects the quality of care in PMTCT programmes. For the purposes of this study, only the birth PCR will be included in the assessment of routine monitoring of the HIV exposed infant.

Study Aim

The aim of this study is to assess routine clinical and laboratory monitoring of HIV- positive pregnant women who delivered at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 1 January 2017 to 30 June 2017, in accordance with the revised South African PMTCT guidelines.

Study Objectives

1. To evaluate the collection of standard baseline blood tests i.e., CD4 count, viral load and creatinine, in HIV-positive pregnant women started on ART.
2. To describe routine laboratory and clinical monitoring during the antenatal period until delivery in women on ART.
3. To assess the documentation of laboratory results and actions taken with abnormal results.
4. To evaluate documentation of clinical screening for pulmonary TB and initiation of IPT.
5. To assess the initiation of appropriate prophylaxis for opportunistic infections based on a CD4 count.
6. To evaluate birth PCR testing for all HIV-exposed neonates and to assess if the appropriate prophylaxis was given according to the risk profile of the mother.

Study Methods

Study Population

The study population will include all HIV positive pregnant women who delivered at CMJAH, from 1 January 2017 to 30 June 2017. There are on average 600 live births per month at CMJAH with approximately 30% of the patient's HIV positive. The expected number of births from HIV positive women is therefore approximately 1080 births within the stipulated time period. The study sample of approximately 200 participants will be randomly selected by choosing every third entry of a live birth from an HIV positive woman in the labour ward and caesarean section theatre register.

Site of Study

The study will take place at CMJAH situated in Parktown, Johannesburg. CMJAH is a tertiary hospital and forms part of the main training and teaching hospitals for the University of the Witwatersrand. The hospital also serves as a referral centre for secondary and district hospitals and community health centres in the catchment area.

Study Design

This will be a retrospective review of antenatal and delivery records of HIV-positive women delivering at CMJAH during the study period. The target group will be selected from registers in the labour ward, obstetrics theatre and postnatal wards. The records will be retrieved from the records room. Results not documented in patient records will be checked on the National Health Laboratory Service (NHLS) labtrack website. The patients name, surname and hospital number will be used to check if blood tests were done and results not recorded.

Data capturing

Data will be extracted from antenatal and delivery records using a standardised data sheet (Appendix A). The data will be captured on an electronic data capturing system, REDCap, and will then be exported onto STATA analytical software for analysis.

Data Analysis

Continuous data will be assessed for normality and where appropriate presented as means and standard deviations, and medians and interquartile ranges. Categorical data will be summarised as frequencies and percentages and the relationships between the categorical data will be assessed using a chi – square test at a significance level of p=0.05.

Ethics

Ethics clearance is still to be obtained from the Human Research Ethics Committee of the University of the Witwatersrand. An application will be made on 7 March 2018. Participants will be kept anonymous and only the researcher and supervisors will have access to personal details. Personal details from the study sample will only be used for data extraction purposes. The project will be registered online with the National Health Research Database in order to obtain CEO approval.

Study limitations

One possible limitations of the study is that some patient records may not be found, thus compromising the study sample. Also, if patient records have inadequate details, the study sample may also be compromised. Another limitation is that this will be a retrospective study.

Timing

	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Literature review														
Preparation of protocol														
Protocol assessment														
Ethics application														
Data collection														
Data analysis														
Write up														
Paper write up														

Funding

All costs will be the responsibility of the research candidate including transport, stationery, photocopying and printing of any materials.

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Data sheet

Participant number_____

Study number_____

Age ____ Parity ____ Gravidity ____ Heamoglobin_____

Booking facility

□Tertiary hospital
□Secondary hospital
□ District Hospital
□Community Health Centre (CHC)
□ Unbooked
□ Other

Referral facility

☐Rahima Moosa Hospital
☐South Rand Hospital
☐Chris Hani Baragwanath Academic Hospital
☐Edenvale Hospital
☐Thelle Mogoerane Hospital
☐Tambo Memorial Hospital
☐Hilbrow CHC
☐Yeoville CHC
☐Witkoppen CHC
☐Jeppe Park CHC
☐Alexandra CHC
☐Other

Gestational age at booking _____

Details of HIV Diagnosis

□Pre-Pregnancy Date/ Year _____
□Antenatal
□ Intrapartum
□ Postpartum
□Test not done

Antiretroviral therapy

Initiation □Pre-pregnancy
□Antenatal
Gestational age at initiation _____

□Post-partum
□ Unknown

Regimen □No treatment given
□FDC (Atrozia)

□2nd line agents

□ Other, specify _____

Change of regimen during pregnancy □Yes □No

Reason for change □Treatment failure

□Side effects

□ Other, specify _____

Baseline Bloods

Creatinine

Barcode in file Y□ N□

□Results not checked

□Test not done

□ <85

□ >85

Actual value _____

Routine repeat test □Y □N

□ 3 months

□ 6 months

□ Inappropriate

Test done for another indication □ Hypertensive disorder

□Renal disease

□Elective caesarean section

□other_____

CD4

Gestational age at testing _____

□ Barcode in file Y□ N□

□Test not done

□ Result not checked

Result: □ <100

□ ≤101 – 200

□ ≤ 350

□ ≥ 351

Actual value _____

Cryptococcal screening done □Y □N

CrAg testing □Positive □Negative

Cryptococcal prophylaxis □Y □N

IPT □Y □N

Routine clinical TB screening □Y □N

Co-trimoxazole prophylaxis □Y □N

Viral load

Gestational age at testing _____

Barcode in file Y□ N□

□Test Not done

□Result not checked

Duration on ART when viral load done _____

Result □ LDL

□ 100 - 400 copies

□ 401 - 1000 copies

□ > 1000 copies

Actual Value_____

Repeat testing □Y □N

If yes □Routine □Adherence monitoring□Treatment failure

Result of repeat _____

Birth PCR

Gestational age at delivery _____ Birth weight _____

Barcode in file Y□ N□

□Test not done

□Results not checked

Result □ Positive

□ Negative

□ Indeterminate

ARV prophylaxis given □Y □N

□NVP for 6 weeks

□NVP for 12 weeks

□NVP and AZT for 6 weeks

□Triple ARV prophylaxis Duration_____

□Other, Specify _____

E. HREC clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Kgwerano Khulu

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180331

NAME: (Principal Investigator)	Dr Kgwerano Khulu
DEPARTMENT:	Obstetrics and Gynaecology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Routine Laboratory and Clinical Monitoring of HIV-Positive Pregnant Women on Anti-Retroviral Therapy
DATE CONSIDERED:	06/04/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr CN Mnyani
APPROVED BY:	Doctor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	09/11/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in March and will therefore be due in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

7 July 2019
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES