A SITUATION ANALYSIS OF THE PMTCT PROGRAMME BETWEEN 2013 AND 2014 IN THE ETHEKWINI MUNICIPALITY

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"As the candidate's supervisor I agree/~~do not agree~~ to the submission of this dissertation"

Supervisor:  **Date:** 18 March 2015

DEDICATION

For Hanna

Who makes it all worth while

And my parents

Who made it possible

Shukran

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Firstly, I would like to acknowledge the sisters in charge, hospital and nursing managers of the various clinics I visited, thank you for accommodating me and all my questions.

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DECLARATION

I Munira Khan declare that:

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ABSTRACT

Background

The contribution of the human immunodeficiency virus (HIV) epidemic to morbidity and mortality in pregnancy has been well documented. Effective antiretroviral treatment (ART) improves maternal and newborn health as well as preventing mother-to-child transmission (PMTCT); yet access to ART for PMTCT in low and middle income countries only reached 62% (66-85%) in 2012. Of the pregnant women who required ART for their own health, 58% accessed treatment. Provider initiated HIV counseling and testing in a number of health care facilities including antenatal clinics, was recommended in an attempt to improve health outcomes within the expanding HIV epidemic. Further, screening for tuberculosis and initiation of isoniazid prophylaxis is advised in high risk groups. The main aim of the study was to explore the implementation of guidelines for the management of both seropositive and seronegative pregnant women as limited information is available in three key areas in the continuum of care for pregnant women: firstly, time to initiation of ART in women living with HIV; secondly, the implementation of the TB screening processes during pregnancy; and thirdly, follow-up (HIV) testing in uninfected pregnant women.

Methods

An exploratory, observational, cross sectional study design presenting both descriptive and analytic statistics was used. A two stage cluster sampling using a 30X7 strategy was applied in the selection of antenatal clinics within the

metropolitan district. Data from records of eligible women between 32 and 36 weeks gestation was captured onto a data collection sheet. Demographic data and details of ART initiation, TB screening and repeat HIV testing practices were collected. All data was then entered onto a Microsoft Excel spreadsheet for importing into SPSS for processing and analysis.

Measures of central tendency were used and chi squared tests and the Mann Whitney tests were applied for the analytic component of the study.

Results

Data was collected from records of 420 women, 210 were recorded seropositive and 210 were recorded seronegative at initial presentation. Overall, records show 202 women (48%) presented before 20 weeks gestation. Nurse initiation of ART occurred upon diagnosis of HIV infection was documented in 97% of women; TB screening practices however did not appear to be consistent and differed statistically according to administrative authority. The offer of a repeat HIV test to those women who initially tested uninfected was recorded to be offered at a standard rather than an individualised time point. Acute seroconversion was recorded in eight women. Statistically significant associations between HIV status and both median gestational age at first antenatal contact and age (in years) as well as between administrative authority and TB screening practices were found.

Discussion, conclusion and recommendations

Implementation of national guidelines for the management of pregnant women does not appear to be consistent within or across sampled clinics. Successful integration

of HIV services was documented; however TB screening processes and feedback mechanisms following referral require strengthening. Deferment and delays in repeat testing in women who initially test seronegative are particularly concerning. Training and support of health care workers on the value of complete medical records for the overall management and continuity of care of a pregnant female is essential. Further, the benefit in implementation of national guidelines in relation to PMTCT must be highlighted.

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Definition of Terms

Antiretroviral therapy in pregnancy is a combination of three antiretroviral drugs. National PMTCT antiretroviral guidelines currently recommend a fixed dose combination of lamivudine or emtracitabine, tenofovir and efavirenz, provided that there are no contra indications to any of the drugs [1].

Maternal mortality: maternal deaths that occur during pregnancy, delivery or within 42 days following delivery (in the postpartum period) [2].

Option A provides pregnant women with prophylaxis during pregnancy with zidovudine (AZT) alone and additional antiretroviral (ART) medications are provided during labor, delivery, and the postpartum period. Infants are also provided with antiretroviral medication [3].

Option B provides pregnant women with triple-drug ART during pregnancy and breastfeeding. Infants are also provided with antiretroviral medication with this option [3].

Option B+ is a modification of Option B proposed by the 2010 WHO PMTCT recommendations in which all HIV-infected pregnant and breastfeeding women are eligible for lifelong antiretroviral therapy (ART) regardless of CD4 count [3].

Preventing mother–to-child transmission (PMTCT): Preventing the transmission of the HI virus from mother to child during the antenatal, perinatal and postnatal periods [1].

Re testing is the repeat HIV rapid testing offered to women who initially test uninfected at their first antenatal visit [1].

Seroconversion is the development of antibodies to the HI virus [1].

List of Abbreviations

ANC	Antenatal care
ART	Antiretroviral therapy
CD4	Cluster of differentiation 4
FDC	Fixed Dose Combination
HCW	Health care worker
HIV	Human immunodeficiency virus
INH	Isoniazid
MDG	Millennium development goal
MMR	Maternal mortality ratio
MTCT	Mother-to-child transmission
NIMART	Nurse initiated management of antiretroviral therapy
OI	Opportunistic infection
PCP	*Pneumocystis jirovecci* pneumonia
PMTCT	Preventing mother-to-child transmission
SSA	sub-Saharan Africa
SPSS	Statistical package, originally used as a Statistical Package for the Social Sciences
TB	Tuberculosis
UNAIDS	Joint United Nation Programme on HIV and AIDS
WHO	World Health Organisation

Chapter One: Introduction

1. 1 Introduction

Globally, women account for over half of the estimated number of people living with human immunodeficiency virus (HIV), with the highest burden of disease concentrated in women in the reproductive age group [4]. The impact on maternal morbidity and mortality is considerable. Of the deaths that occurred in women worldwide, an estimated 1.5 million occurred in women of childbearing potential living with HIV [5]. Furthermore, vertical transmission of HIV from mother to child during pregnancy, labour and delivery or during breastfeeding has been identified as the primary source of childhood HIV infections.

Antiretroviral interventions implemented during pregnancy and breastfeeding have impacted positively on maternal health and on vertical transmission of HIV from mother to child [6-11]. Access to effective antiretroviral treatment (ART) reached an estimated 62% (66-85%) in low and middle income countries with 58% of pregnant women who required ART for their own health accessing treatment [4]. Antiretroviral coverage for preventing mother-to-child transmission (PMTCT) expanded to 83% [75%-90%] within sub-Saharan Africa (SSA) with a resultant mother-to-child transmission (MTCT) of 7% [4].

Antenatal care (ANC) is often the first point of contact with health services for many women living with HIV. Provider initiated HIV counseling and testing is currently the standard of care within health care facilities worldwide and is identified as a key objective in the South African National HIV and AIDS and STI Strategic Plan [12]. The

provision of HIV services within ANC simplifies access to HIV rapid testing and facilitates the introduction of an appropriate PMTCT intervention [3]. The guidelines state that first time antenatal attendees should be counselled on the benefits and consequences of an HIV test. Rapid HIV tests are performed and women receive post test counseling [1]. Women who test seronegative should be offered a repeat HIV test after 12 weeks and/ or between 32 and 36 weeks of gestation. It is recommended that women diagnosed with HIV be initiated on ART on the same day of diagnosis. Additional procedures at this first visit involve screening for opportunistic infections particularly TB and obtaining CD4 assays [1].

Some of the measures of successful implementation of the national guidelines include known HIV status at first antenatal booking, access to ART in pregnancy, offer of a repeat test in seronegative women, transmission of HIV from mother-to-child and the impact of an appropriate intervention on maternal and newborn morbidity and mortality. These outcome measures are designed to assess the realisation of the national PMTCT guidelines and are evaluated annually in the antenatal sentinel survey [1].

1. 2 Background

The current South African national PMTCT policy has been extended beyond a purely PMTCT approach, rather a broader maternal and newborn health approach has been adopted. The four elements of this policy include primary prevention of HIV, especially among women of child-bearing age; integration of HIV interventions with basic

antenatal care, sexual and reproductive health, child and adolescent health and TB services; strengthening postnatal care for the mother-baby pair and provision of an expanded package of PMTCT services [1].

The national antenatal HIV prevalence is 29.5% (95% CI: 28.7 – 30.2) with an estimated prevalence of 37.4% (95% CI: 35.8 – 39.0%) in KwaZulu-Natal [13]. A number of districts within KwaZulu-Natal have a higher antenatal HIV prevalence than the national prevalence, including the eThekwini Metropolitan District with an estimated prevalence of 38% [13]. The HIV prevalence amongst 15 to 49 year olds living in KZN was 27.6% in 2012. A 10% gender difference in HIV prevalence was documented in this age category with a higher prevalence in females. An estimated 82.7% of pregnant women from KZN were tested for HIV with antenatal ART initiation occurring in 85.4% of those infected between 2013 and 2014. Fifty six percent of women attended antenatal clinics prior to 20 weeks of gestation during this time frame [13].

The recent Savings Mothers report, on maternal deaths in South Africa between 2008 and 2010, identified HIV infection as the commonest non pregnancy related contributor to maternal deaths [6]. The institutional maternal mortality ratio (MMR) in HIV infected women was almost six fold higher than that in HIV uninfected women [14].

Tuberculosis has been identified as one of the commonest opportunistic infections in women in the reproductive age group. Further TB is classified as the leading cause of non-obstetric related maternal deaths in South Africa [14]. Antenatal contact provides

the opportunity to screen for TB as early detection and treatment improves maternal and neonatal outcomes [15]. The intertwining of the TB and HIV epidemics in young women, and the individual and combined impact of TB and HIV on both maternal and neonatal outcomes, is striking [15-20].

Implementation of the national PMTCT guidelines for the management of pregnant women is critical to the outcome of the mother-baby dyad. However, the extent of implementation of the guidelines by health care workers in the management of seropositive and seronegative pregnant women is largely unknown.

1. 3 Problem statement

Despite the overwhelming impact of HIV on maternal and child health globally, few countries have achieved the 2015 target of 90% ART coverage during pregnancy. Successful programmes in high income countries have attained high coverage, thus reducing MTCT to 1%. However, ART coverage in low and middle income countries is 62% (66%-85%) [4]. Consequently, MTCT remains high in low income countries due to lack of intervention, and is estimated to be between 15 and 40% [21]. Mother to child transmission in South Africa has decreased from 13% in 2009 to 7% in 2012 [21]. The number of new HIV infections in South African children decreased by 46% between 2009 and 2012 with an estimated 21 000 children acquiring HIV in 2012 compared to an estimated 38 000 in 2009 [4]. Revision and implementation of guidelines for the management of HIV in pregnancy and guidelines for PMTCT have contributed to this achievement.

Although guidelines exist for the optimal management of women during the antenatal period, limited success on improved maternal outcomes and MTCT is apparent. Factors contributing to the partial success of the SA PMTCT programme need to be investigated. Information is available on certain aspects of antenatal care. However, inadequate information is available in three key areas in the continuum of care for pregnant women. These include: firstly, time to initiation of antiretroviral therapy (ART) following presentation at ANC in women living with HIV; secondly, the implementation of the TB screening processes during pregnancy; and thirdly, follow-up (HIV) testing in uninfected pregnant women.

1.4 Aims

In light of what remains unknown, as discussed above, this study aimed to explore the implementation of the national guidelines for the management of both seropositive and seronegative pregnant women in antenatal care in the metropolitan district of eThekwini.

1.5 Objectives

Aligned with the above aim, specific study objectives were developed to assess the implementation of national guidelines with regard to pregnant women who at initiation of ANC were found to be seropositive, and with regard to those that were found to seronegative.

The study objectives for women who were found to be HIV infected at the initiation of ANC were to determine:

- the median gestational age at diagnosis of HIV infection;
- the median gestational age at initiation of antiretroviral treatment;
- the distribution of CD4 counts;
- screening practices for tuberculosis and opportunistic infections.

The study objectives for women who were found to be HIV uninfected at initiation of ANC were to determine:

- the median gestational age at initial and repeat HIV test;
- the proportion who seroconvert during pregnancy.

The rationale for the study was to identify potential barriers to the successful implementation of the national guidelines which could be addressed to improve maternal and newborn outcomes. Further, this exploratory component of the study could provide the basis for future research studies.

1.6 Organisation of the dissertation

This chapter provides an introduction and background to the problem statement, as well as the aims and objectives of the study.

Chapter two contains the literature review focusing on the burden of HIV disease in women in the reproductive age group, the impact of HIV infection on maternal and neonatal outcomes and the implementation of PMTCT guidelines to improve these outcomes.

Chapter three comprises a journal manuscript which will be submitted to BMC Health Services Research Journal, and has thus been prepared according to the guidelines to authors for the journal. The instructions to authors are contained in the appendices and the contribution of each author is defined within the manuscript.

Chapter four is the final chapter and includes an integrative discussion, recommendations and limitations.

The appendices which follow chapter 4 include the protocol submitted to the post graduate research committee, figures not included in the manuscript, the approvals required for the conduct of the study and the guidelines to authors for the journal submission.

Chapter Two: Literature review

2. 1 Introduction

A literature review is presented in this chapter. Section one contextualises the burden of HIV disease in women. Section two describes the impact of antenatal HIV infection on maternal and neonatal outcomes. The third section discusses the practical aspects of the management of seropositive pregnant women with the challenges, successes and evolution of the PMTCT programme, as well as the integration of HIV services into antenatal care in an effort to improve maternal and newborn health. The significance of the continuum of care for women who test HIV uninfected at their first antenatal visit is highlighted in the latter part of the third section.

The search strategy applied to identify articles relevant to this literature review used a combination of keywords and terms related to HIV prevention, PMTCT, pregnancy, antenatal TB, impact and outcomes of HIV infection in pregnancy in the PubMed, Ovid and Cochrane databases, as well as publications by the South African Department of Health, the World Health Organisation (WHO) and the Joint United Nation Programme on HIV and AIDS (UNAIDS). The limiters applied to the search of electronic databases were for articles published in English in the last 15 years. For publications emanating from national and international organisations, the focus was on publications in the last five years.

2. 2 The burden of HIV infection in women

An estimated 35.3 million people [range 32.2–38.8 million] were living with HIV at the end of 2012 [4]. Sub-Saharan Africa (SSA) continues to bear the burden of disease with 71% of the epidemic evidenced in this region. Further, despite the reported decline in the number of new infections, adults and children in SSA were responsible for 70% of incident cases [4]. Women and girls account for 58% of those living with HIV, with the highest burden of disease in the reproductive age group.

Approximately 90% of pregnant women living with HIV reside in 22 high priority countries, 21 of which are located in SSA [21]. South Africa ranks fourth amongst these high priority countries, where the number of pregnant women living with HIV is estimated to be 280 000 [22]. The estimated South African national HIV antenatal prevalence is 29.5% (95% CI: 28.7–30.2) with an estimated prevalence of 37.4% (95% CI: 35.8–39.0) in KwaZulu-Natal [13]. A number of districts within KwaZulu-Natal have a higher HIV antenatal prevalence than the national prevalence including the eThekwini Metropolitan District with an estimated prevalence of 38% [13]. The peak of the epidemic is seen in young women between the ages of 15 and 24 years, with an estimated prevalence in this age group of 20.5% (95% CI 19.7-21.3). Strategies to improve maternal and newborn health against this backdrop, are outlined in the four pronged approach set out in the national guidelines for the management of HIV in pregnancy [1].

Globally, more than 90% of childhood HIV infections are due to vertical transmission of the virus during pregnancy, labour and delivery or breastfeeding. In 2012, an estimated 3.5 million children (range 1.7 million-3.4 million) were living with HIV, approximately 260 000 (range 230 000–320 000) acquired HIV infection and 210 000 (190 000-250 000) children died from AIDS-related illnesses [4].

Provision of antiretroviral interventions in low and middle income countries has prevented an estimated 850 000 children from acquiring HIV infection between 2005 and 2012 [22]. Clinical trials have shown a triple drug combination to be more efficacious than single and dual therapy when provided during pregnancy for the management of maternal HIV infection. Antenatal ART offered to women not eligible for ART for their own health, reduced MTCT rates to 4.9% and 5.4% at six months and one year postpartum respectively in Kenya, Burkino Faso and South Africa [6]. In women requiring ART for their own health, transmission rates of 4.9% four to six weeks post delivery [7] and 2.3% one year post delivery [8] were achieved. Additional interventional strategies have extended beyond the antenatal period into the breastfeeding period to prolong the protection afforded to the infant. These strategies have lowered the MTCT rates in Kenya to 5.0%, 5.7% and 7.0% at 6, 12 and 24 months respectively [9]. Comparable MTCT rates were seen six months postpartum in Tanzania [10] and Botswana [11].

In addition to the diagnosis and appropriate management of HIV infection in pregnancy, other efforts to limit the HIV epidemic have been mobilised. Counselling

and testing of couples, provision of ART to sero discordant couples [23] and extension of PMTCT coverage into the breastfeeding period [6,9,10] form part of these efforts.

2. 3 The Impact of Antenatal HIV infection on Maternal and Neonatal Outcomes

2.3.1 Contribution of HIV infection to Maternal Mortality

The impact of the HIV epidemic on maternal and neonatal mortality has been well documented [14,24,25]. Deaths that occurred in women of the reproductive age group were estimated at 3.5 million in 2010 [5]. Women living with HIV/AIDS accounted for 1.5 million of these deaths [5]. The UNAIDS recorded a reduction in the number of HIV-related deaths during pregnancy and within 42 days post delivery from an estimated 46 000 (23 000–93 000) deaths in 2005 to 37 000 (18 000–76 000) in 2010 [26]. Improved access to ART coupled with the natural history of the HIV epidemic contributed to this decline.

The fifth millennium development goal (MDG 5) is aimed at improving maternal health and progress towards this goal was assessed by collating data on maternal deaths from 181 countries [27]. A distinct difference in MMRs was observed between high and low income countries and in the relative contribution of HIV to maternal mortality. The overall MMR was estimated at 210 per 100 000 live births (170-300 per 100 000) with the MMR in developing regions 15 times higher than in developed regions. Causes of death were categorised as direct or indirect, with HIV classified as an indirect cause. An estimated 19 000 maternal deaths globally were as a

consequence of HIV infection, with 17 000 of these deaths concentrated in SSA. Reports from SSA also demonstrate a higher MMR in women living with HIV as compared to those who are HIV uninfected [28-30]. Maternal deaths only occurred in women living with HIV as compared to those who were not, in a multi centre study in Malawi, Tanzania and Zambia [28]. The MMR in HIV infected women in Uganda was 6.2 fold (95% CI 1.98- 14.93) [30] higher than the MMR in HIV uninfected women. The MMR in the same categories of pregnant women in South Africa was 0.8 fold lower than in Uganda [29]. Detailed analysis of maternal deaths in South Africa is undertaken by the committee for Saving Mothers.

The Saving Mothers Report is a confidential enquiry into maternal deaths in South Africa. The recent fifth Saving Mothers report showed an increase in the institutional MMR to 176.2 per 100 000 live births between 2008 and 2010 [14]. Non pregnancy related causes were the commonest contributor to maternal deaths with HIV infection diagnosed in 70.4% of deaths. Interventions for infected women were possible antenatally as the diagnosis of HIV infection was made in 52% of mothers during pregnancy and 61% of the deaths occurred postnatally. Tuberculosis (26.9%), *Pneumocystis jirovecci* pneumonia [PCP] (13.3%) and non-specified pneumonia (26%) were the prevalent respiratory complications identified amongst women diagnosed with HIV. The recommendations for reducing maternal mortality in the fifth report are fundamentally the same as those in the first report [14]. Screening for and management of opportunistic infections (OIs) must be optimised [14,29]. Health care worker training, support and supervision, adequate staffing, establishment and

strengthening of referral pathways, access to ART and laboratory tests are some of the critical factors which need to be addressed [14,31,32].

2.3.2 Impact of HIV infection on Maternal Morbidity

Complications associated with maternal HIV infection include pre term labour, spontaneous abortions and OIs [33]. Opportunistic infections in pregnancy increase the risk of transmission of HIV as well as other organisms to the neonate. Disseminated cytomegalovirus is one of the most common OIs seen in advanced HIV with cytomegalovirus being the commonest transplacental infection documented in neonates [33]. Antepartum pneumonias due to PCP, *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* are significant contributors to maternal morbidity and mortality [14,33]. Complications associated with treatment of OIs, in particular fungal infections, have also been documented [33].

Tuberculosis is an opportunistic infection of public health concern. The latest World Health Report estimated 8.6 million incident cases and 1.3 million deaths as a result of TB in 2012 [34]. Co-infection with HIV occurred in approximately 13% of TB cases with 75% of the HIV infected new TB cases being concentrated in the African region [34]. South Africa ranked third amongst 22 high TB burden countries with an incidence of 1003 per 100 000 [34]. In South Africa, KwaZulu-Natal is at the epicentre of both the TB and HIV epidemics.

The HIV epidemic has shifted the burden of TB disease to women of reproductive age with the peak of both epidemics converging in this age group [35]. Females accounted

for 2.9 million of the 8.6 million incident cases of TB. Further 410 000 of the 1.3 million TB deaths occurred in females, 160 000 of whom were HIV co infected. The consequences of co-infection in pregnancy include pre term labour, maternal mortality [15] and an acceleration of the HIV replicative and disease processes.

The contribution of antepartum TB to maternal and neonatal morbidity and mortality is evident [16-18]. Tuberculosis is also recognised as an independent risk factor for the vertical transmission of HIV [19,20]. Prevention of active disease is therefore critical in highly endemic areas of HIV and TB and recommended collaborative TB and HIV activities for prevention include intensified case finding, isoniazid (INH) prophylaxis and infection control. In 2012, only 66% of people living with HIV who presented for health care were screened for TB and INH initiation occurred in 520 000 (31%) new persons [34]. Pregnant women are considered at high risk for TB and therefore the expanded package of PMTCT services advises the administration of the TB symptom questionnaire at first antenatal contact [1]. Training of nurses to administer the TB symptom questionnaire within antenatal clinics improved coverage of TB screening and active cases of TB were detected [36,37].

A six month course of INH is advised upon the exclusion of TB symptoms [38]. The benefit of INH use in reducing active disease, the duration of prophylaxis, and the screening tests needed to exclude active disease remain controversial [39-41]. Additionally there is a lack of data on the tolerance, safety, side effects, efficacy and levels of adherence in the pregnant population to INH as well as a lack of clarity on timing of INH use in relation to antiretroviral treatment. The prescription of INH is further influenced by health care worker concerns regarding resistance, lack of recent training and unfamiliarity with national guidelines [42,43]. However, the provision of

ART together with regular screening for TB at antenatal contact visits could potentially improve adverse maternal and neonatal outcomes associated with TB and HIV.

2.3.3 Contribution of Maternal HIV Infection to Neonatal Morbidity and Mortality

Maternal HIV infection and neonatal outcomes are closely intertwined. Gestational exposure to HIV can result in stillbirths, low birth weight neonates, preterm deliveries, and an increased rate of neonatal mortality [28,32,44]. These outcomes are more likely if mothers experienced a serious adverse event or had advanced disease [28,44]. Tuberculosis predominantly affects women in the reproductive age group and prematurity, small for gestational age newborns, low birth weight, and perinatal death are associated complications [45,46]. These complications, as with maternal HIV infection, are more evident with advanced (maternal) disease. Maternal co-infection can result in fetal growth restriction, congenital TB and neonatal mortality [15]. Lastly, the risk of vertical transmission of HIV and TB from mother to child is increased with advanced untreated disease or late initiation of treatment during pregnancy. This impact on neonatal outcomes underscores the need for intensified antenatal TB screening, appropriate implementation of PMTCT and TB guidelines and timeous linkage to interventions for both diseases.

2.3.4 Social impact of maternal HIV infection

The social impact of HIV infection is multifaceted. The immediate impact on households and family structure is the loss of a parent and/or caregiver. However, the number of orphans has stabilized following the establishment of the ART programme in South Africa as the lives of those living with HIV has been prolonged and improved. The overall orphanhood prevalence in South Africa is 16.9% [47] with the highest number of orphans concentrated in KwaZulu-Natal. This could be a reflection of the provincial HIV prevalence as well as the quality of services available to those individuals living with HIV. Child headed households have emerged following the loss of a parent and/ or caregiver, with the child then being responsible for the provision of daily needs [48].

Aside from orphanhood and the associated consequences, fear of stigma and disclosure remain widespread issues impacting on health seeking behaviour in SSA [49]. Both these factors influence attendance at maternal and child health clinics, as well as initiation and maintenance of the appropriate ART intervention for both mother and child [49,50,48]. Other factors affecting treatment access are concerns of gender based violence and abandonment [51].

Addressing and improving the social factors impacting on access to HIV services would ultimately benefit both mother and child.

2. 4 Guidelines for the Management of HIV infection in pregnancy

The management of HIV in pregnancy initially focused on a PMTCT intervention in the antenatal period. The guidelines have subsequently developed to incorporate a comprehensive maternal and newborn health service extending from the antenatal to the postnatal period. The historical progression of the PMTCT guidelines and its integration into health care systems is outlined below.

2.4.1 Evolution of PMTCT Guidelines

Programmes aimed at reducing MTCT have evolved with evidence based research and practice to integrate HIV prevention, care and treatment into the package of maternal, neonatal and child health and nutrition services. Antenatal care provides an entry point into health care for women living with HIV. The first step in linkage to appropriate care in the antenatal period is the offer of an HIV test. Provider initiated HIV counseling and testing was recommended in an attempt to improve access [3,52]. The integration of HIV services into antenatal services is aimed at expediting access to HIV rapid testing and initiation of ART during pregnancy.

Triple ART was recommended by the World Health Organization in 2013 for all pregnant women for the duration of MTCT risk [53]. Women who qualify for ART for their own health should continue on lifelong therapy and countries with generalised HIV epidemics are advised to adopt this approach. Women who are not eligible for lifelong ART are advised to continue ART until the risk for MTCT ceases [53].

The decision to initiate lifelong ART in pregnancy was previously based on clinical and immunological staging. Women living with HIV were then assessed for Option A or Option B [3]. Option A recommended the use of different ART during the antenatal, intrapartum and postpartum periods. Initially Option A was recommended at the onset of pregnancy [54], earlier initiation during the first trimester of pregnancy was recommended in the later guidelines [3]. The quality of evidence for this recommendation is low and based on observational studies which demonstrated the benefit of early prophylaxis in the prevention of in utero transmission of HIV. Reports of drug resistance [55] and virologic failure following single dose nevirapine use [56] prompted the addition of other ARTs to Option A [57,58]. The challenges associated with Option A included the changes in ART from the antenatal to the postpartum periods for both the patient and the health care worker (HCW) and the requirement of a CD4 count prior to ART initiation.

In comparison, all pregnant women are initiated and maintained on a fixed drug combination from 14 weeks gestational age until post delivery with Option B [3]. This latter option is identical to the treatment used in the non pregnant population and is a simpler, more practical alternative for HCWs. A baseline CD4 count result prior to ART initiation is also not necessary and with same day initiation, an improvement in PMTCT coverage was anticipated.

Malawi introduced Option B+ mid 2011 in an attempt to accelerate ART coverage during pregnancy and to decrease the incidence of HIV infection in children [59,60]. A seven fold increase in PMTCT coverage was documented following the introduction of

Option B+ [60]. This achievement resulted from the decentralization of services, expansion and integration of ART sites into existing antenatal services, training of HCWs and commitment from the Ministry of Health [60]. Seventy seven percent of women initiated on ART were retained in care one year later [60]. Different "models of care" however were used to introduce Option B+ within health care facilities in Malawi. The impact of the choice of model on uptake of ART and retention within the programme in a defined area in Malawi, recently showed difficulties in continuum of care postdelivery [61]. A combination of health care factors and patient factors were responsible for the varying retention levels. In another report looking at factors responsible for 'loss to follow up' following initiation on Option B+ in Malawi, 20% of women who initiated ART during pregnancy or breastfeeding missed a scheduled appointment and 24% were lost to follow up within the first six months [62]. Loss to follow up occurred more frequently in the early stages of the programme, when ART was introduced during pregnancy and in younger women. Education and financial factors were other factors identified as barriers to retention in care [62].

Other long term concerns with option B+ include cost effectiveness, suboptimal adherence [63] and subsequent drug resistance and adverse pregnancy outcomes resulting from long term exposure to ART [64]. Despite the challenges associated with Option B+, 13 of the 22 Global Plan priority countries had adopted this strategy by June 2013 [22]. Clinical outcomes and retention within care have yet to be published. In a meta-analysis of 51 studies with 20 153 pregnant women, adequate adherence to treatment was achieved in only 73.5% (95% CI 69.3–77.5%) with poorer adherence observed in the postpartum period [63]. An early qualitative study from Tanzania

regarding the acceptability of the PMTCT options, found that participants favoured Option B over Option A [65]. Concerns related to long term adherence and side effects to treatment mirrored the Malawian experience.

The additional benefits associated with Option B+ are far reaching and include the protection for future pregnancies [66], improvement in maternal health and reduction in the transmission to HIV uninfected partners [67]. These advantages prompted a WHO programmatic update in 2012 [68] and the current consolidated guidelines of 2013 no longer recommend Option A [53]. The updated South African PMTCT guidelines were based on these WHO guidelines. All HIV infected pregnant women are to be initiated on ART at first antenatal interaction [1] with ART to be continued lifelong if the (maternal) CD4 count 350 cells/mm^3 and below. The duration of ART prophylaxis in women who have CD4 counts above this threshold is directed by infant feeding choice [1].

In summary, the choice of implementation of Option B or Option B+ is country dependent. New PMTCT policies have been adopted in a concerted effort to curb MTCT and achieve the MDGs four, five and six of reducing child mortality, improving maternal health and combating HIV, malaria and other diseases.

2.4.2 Integration of Guidelines into existing Programmes and The Role of Nurse Initiated Management of Antiretroviral Treatment

Integration of PMTCT interventions into existing maternal and child health services is considered to be the key to successful programmes. This strategy could possibly expand access, improve efficiency, effectiveness and quality of health facilities. In a South African study, time to initiation of ART in pregnancy was reduced by median number of 19 days with the integration of key HIV services within antenatal facilities in [69]. The number of Zambian women initiating ART during pregnancy doubled with the integration of ART into antenatal services; however, this did not improve duration on ART prior to delivery [70].

Nurse initiated management of ART (NIMART) is a task shifting strategy [59] adopted by the South African government to address the scale up required of public sector ART provision. By capacitating nurses to effectively initiate and manage stable patients on ART, fewer referrals and linkages to other health care facilities are required. Little has been written about the contribution of nurses to the antenatal sector in this regard [60,71]. In a comparison of time to initiation of ART prior to and following NIMART in five antenatal clinics in the Johannesburg Health District, a delay in ART initiation was found in four of the five facilities reviewed [71]. Suggested contributory factors include possible staff shortages and the dedication of certain clinic days to NIMART.

Integration of services provides a comprehensive service to patients and would impact on referrals and retention within the health care system. It is essential however to address health system factors affected by the increased workload.

2.4.3 Guidelines for dealing with pregnant women who test HIV uninfected at first antenatal visit

Pregnant women who test HIV uninfected at their first antenatal visit also require intensive follow up care. The World Health Organisation Guidelines of 2007 [63] as well as the current South African guidelines [1], advocate the re testing of this category of women 12 weeks after the initial test and/or between 32 and 36 weeks gestation.

Reports of acute seroconversion later in pregnancy and its contribution to the paediatric burden of disease are the basis for global concern. The increased risk of vertical transmission is linked to the viraemia associated with acute seroconversion [72,73]. In a mathematical model developed to estimate changes in MTCT in South Africa over time, it was calculated that by 2014, 34% (95% CI: 29%-39%) of MTCT would be due to seroconversion in pregnant women following their first antenatal booking and during breast feeding [74]. Additionally risky sexual behaviour following an initial seronegative result has been documented [72,73].

The risk of incident HIV in pregnancy remains controversial. Some reports from SSA reflect significant risk of incident HIV in pregnancy [75-77] with the incident rate per

100 person years ranging from 2.3 cases [75] to 10.7 cases [77]. Further, incidence was higher during pregnancy than non pregnancy [76,77]. The transmission of HIV from mother-to-child was not assessed in these three studies [75-77].There have been reports on the other hand, that show no increase in HIV risk during pregnancy [78,79]. Regardless of the risk, counseling messages should encompass HIV prevention strategies to remain seronegative.

International focus has shifted from a purely treatment based approach to include the prevention of incident HIV. Strategies aimed at protecting young women from HIV infection include the use of ART prior to and following high-risk exposure, vaginal microbicides, female condoms and medical male circumcision.

2.5 Challenges and Successes of Maternal and Newborn Health programmes

Despite the overwhelming impact of HIV on maternal and child health globally, few countries have achieved the 2015 target of 90% coverage of ART for PMTCT [4]. Successful PMTCT programmes in high income countries have reduced the MTCT rate to less than 1%. In the absence of a PMTCT intervention however, MTCT remains high in low income countries at 15% to 40% [4,80]. Access to effective ART for PMTCT in low and middle income countries reached 62% (66%-85%) in 2012 with only 58% of pregnant women who required ART for their own health accessing treatment [4]. Within SSA, antiretroviral coverage for PMTCT expanded to 83% (75%-90%) with a resultant MTCT rate of 7%. Botswana, Namibia, Zambia and Ghana achieved the 90%

coverage target whilst South Africa, Mozambique, Swaziland and Zimbabwe have made moderate progress towards this goal. The current concern is the deterioration in coverage detected in some countries [4].

Health system and patient related factors contribute to the successes and challenges associated with the PMTCT programme. Improved ART coverage and increased numbers of women accessing HIV testing reflect successes achieved by the programme [1]. Health system factors contributing to poor coverage include attrition along the PMTCT pathway, referral to ART clinics for initiation of ART, accessibility and availability of CD4 assays, complexity of national guidelines and a lack of HCW understanding of national guidelines [48,81]. Contributory patient factors include lack of knowledge, fear of stigma and non- disclosure [48,81]. Several high priority countries addressed some of these factors resulting in a 50% reduction in the estimated number of new infections among children. South Africa has made moderate strides towards achieving this latter goal.

The 90% target for PMTCT coverage has been achieved by some countries with a subsequent reduction in the number of incident cases in children. Comprehensive coverage globally however still needs to be achieved with renewed and concerted effort from all stakeholders. The continual revision of PMTCT guidelines is one such effort.

2.6 Summary of literature review

The literature review has highlighted the contribution of HIV and its associated opportunistic infections on both maternal and neonatal outcomes. Guidelines for the management of pregnant women have evolved based on evidence based research and have been implemented worldwide to reduce vertical transmission of HIV from mother to child. Achievement of 90% PMTCT coverage has been achieved in some countries, others continue to strive towards this goal. An improvement in access to HIV services has been documented in South Africa. Assessment of the implementation of national guidelines could further identify gaps in available information and obstacles to the implementation of PMTCT programme guidelines could be addressed.

Chapter Three: Journal Manuscript

Title page

A situation analysis of the PMTCT programme between 2013 and 2014 in a metropolitan district of KwaZulu-Natal

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Abstract

Background

The human immunodeficiency virus (HIV) epidemic has contributed significantly to maternal, newborn and childhood morbidity and mortality. Guidelines for the management of pregnant women form a basis for the care within health care systems. Few studies have evaluated the adequacy of the quality of care in primary health care facilities in South Africa. This study explored the implementation of national PMTCT and TB guidelines by health care workers in the management of seropositive and seronegative pregnant women. Initiation of ART and tuberculosis screening process in seropositive pregnant women and follow-up HIV rapid testing in seronegative pregnant women were assessed.

Methods

An exploratory, observational, cross sectional study design presenting both descriptive and analytic statistics was used. Thirty antenatal clinics within the metropolitan district were sampled using a 30x7 strategy and eligible women between 32 and 36 weeks gestation were enrolled. Variables of interest were captured onto a data collection sheet, entered onto a Microsoft Excel spreadsheet and imported into SPSS for processing and analysis. Measures of central tendency, chi squared tests and Wilcoxon rank tests were applied.

Results

Data was collected from records of 420 women, 210 were seropositive and 210 seronegative. Overall, 48.1% of women presented before 20 weeks gestation. Nurse initiation of ART upon diagnosis of HIV infection was documented in 96% of women;

TB screening practices however did not appear to be consistent and differed statistically according to administrative authority. Repeat HIV testing in women who were initially seronegative occurred at a standardised rather than an individualised time point. Seroconversion was recorded in eight women (4.5%).

Conclusion and interpretation and recommendations

Implementation of national guidelines for the management of pregnant women does not appear to be consistent within or across sampled clinics. Successful integration of HIV services was documented; however TB screening processes and feedback mechanisms following referral require strengthening. Records of deferment and delays in repeat testing in women who initially test seronegative are particularly concerning. Training and support of health care workers on the value of complete medical records for the overall management and continuity of care of pregnant women is essential. Further, the benefit of implementating national guidelines in relation to PMTCT must be highlighted.

Keywords:

acute seroconversion in pregnancy, antenatal tuberculosis screening, retesting for HIV in pregnancy.

Background

Sub-Saharan Africa bears the brunt of the human immunodeficiency virus (HIV) epidemic with 71% of people infected with HIV located in this region [1]. Women account for 58% of those living with HIV in 2012, with the highest burden of disease in the reproductive age group. An estimated 280 000 pregnant women are living with HIV in South Africa [2] with an estimated national HIV antenatal prevalence of 29.5% (95% CI: 28.7–30.2) in 2011 [3]. The estimated antenatal HIV prevalence in KwaZulu-Natal (KZN) and some of its districts is higher than the national prevalence [3].

Effective antenatal antiretroviral interventions aimed at preventing mother-to-child transmission (PMTCT) of HIV have been implemented worldwide as more than 90% of childhood HIV infections are due to vertical transmission of the virus during pregnancy, labour and delivery or breastfeeding. Provision of antiretroviral interventions in low and middle income countries has prevented an estimated 850 000 children from acquiring HIV infection between 2005 and 2012 [2]. In SSA, the implementation of effective antiretroviral treatment during pregnancy and breastfeeding has positively impacted on mother-to-child transmission (MTCT) of HIV [4-9]. Antiretroviral coverage for PMTCT in this region in 2012 however only expanded to 83% (range 75%-90%) with a resultant MTCT of 7%. South Africa is categorized as a country that has made moderate progress with PMTCT coverage estimated at 83% [1].

In South Africa, since 2008, the offer of an HIV test to all pregnant women is standard at initiation of antenatal care. First time attendees receive group counselling on the benefits and possible outcomes of an HIV test and individual rapid testing and disclosure of the result is performed by the clinic nurses or counsellors. In addition to HIV testing, a clinical history and examination is performed by the attending clinician

or nurse. CD4 assays are required in women diagnosed as living with HIV at this first visit.

The recent South African PMTCT guidelines recommend the initiation of antiretroviral treatment (ART) in all pregnant women living with HIV irrespective of CD4 count [10]. Fixed dose combination (FDC) drugs have been made available and are to be initiated on site on the day of HIV diagnosis. In women who initially test HIV uninfected, a repeat HIV test 12 weeks after the initial test and/or between 32 and 36 weeks of gestation is advised. Additionally, at the time of HIV diagnosis, TB screening as well as isoniazid prophylaxis is advised in all pregnant women living with HIV [10].

Although significant progress has occurred in the implementation of PMTCT programmes a number of health system factors and patient factors have impeded the success of the programme. Time to initiation of ART, testing pregnant women for HIV and detection of acute seroconversion during pregnancy are some of the health service factors identified [11,12]. Screening for and treatment of opportunistic infections associated with HIV infection, particularly tuberculosis (TB), are additional challenges faced by health care workers in the management of a pregnant woman. Addressing these challenges is critical as acute seroconversion is associated with an increased vertical transmission rate and untreated OIs, particularly TB, impact on maternal and neonatal outcomes [13-17].

Assessment of these factors within the South African PMTCT programme is necessary. Information is available, from routine collection of surveillance data, on the uptake of antenatal counselling and testing services for HIV in KZN. However, limited information is available in three key areas: firstly, time to initiation of ART following diagnosis of HIV; secondly, implementation of TB screening processes in pregnant women living with HIV; and thirdly, follow-up (HIV) testing in uninfected pregnant

women. The aim of this study was to explore the implementation of guidelines for the management of both seropositive and seronegative pregnant women in antenatal clinics in the metropolitan district with a focus on the following objectives: determining the median gestational age at diagnosis of HIV infection and at initiation of ART, ascertaining the distribution of CD4 counts among women living with HIV and assessing the application of TB screening process. In those women who were HIV uninfected, the study aimed to determine median the gestational age at initial and repeat first HIV test, and to describe the proportion of pregnant women who seroconvert.

Methods

Study design

An exploratory, observational, cross sectional study design presenting both descriptive and analytic statistics was implemented. Data was collected for a period of one year for women attending antenatal clinics between June 2013 and June 2014.

Study setting and location

The study was conducted in antenatal clinics within the Metropolitan district of eThekwini, in the KwaZulu-Natal Province of South Africa.

Study population

Patient records of women over the age of 18 years, presenting for follow-up care between 32 and 36 weeks of gestation and unaware of their HIV status at initiation of antenatal care were reviewed. Records of women, who presented for their first antenatal visit after 32 weeks, who had delivered prior to 32-36 weeks gestation or experienced pre-term labour, or in whom the HIV status was known prior to the current pregnancy, were excluded from the study population.

Study sampling

Data sets from antenatal clinics within the Metropolitan District were obtained from the District Health Information System. A total of 154 clinics offered antenatal care. Clinics with an average of less than 10 first time antenatal clients per month were excluded from the sampling frame (n=54). In addition clinics in which attendance totals did not tally, were also excluded (n=5). A total of 95 clinics from all administrative authorities were therefore eligible for inclusion in the study.

A two stage cluster sampling, using a 30X7 strategy, was applied in the study; the first stage was implemented for the selection of clinics from the 95 eligible clinics; the second stage was to sample the records of pregnant women attending antenatal care within the clinics. Clinics were stratified into three categories depending on the average monthly number of first time antenatal attendees. Fifty four clinics had less than 50 attendees, 28 clinics had between 50-99 attendees and 12 clinics had a 100 or more attendees. A total of 30 clinics were sampled with probability proportional to size to achieve representativeness. Seventeen clinics from the first stratum, nine from the second and four from the third stratum were selected.

With regards to the records of pregnant women, we assumed that pregnant women present in random order to clinics and that consecutive, systematic sampling of clinic attendees would generate a representative sample of pregnant women. Seven HIV infected and seven uninfected women (based on the 30X7 sampling frame) were selected from the registers of each clinic.

Data collection

Data was collected from registers utilized in the antenatal servicesin the clinics. Data was extracted from the antenatal register, daily consultation registers, and antiretroviral

registers maintained by the nursing staff. For triangulation purposes, HIV counseling and testing logs were also reviewed to complete and verify data collected.

All routinely collected data was collated and entered by the principal investigator onto the data collection sheet. Confidentiality was maintained by recording only patient initials and the clinic identifier.

Variables of interest comprised both outcome and exposure variables. Exposure variables included age, parity, gestational age at first presentation to antenatal care, gestational age at initial HIV test, result of initial and rapid HIV rapid testing, CD4 assay results and outcome of TB symptom checklist. Outcome variables comprised gestational age at which CD4 assay performed, administration of TB symptom checklist in women living with HIV and whether ART initiation occurred at the clinic level or referral occurred and whether ART was initiated by a nurse or doctor.

Selected clinics were visited by the principal investigator for data collection. The antenatal register and daily consultation logs were reviewed first followed by a review of the supporting registers outlined above. Incomplete data sets were excluded from the data collection process and the replacement record was the next consecutive record.

Data analysis and ethical approval

All data for variables of interest were entered onto a Microsoft Excel spread sheet and imported into SPSS (IBM SPSS statistics version 21).

Summary statistics are presented for demographic characteristics, initiation of FDC, TB screening processes and repeat testing in women who tested HIV uninfected. Statistical analysis was performed on exposure variables in relation to HIV status and the offer of a repeat test, the association between the administrative authority and practices within

and across clinics. Chi squared tests, Mann Whitney tests and t-tests were used to compare maternal characteristics.

Ethical approval was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (reference number BE096/11). Permission to conduct the study at the health care facilities was also obtained at a provincial (HRKM 20/12) and municipal level.

Results

Data was collected from records of four hundred and twenty women, 210 living with HIV and 210 uninfected at the initial antenatal visit.

Demographic profile

Data extracted on the demographic profile is summarised in Table 1. Records showed that 94% of the women were from the black population. The mean age recorded was 25 years (range 19-43 years, SD 5.3) and the mean gravidity recorded was 2.1 (range 1-7, SD 1.1).

Booking at antenatal clinic

Data extracted on the initiation of antenatal care showed that the majority of women (67.4%) presented for their first visit in the second trimester, with a median gestational age of 20 weeks (range 3-31, IQR 9). One hundred and nine women (51.9%) living with HIV and 93 HIV uninfected women (44.3%) presented before 20 weeks gestation.

Initiation of FDC

With regard to the initiation of FDC, records show that initiation at the first antenatal visit occurred in 203 women (96.7%) at a median gestational age of 19 weeks (range 5-31, IQR 8). Twenty seven (13%) of these women living with HIV were recorded as having booked in the third trimester at a median gestational age of 28 weeks (range 27-

31, IQR 5.8). Delayed initiation was observed in women who were recorded as not initiated on FDC in the antenatal clinic but referred to the facility based ART clinic for ART initiation. Of the women who were referred for ART access, records showed that one participant presented in the first trimester, five in the second and one in the third trimester. There was lack of documentation in the records of these six women regarding initiation of FDC following referral.

Distribution of CD4 counts in women living with HIV

Of the 210 HIV infected women included in this study, 182 (87%) baseline CD4 counts were available for review. For 28 women, records of 28 CD4 results were not accessible; in 26 records the CD4 results were not documented, one record did not have any evidence that a sample was taken and in one record, there was no documentation that a repeat test was carried out after the initial sample was reported to have clotted. The median CD4 count was 399 cells/mm^3 (range 1- 1158, IQR 229) with 57.7% of results concentrated between 200 to 500 cells/mm^3. Figure one shows the baseline frequency distribution of CD4 counts.

Tuberculosis screening practices

Administration of the TB symptom questionnaire at the initial antenatal visit was documented in 191 (91%) of the 210 seropositive antenatal attendees. Six women were recorded as symptomatic and investigated by sputum sample collection. The CD4 counts in these symptomatic women ranged between 145-812 cells/mm^3. Records of TB screening (inclusive of the TB symptom questionnaire and sputum examination) were captured from a further 75 attendees.

Adherence to TB guidelines

Adherence to the guidelines did not appear to be consistent. The records of pregnant women from 24 clinics (80%) showed that TB symptom screening for women living

with HIV was implemented as advised by the guidelines. The records of pregnant women in five clinics did not have clearly detectable practices and in one clinic none of the records of pregnant women had any evidence of TB screening having been implemented. Isoniazid prophylaxis was documented in the records of 58 (30%) of the 191 attendees screened. For one woman, initiation of isoniazid was recorded as occurring prior to FDC initiation, in 27 (46.6%) as occurring on the same day as FDC initiation, in 12 (20.7%) within two weeks, in 13 (22.4%) as being initiated a month later and in the remaining 5 (8.6%), as initiation occurring more than a month (range 2-4) after initial antenatal contact.

Repeat HIV rapid testing in women who test uninfected at first antenatal visit

The records of pregnant women found to be HIV uninfected at initiation of antenatal care showed that retesting was recorded for 185 (88.1%) women. One hundred and seventy seven women were recorded as remaining HIV uninfected and eight (4.5%) were recorded as having seroconverted. The median gestational age at which repeat testing occurred was found to be 32 weeks (range 32-36, IQR 2). Records showed that 84 women (45%) presented for antenatal care at or before 19 weeks and would have qualified for a repeat HIV test within 12 weeks of the initial test (at or before 31 weeks gestation). However, none of the women however were recorded as having been tested within 12 weeks but rather between 32 and 36 weeks gestation. The median delay in the offer of a repeat test was 9 weeks (range 0-19, IQR 6).

The eight women who were recorded as having seroconverted attended six of the 30 clinics sampled. The mean age of the seroconverters was noted to be 25 years (range 21-34, SD 4.6). Three of the eight were recorded as primigravidas and were documented as the youngest of the eight. Presentation for the baseline antenatal visit in this subgroup was logged at a median gestational age of 14 weeks (range 9-21, IQR

7.5). Five of the eight women qualified for a repeat test within 12 weeks of initial booking according to documentation. However the repeat rapid HIV test was performed between 32 and 36 weeks with a median delay of 9 weeks (range 2-13, IQR 7). Records indicate that all women were initiated on FDC on the day that HIV infection was diagnosed.

Women, for whom no repeat HIV rapid test results were recorded, can be categorized into two groups. One category in which documentation of deferment of these tests was captured and the other category for which no records were available in any of the registers reviewed. Testing was recorded as being deferred until the post delivery period in twelve women (48%). This deferment practice appeared to be clustered in five clinics with nine of the twelve women in whom testing was recorded as being deferred post delivery attending two clinics. For the thirteen women (52%) for whom no records were available, it can be assumed that repeat testing was not performed and these women were clustered in three of the sampled clinics. Both categories of women described above have documented regular antenatal visits following initiation of antenatal care, including visits during the recommended 32-36 week period for repeat testing.

A summary of the movement of a typical seropositive and seronegative woman through the clinic processes is illustrated in figures one and two. Barriers identified within the clinic are highlighted in these figures.

Statistical analysis

Descriptive data illustrated certain trends which were subjected to analytic statistics to measure and associations were measured. An association was detected between HIV status and the median gestational age (Mann Whitney 0.076) at first antenatal visit. A statistically significant association was detected between HIV status and age (x^2 18.739,

P<0.001) as well as HIV status and parity (x^2 26.857, P=0.000). In women living with HIV, a higher immunological status as measured by the CD4 count was not associated with earlier health seeking behavior (x^2 0.297, P<0.862).

Recorded age of the women, gestational age at first antenatal visit, parity and the administrative authority of the clinic were not associated with the offer of a repeat HIV test. The association between the administrative authority and the implementation of TB screening practices (x^2 7.949, P=0.019) and availability of CD4 counts (x^2 7.183, P=0.007) was statistically significant. However no association was established between the administrative authority and the availability of records for repeat HIV testing ($x^2$2.593, P=0.0107).

Operational observations

There were gaps observed and inconsistencies noted in record keeping. Of primary concern was the lack of data on baseline CD4 counts and results for the repeat HIV testing in women who initially tested uninfected. Upon review of missing records per clinic, four clinics did not record either of variables. Based on the data extracted from the department of health database, one of these clinics averaged more than 100 first time antenatal attendees and the other three averaged less than 50.

Discussion

This study describes the implementation of PMTCT guidelines for the management of HIV in pregnancy in antenatal clinics within the metropolitan district of eThekwini, in the KwaZulu-Natal Province of South Africa.

Demographic profile:

In this study women recorded as being HIV infected were mostly young between and including the ages of 19 and 33 years, and predominantly seeking antenatal care early

in the second trimester. The mean age of women living with HIV reflects the distribution of HIV infection in the general population, concentrated in the reproductive age group both in South Africa [3] and the international arena [1]. A statistically significant difference in recorded mean age of women infected and uninfected was detected in this study highlighting the continued vulnerability of young women to the HIV epidemic.

A comparable median gestational age at first antenatal contact was recorded for both seropositive and seronegative women is reported probably reflecting similar health seeking practices. Equivalent mean gestational ages at first antenatal visit of 22 [18] and 19.2 weeks [19] have been documented in other South African studies. In the current study close to 20% of women presented in the first trimester, which provides significant opportunity to introduce two key interventions encapsulated in a successful PMTCT programme: the early initiation of FDC to improve maternal health and reduce vertical transmission to the neonate; and individualized repeat HIV testing within 12 weeks in women who test HIV uninfected at the initiation of antenatal care. The records of a majority of HIV infected women showed FDC initiation concurrent with HIV diagnosis, where HIV care was integrated with antenatal care. However, a delay in initiation of FDC was evidenced in the records of women referred to an on site antiretroviral clinic separate from antenatal care, emphasizing the deleterious effects of fragmented care [48,79]. Repeat HIV testing in women who tested HIV uninfected at initiation of antenatal care was recorded in 88% of women. However, rather than inidvidualised repeat testing within 12 weeks of the first antenatal visit, the offer of a repeat test was recorded as occurring routinely at a median gestational age of 32 weeks. Fragmentation of care and incorrect implementation of care guidelines contribute to a missed opportunity for optimal protection against vertical transmission offered both by

ART initiation and adequate duration of therapy. Lowered or suppressed maternal viral load is a benefit of a longer duration on ART thereby reducing the rate of vertical transmission [20]. Women in our study commenced FDC at an earlier median gestational age; however we are unable to comment on vertical transmission rates. The median gestational age at initiation of ART in the United Kingdom and Ireland was 25.9 weeks (IQR 22.4–28.9 weeks) with an adjusted odds ratio of 0.90 per week of ART (p=0.007). Multivariate analysis showed that the lack of an (ART) intervention was the strongest risk factor for vertical transmission [20]. Evidence from a study in the Johannesburg area showed a marked difference in transmission rates between women on ART prior to pregnancy (0.7%) as compared to women initiated during pregnancy (5.7%) [5].

Inconsistent Tuberculosis screening practices

Tuberculosis screening practices did not appear to be applied consistently across or within clinics and was dependent on administrative authority and a statistically significant difference between different administrative authorities and TB screening practices was detected. One third of the infected women who were screened, were initiated on INH at various time points after initial ANC contact. A possible reason for this is the lack of clarity in the national TB guidelines with regards to isoniazid initiation in relation to ART [21].

The World Health Organisation [22] and the South African National TB guidelines [21] recommend TB screening for those living with HIV and in individuals at high risk which includes pregnant women.

Active TB disease has been detected in the pregnant population with the use of the TB symptom questionnaire and a variety of screening tests [23,24] underlining the importance of this antenatal opportunity. Routine screening however is not standard of

care in many facilities. Training of nurses to administer the TB symptom questionnaire within antenatal services was required to improve coverage of TB screening [23,24]. Symptomatic pregnant women should be investigated as per country guideline and commenced on anti TB drugs if indicated. Untreated TB, advanced disease or delayed initiation of treatment is associated with adverse maternal and neonatal outcomes. Prematurity, small for gestational age newborns, low birth weight and perinatal death are associated with maternal TB [25,26]. The consequences of TB HIV co-infection in pregnancy include pre term labour, maternal mortality [14], fetal growth restriction, congenital TB, neonatal mortality [15], and an acceleration of the HIV replicative and disease processes. Tuberculosis is also recognised as an independent risk factor for the vertical transmission of HIV [27,28]. The importance of detection and immediate treatment of antenatal TB is therefore essential to improve maternal and neonatal outcomes.

The South African TB guidelines recommend the use of INH despite the lack of evidence regarding its benefit in reducing active disease, the duration of prophylaxis and whether a second drug should be used [21]. Additionally there is a lack of data on the tolerance, safety, side effects and levels of adherence to INH in the pregnant population. The prescription of INH is further influenced by health care worker concerns regarding resistance, the ability to exclude active disease, the controversy surrounding the choice of screening tests [29,30,31] and unfamiliarity with national guidelines [32,33]. Training of health care workers on the evidence that is available on INH use and on the national guidelines could improve uptake of INH use in pregnancy.

Retesting of women who initially test uninfected

Women who tested uninfected at their first antenatal visit also accessed care early in the second trimester and were younger than those living with HIV. Retesting records were

available for 185 (88.1%) women and lack of documentation and deferment of tests occurred in 25 women (13.5%).

The lack of re testing records, deferment of re testing and retesting only in the third trimester are matters of concern. Perhaps the confusion in retesting lies within the wording of the national PMTCT guidelines where it is recommended that seronegative women be retested within 12 weeks of the initial test **and/or** between 32 to 36 weeks of gestation. Not only does it highlight the need for reinforcement of PMTCT guidelines and the risk of vertical transmission but it also represents missed opportunities for re testing, the introduction of an appropriate PMTCT intervention and a possible under estimation of other seroconversions. A Tanzanian study also observed lack of records for HIV repeat testing in pregnancy despite national guidelines advocating retesting three months after the initial HIV test [34]. A lack of understanding of the window period was identified as the barrier to the offer of a repeat HIV test and retraining of HCWs was recommended [34].

A significant risk of incident HIV in pregnancy [18,35,36] as compared to non pregnancy [18,36] has been reported in studies in SSA. The incident rate per 100 person years during pregnancy ranged from 2.3 cases [35] to 10.7 cases [18]. Some reports on the other hand show no increase in HIV risk during pregnancy [37,38].

In this study, the proportion of HIV uninfected women who acutely seroconverted was 4.5%. All eight women were between 21 and 34 years of age underlining the continued HIV transmission in this age group. Subsequent antenatal visits in women who initially test HIV uninfected should be capitalized upon to highlight the importance of safe sexual practices, the risk of acute seroconversion and its associated risk of vertical transmission.

Implementation of Guidelines

It appeared that there were inter and intra clinic differences in the application of the national PMTCT and TB guidelines. Possible reasons for this could be the patient workload, the number of tasks performed by the health care worker, lack of support, mentorship, and regular feedback to staff, frequent staff turnover with no training of new staff, increased demand on services with the change in the national antiretroviral guidelines and increased consultation time.

Efforts to improve the SA PMTCT programme

The revision of the national PMTCT guidelines [10], the integration of HIV services into maternal health services [39] and the implementation of NIMART [40] are efforts to improve PMTCT coverage in South Africa.

Integration of services

Successful integration of HIV services into maternal health services is demonstrated in this study. At the first antenatal visit, all women accessed an HIV test and the majority of women living with HIV initiated FDC. Lack of information on CD4 counts and FDC initiation in women referred to ART clinics for FDC however shows poor continuity of care and loss of information important to the overall management of the pregnant woman. This study was not designed to address the impact of integration of services on the number of women tested for HIV, time to initiation on ART or retention within care following ART. Other studies in SSA have shown a reduced time to initiation of ART in pregnancy with a 60% improvement in retention in care [41]. In South Africa [42] a median reduction of 19 days (P = 0.041) for time to initiation of ART was calculated and in Zambia, the odds of enrollment into HIV care (AOR 2.06) and initiation of ART (AOR 2.01) was higher in integrated facilities as compared to independent facilities [43]. Further rigorous research is required in these areas.

Poor integration of TB services into maternal health services was illustrated in this study as the administration of the TB symptom questionnaire, the investigation of all women living with HIV for TB and the offer of INH did not appear to be consistently administered across all facilities. Further the lack of feedback following referral of symptomatic women to the facility based TB unit for investigation suggests a fragmented rather than integrated approach.

Nurse initiated management of ART

Nurse initiated management of ART (NIMART) is a task shifting strategy adopted to address the scale up required of public sector ART provision [40]. Nurses are enabled to initiate and manage stable patients on ART. Access to ART has been 'accelerated' with the advent of NIMART. However, little has been written about the contribution of nurses to the antenatal sector in this regard. The immediate prescription of FDC by nurses in this study for women who were initially seropositive, who presented at an advanced gestational age and who seroconverted was facilitated by this training. These results were similar to another South African study which demonstrated the benefit of NIMART to women who presented in the third trimester and who would have been unable to access HIV care during pregnancy prior to NIMART [44].

Another South African study however described a delay in ART initiation following the introduction of NIMART in four of the five facilities reviewed [19]. Suggested contributory factors to this delay included possible staff shortages and the dedication of certain clinic days to NIMART in the early stages of the programme.

Initiation of Antiretroviral treatment in pregnancy

South Africa currently promotes Option B [38]. The CD4 count threshold for lifelong ART for the mother is 350 cells/mm^3 and below with the duration of ART prophylaxis in women who have CD4 counts above this threshold directed by infant feeding choice

[38]. The CD4 result is no longer a requirement for the initiation of ART and the lack of CD4 results in women enrolled onto this study did not impact on their immediate access to ART. Access to and availability of CD4 results were often an obstacle to ART initiation in low income countries particularly when CD4 thresholds were used to determine ART eligibility. In a cross sectional retrospective evaluation at a large tertiary centre in KZN, a CD4 assay was not performed in 2.9% of women and an additional 31.3% did not receive their CD4 results [45]. As the CD4 count was used as a determining factor for ART eligibility at the time of the study, this lack of information prevented access to ART. Further 71.9% of women who qualified for ART according to their CD4 counts, did not access ART during pregnancy which resulted in a threefold higher in utero transmission of HIV to their neonates [45].

Implications of our study

This exploratory, observational cross sectional study forms the basis for future research on health system factors affecting care offered to pregnant women specifically in relation to ART initiation, TB screening practices and offer of repeat HIV tests. Training of staff on data collection principles and the national guidelines is crucial on two levels, one in relation to robustness of data and secondly and more importantly, the appropriate management of patients according to guidelines.

Challenges and Limitations:

Although due diligence was maintained in ensuring the integrity of this study, the following were the challenges and limitations of the study:

Information bias: Data was extracted primarily from the antenatal register which is maintained by HCWs. These registers were poorly completed and data fields were completed differently at both the first and follow up visits in the majority of clinics. A

number of other registers were maintained by different clinics and were consulted to ensure completeness of data. Sharing of the antenatal register amongst various categories of HCWs, staff shortages, lack of a unique patient identifier to link daily registers to entries in the antenatal register and lack of dedicated time to update the register are all possible contributors to the incomplete register.

Conclusion and Recommendations:

The focus of all PMTCT interventions is the prevention of transmission to the neonate and this is achieved by a lowered viral load resulting from a longer duration on ART. In this study, women presented at an early gestation allowing for timeous PMTCT interventions as required. The benefit of NIMART is evident in the immediate linkage of the majority of women living with HIV to ART. The deferment and the delays in the offer of a repeat test in women who initially test HIV uninfected are particularly concerning as is the loss to follow up of women referred for TB investigation and the delayed access to FDC.

The following recommendations are proposed based on the findings of the study:

Improving patient record keeping to ensure continuity of care - Careful attention to the completion of records for all patients accessing maternal health services is critical to the overall management and continuity of care of a pregnant female.

Capacitation of health workers on correct application of national PMTCT and TB guidelines.

Focus on HIV counseling and testing- attention to information provided to women who initially test seronegative and to ensure intensive counseling and interventions to remain seronegative.

Improving data for action- Training specifically on data fields and the importance of complete data sets should be highlighted.

Ongoing mentoring and supervision of Health Care Workers, particularly those involved in antenatal care.

Further research using a more rigorous study design is required to investigate the gaps highlighted in this study.

At a national or provincial level an audit of registers should be conducted and adaption of registers for ease of use by the health care worker, to capture salient information with the least amount of duplication should be considered.

List of abbreviations

HIV	human immunodeficiency virus
ART	antiretroviral treatment
PMTCT	preventing mother-to-child transmission
MTCT	mother-to-child transmission
TB	tuberculosis
CD4	cluster of differentiation 4
FDC	fixed dose combination
SPSS	statistical package, originally used as a Statistical Package for the Social Package

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MK was responsible for conception and design of study, acquisition and interpretation of data, drafting the manuscript.

ASV was responsible for critiquing study design, assisted with the interpretation of data and drafting of manuscript.

GBM assisted with sampling strategy and sampling of clinics, analysis and interpretation of data.

All authors read and approved the final manuscript.

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Table 1: Demographic profile of antenatal attendees in 30 clinics within the metropolitan district

Variable	HIV infected	HIV uninfected
	Number (%)*	Number (%)*
Age in years in:		
19- 23	68 (32.4)	109 (51.9)
24- 28	75 (35.7)	61 (29.0)
29- 33	41 (19.5)	22 (10.5)
34- 38	19 (9.0)	15 (7.1)
≥39	7 (3.3)	3 (1.4)
Primigravid		
Yes	54 (27.0)	103 (50.7)
No	146 (73.0)	100 (49.3)
Baseline gestational age in weeks		
0-13	43 (20.5)	34 (16.2)
14-26	139 (66.2)	144 (68.6)
≥27	28 (13.3)	32 (15.2)
Median baseline gestational age (in weeks)	19 (range 5.0-31.0, IQR 8.3)	20 (range 3.0- 30.0, IQR 8)
Median gestational age (in weeks) at repeat HIV rapid test	32 (range 32-36, IQR 2)	
CD4 count (cells/ mm^3)#		
≤200	19 (10.4)	
201- 500	105 (57.7)	
≥501	58 (31.9)	
Median baseline CD4 count (cells/ mm^3)	399 (range 1-1158, IQR 229)	
Number initiated on fixed drug combination on first visit	203 (96.7)	
Nurse initiated FDC	203 (96.7)	
Mean number of days on ART at enrollment onto study	150 (61-253, SD 39.2)	

*Percentages calculated after missing data was excluded
182 CD4 counts included

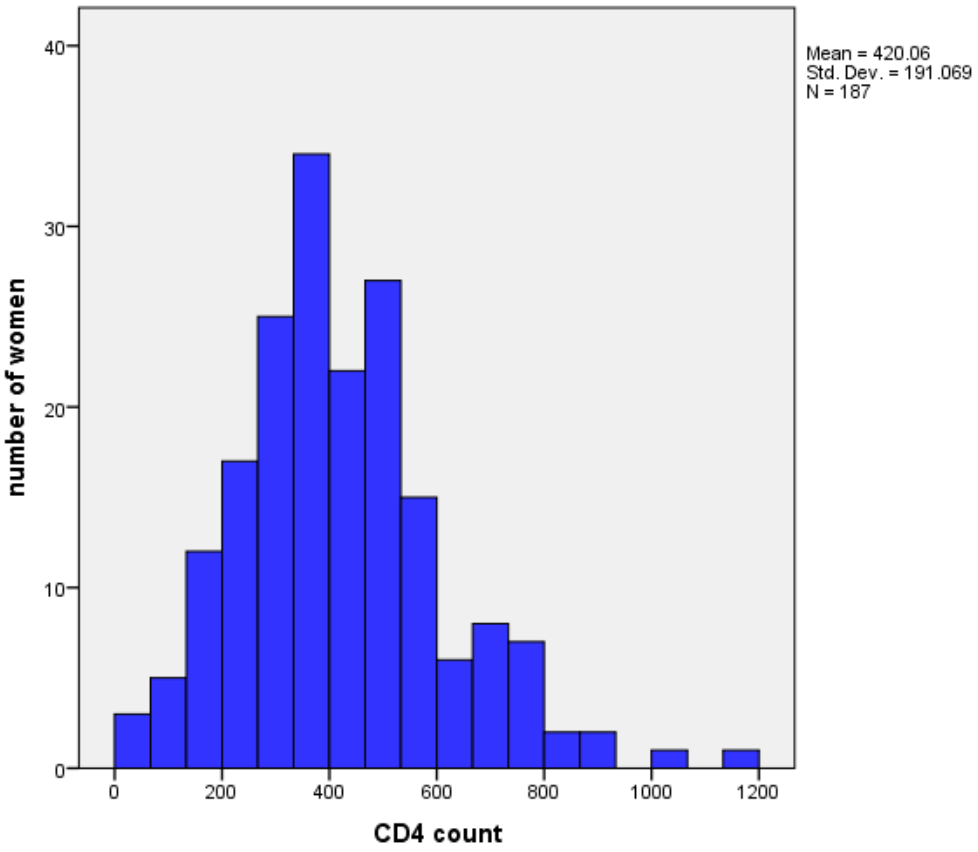

Figure One: Frequency distribution of baseline CD4 counts in seropositive women

Figure one shows the frequency distribution of CD4 counts at first antenatal visit in women who were diagnosed with HIV. This objective was included in the previous protocol as it was a determinant of initiation of ART with the CD4 threshold being above or below 350 cells/ mm3. With the introduction of the new PMTCT guidelines however, all women living with HIV are initiated on FDC upon diagnosis. The data presented in the figure serves to demonstrate the distribution of the CD4 assays.

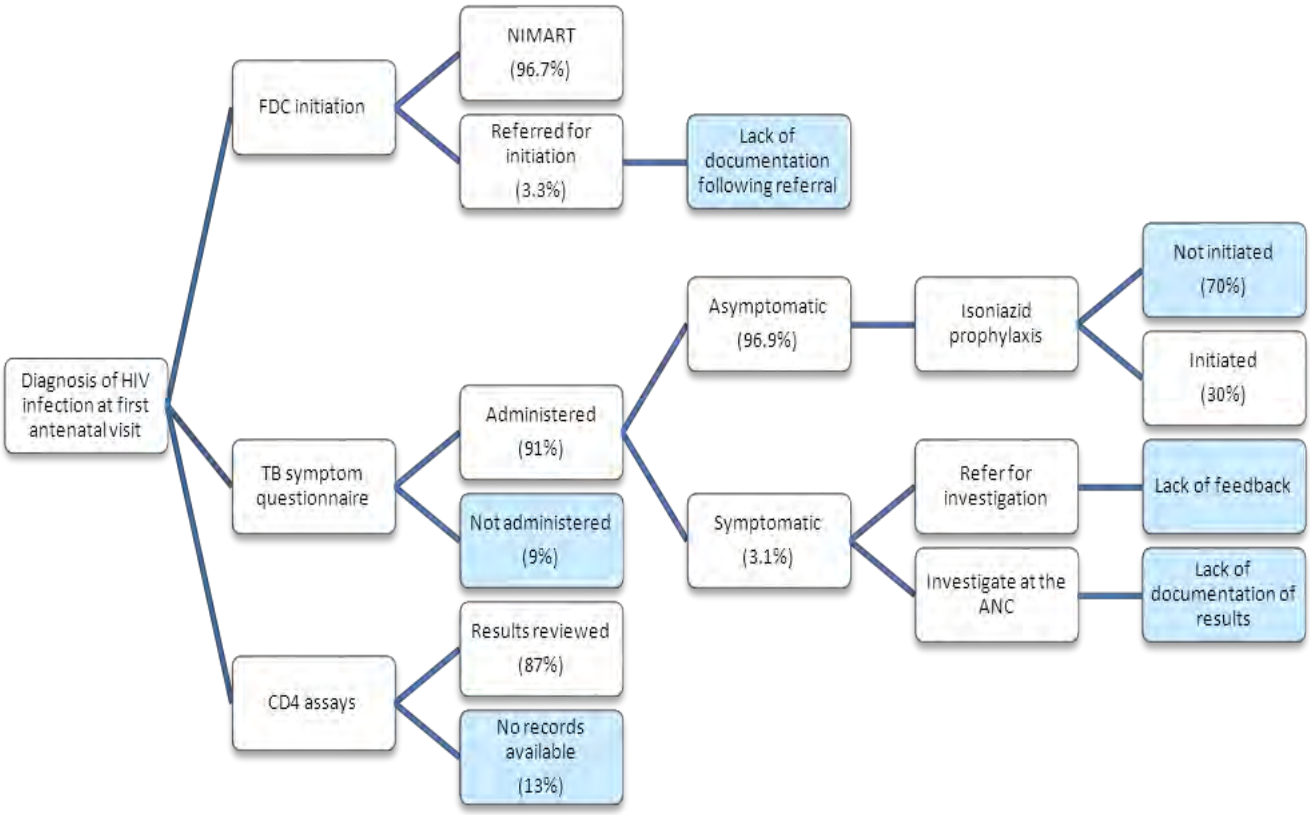

Figure two: Flow of a typical patient through antenatal processes following a seropositive diagnosis of HIV

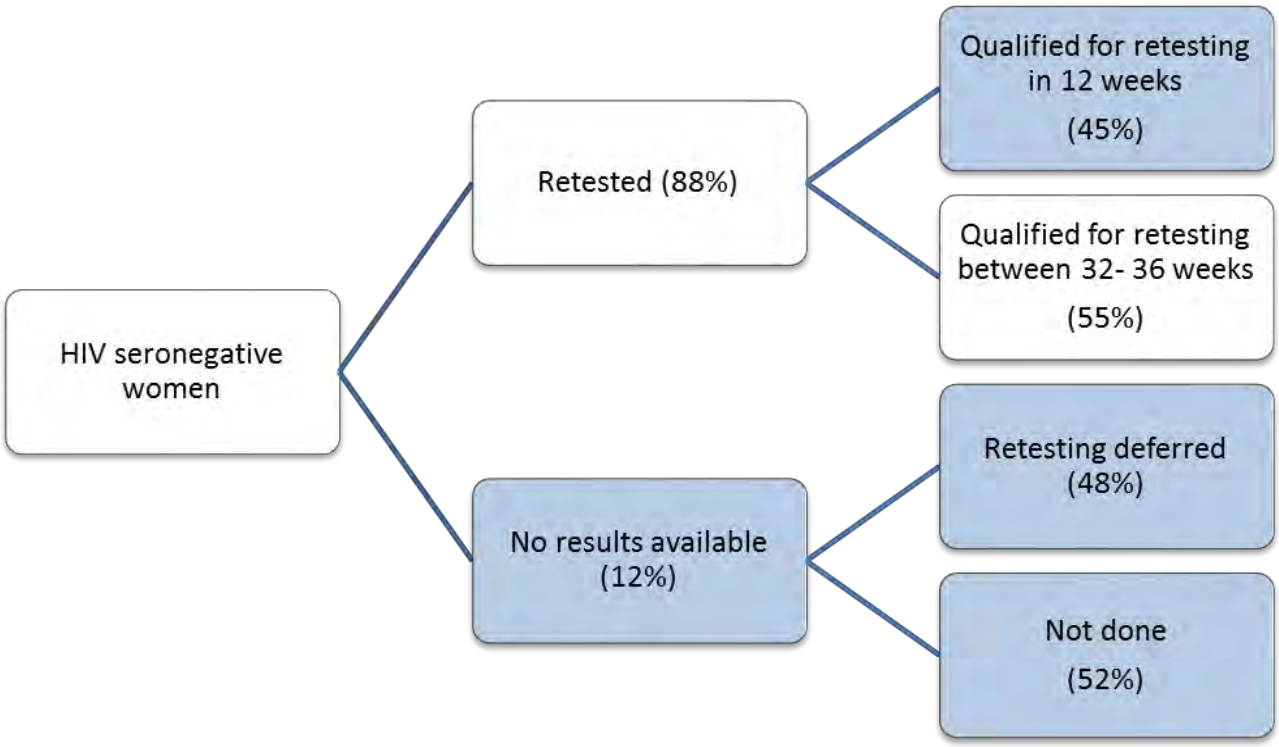

Figure three: Flow of a typical patient through antenatal processes following a seronegative diagnosis of HIV

Chapter Four: Integrative Chapter

Discussion

This study aimed to assess the implementation of national PMTCT guidelines in seropositive and seronegative pregnant women attending antenatal clinics within the eThekwini metropolitan district between 2013 and 2014. The objectives of the study encompass the diagnosis and management of women tested for HIV in the antenatal period.

Implementation of guidelines in women who test seropositive at initiation of antenatal care:

The age group of women who were recorded as seropositive is reflective of the global HIV epidemiology and highlights the highest prevalence within the 18- 33 age group. With regard to initiation of antenatal care, the records showed that 18% of women booked prior to 14 weeks gestation and 48% presented early in the second trimester. The recorded ANC initiation is comparable to other South African studies where women presented at a median gestational age of 22 weeks [77] and 19.2 weeks [71]. The shift towards earlier antenatal attendance provides HCWs the opportunity to introduce an antiretroviral intervention in women who test seropositive at the initial antenatal visit. It also permits HCWs to increase awareness and re inforce HIV prevention strategies in women who test seronegative at the initial antenatal visit.

With regard to ART initiation, the records showed that 97% of women were initiated at first antenatal visit upon diagnosis of HIV infection as per national PMTCT

guidelines. Referral of seven women (3.3%) for the initiation of ART was documented. Further, the unavailability of CD4 results in 28 (12.8%) women did not appear to impede access to ART. The National Guidelines recommend that all seropositive pregnant women be initiated on ART prior to the availability of CD4 results partly to reduce the system challenges associated with accessibility and availability of CD4 assays. These challenges impeded access to ART when CD4 results were used to determine ART eligibility [32,66,80,81]. A three-fold higher in utero transmission of HIV was associated with delayed access to ART [83].

This study was not designed to assess the impact of the change in PMTCT guidelines on time to initiation of ART in the antenatal period and the duration on ART prior to delivery. Studies have shown differing outcomes in relation to this, from a reduction in median time to initiation of ART [69] to a lack of improvement in the duration on ART prior to delivery [68]. The overall number of women initiated on treatment however, did improve due to the integration of services [69,70].

The distribution of CD4 counts in this study indicated approximately one tenth of women had CD4 counts below 200 cells/mm^3 and CD4 counts in the majority of women (57.7%) were clustered above 200 cells/mm^3 and below 500 cells/mm^3. The adoption of Option B+ in South Africa could present a challenge for the retention of clinically stable women with high CD4 counts within a post natal treatment programme as evidenced in Malawi [61]. The improvement in maternal health, the benefit to future pregnancies and the reduced risk of transmission to partners should be highlighted as additional benefits of adherence to Option B+ in an effort to retain women within the treatment programme.

Tuberculosis is a worldwide public health concern and co infection with HIV is seen in 13% of HIV [34]. The HIV epidemic has triggered a shift in TB disease to women in the reproductive age group [35]. The expanded package of PMTCT services therefore recommends screening for TB and INH prophylaxis [1]. The TB symptom questionnaire should ideally be administered on an ongoing basis to seropositive pregnant women during the antenatal period [1]. Isoniazid should be introduced following the exclusion of active TB disease. In this study the symptom questionnaire was recorded as being administered in 91% of women and INH was recorded as being initiated in one third of women at varied time points following initial antenatal contact. Lack of clarity in guidelines regarding INH prescription, lack of information of INH use in pregnancy, lack of an understanding of guidelines and HCW concerns regarding resistance are some of the possible factors in the poor implementation of TB screening practices [39-43]. Some of these factors may have contributed to the statistically significant difference in the recorded TB screening practices by administrative authority.

Routine TB screening and INH use does not appear to be standard practice within health care facilities. Tuberculosis screening practices were assessed in a 24 country HIV/ AIDS programme; only 15 sites recorded incident TB cases. Five sites routinely administered INH following the exclusion of active disease by the application of the TB screening questionnaire [81]. Reports of routine screening for TB and INH prescription within the pregnant population are limited. An improvement in the administration of the TB symptom questionnaire however, was detected following training of HCWs on the integration of TB services within routine antenatal services [23,24].

The implementation of the guidelines in HIV uninfected women at initiation of antenatal care:

Over 80% of women, who were recorded as seronegative at first presentation, were recorded as receiving a repeat test and more than half had qualified for a repeat test within three months of initial presentation. Two areas of concern were identified within this study that reflects inadequate implementation of guidelines. The first concern is that the repeat test was effected at a standardized rather than an individualized time point and is an important training point highlighted later. Although more than half of the seronegative women were recorded as qualifying for a repeat test within three months, all of them received a repeat test between 32 and 36 weeks gestation. The second concern was records showing the lack of and the deferment of a repeat test in women who are accessing regular antenatal care. The practice of deferring a repeat test until the post delivery period was documented in two clinics and is an additional training point. This is a critical oversight in the continuum of care as it has far reaching consequences. This single intervention of a repeat HIV test has the ability to impact on three of the eight Millenium Development Goals, specifically the reduction in child mortality by reducing vertical transmission of HIV, improvement in maternal health by improving the linkage to ART and combatting HIV/ AIDS, malaria and other diseases.

Acute seroconversion was documented in eight women who received a repeat HIV test. The age of these eight women ranged between 21 years and 34 years highlighting the sustained acquisition of HIV in young women. All eight women were recorded as presenting at median gestational age of 14 weeks and the records of five women showed that they qualified for, but did not receive, a repeat HIV test within three

months. Seroconversion was at least two fold higher among 25 to 29 year olds (3.8%) and 30 to 34 year olds (4.5%) in another South African study [77].

Integration of services:

Current PMTCT guidelines encompass both the antenatal and postnatal periods in an effort to improve maternal and newborn health outcomes. The shift in approach towards the integration of HIV services within an established PMTCT network could result in strengthening and efficiency of the health system.

Successful integration of HIV testing, linkage to ART and nurse initiation of ART within antenatal care was displayed in this study. Two areas of concern include the referral of women for ART initiation and the lack of CD4 results in records reviewed. Improvement in maternal HIV care following the integration of services has not always been demonstrated [69-71]. Partial integration of TB services into maternal health services is detailed above. Records of symptomatic women who were referred for further investigation did not reflect the outcome of these investigations. Feedback mechanisms and communication between different services within a clinic clearly needs to be strengthened for both TB and HIV referrals and investigations as it impacts on overall management of the mother.

Missed opportunities and the impact of these challenges:

A missed opportunity refers to instances where patients come into contact with the health care system and an appropriate intervention does not occur. The missed opportunities in this study with the possible implications are outlined below.

1. The WHO guidelines [54] and the national PMTCT guidelines [1] recommend the introduction of ART upon diagnosis of HIV infection at first antenatal interaction. Referral for initiation of ART however was documented in this study in some clinics, with a resultant delay in linkage to ART and a decreased duration on ART prior to delivery. Difficulties in the linkage of pregnant women to an appropriate ART intervention were widespread prior to integration [82] and the risk of transmission to the fetus subsequently increased with delayed initiation [83].
2. The delay in the offer of a repeat HIV test within 12 weeks of initial test (as per guidelines) in 45% of women was identified in this study. The basis for repeat testing is two-fold: firstly to detect acute seroconversion and initiate ART upon detection of seroconversion. Acute seroconversion is associated with an increased risk of MTCT and a PMTCT intervention should be offered timeously to reduce this risk. From a maternal health perspective, HIV has been identified as the commonest non pregnancy related cause of maternal deaths and the introduction of an appropriate ART regimen could impact on maternal mortality [14]. There appears to be a consistent misinterpretation of country specific guidelines [86] and the lack of individualised repeat testing may be poorly understood. This lack of understanding could be as a result of poor formulation of the guidelines or poor understanding of guidelines or a combination of both factors.
3. Inconsistent TB screening practices were detected within and across sampled clinics. Of concern were the clinics which did not have clearly detectable practices and the clinic that did not adhere to the guidelines. Although the diagnosis of TB in pregnancy is problematic, a high index of suspicion should be maintained in areas with a high TB burden. Maternal and perinatal deaths, low birth weight and small

for gestational age newborns are a consequence of untreated TB or delayed TB treatment [16-18].

Recommendations:

It is evident that training and support of health care workers on multiple levels is essential. The following were identified as areas requiring training and support.

1. Limited understanding of the PMTCT guidelines:

   Strengthening and improving health worker understanding of the national PMTCT guidelines and the impact of precise implementation on maternal health and vertical transmission of HIV, particularly with regard to acute seroconversion, is fundamental. An additional intervention at improving implementation is for ongoing facility level monitoring, evaluation and feedback to occur following this training the intervention.

2. Inconsistent TB screening practices:

   It appeared that there was a variation in the application of the guidelines within and between clinics. This variation could potentially be rectified by additional training of HCWs or mentorship of HCWs as evidenced by other studies [36,37,86]. The inconsistent INH initiation needs to be addressed at facility level in relation to understating of guidelines and at a national level to clarify its use.

3. Inconsistent and incomplete data collection:

   The integration of services warrants additional attention be directed to the capturing of records. At first contact, prescribed data fields are captured in the antenatal register and subsequent consultations are captured on a daily basis in

facility specific tools. The completion of data fields in the antenatal register varies and reconciliation of data from subsequent visits is difficult as patient identifiers are log specific. Improvements in data completion and collection require training and mentoring at facility level on the importance of robust data sets . Regular review of registers should be conducted with feedback within facilities and adaptation of registers to capture salient information with the least amount of duplication is suggested at a national level. Other interventions include maintenance of a centrally located register in a facility that is shared and updated by various categories of HCWs with dedicated time to updating this register. Nurse quality mentors were trained to supervise HCWs in three provinces in SA and through this intervention, data quality improved [86].

4. It is recommended that health care providers capitilise on subsequent antenatal visits for women who initially test seronegative to improve awareness related to HIV prevention and acquisition. The risks of acute seroconversion, the importance of consistent condom use, partner involvement and counseling as well as the offer of ART in sero discordant couples should all be addressed.
5. Suggested future research based on the exploratory analysis within this study:
    a. Multi centre, prospective cohort study in seropositive focusing on the following parameters:
        i. Time to initiation of ART prior to and following introduction of Option B
        ii. Retention within care following the initiation of FDC in the antenatal period.

iii. Impact of earlier initiation of ART on maternal and newborn outcomes within a South African context.

b. Health systems research:

i. Interventional studies following training of HCWs on national guidelines and on data capturing.

c. Facility level monitoring and evaluation with feedback, assess the impact of

Conclusion

This exploratory, observational, cross sectional study demonstrated successful integration of HIV testing and initiation of ART into antenatal services. Implementation of HIV repeat testing within prescribed time frames however was identified as an area of concern. The implementation of TB screening practices and INH initiation was partially successful. Interventions to improve the delivery of TB and HIV services within the extended PMTCT programme are needed. This study forms the basis for future interventional research with rigorous study designs.

LIST OF APPENDICES

APPENDIX ONE

Amended version

DIAGNOSIS AND MANAGEMENT OF HIV INFECTION IN WOMEN ATTENDING THE ANTENATAL CLINICS IN THE eTHEKWINI MUNICIPALITY IN 2011

Submitted to:
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

For:
In Partial Fulfilment of the Requirement for the
Master of Public Health
Contributes 50% towards the qualification

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Supervisor:
Dr A Voce

2014

Summary

Background: The contribution of the HIV epidemic to morbidity and mortality in pregnancy has been well documented. Despite the overwhelming impact on maternal and child health globally, less than a quarter of women accessed counseling and testing for HIV in pregnancy and less than half accessed an intervention aimed at preventing mother-to-child transmission (PMTCT) following counseling and testing. Provider initiated HIV counseling and testing in a number of health care facilities including antenatal clinics, was recommended in an attempt to improve health outcomes within the expanding HIV epidemic.

Purpose: The study aims to explore the implementation of care for pregnant women living with HIV, specifically initiation of antiretroviral therapy and the tuberculosis screening process. Further, the study aims to determine follow up HIV testing in women who are uninfected at their first antenatal visit.

Objectives: The objectives for women living with HIV are to determine the gestational age at which women are diagnosed with HIV infection, describe the distribution of CD4 counts, determine the gestational age at which antiretroviral treatment is initiated and to determine the proportion of pregnant women living with HIV who are screened for tuberculosis at the visit at which HIV infection is diagnosed. The objectives in those women who are HIV uninfected are to determine the gestational age at which diagnosed uninfected, determine the gestational age at which a second HIV test is offered and to describe the proportion who seroconvert.

Study design: An exploratory, observational, cross-sectional study design presenting both descriptive and analytic statistics will be used.

Setting: The study will be conducted at a sample of clinics within the eThekwini Municipality offering antenatal care. Offering an HIV test to all pregnant women is standard of care at all antenatal clinics.

Study population and study sample: The study population will be those women attending the ANC between 32-36 weeks gestation for the current pregnancy. The management of both women

living with HIV and those that are HIV uninfected, will be documented according to the objectives outlined above.

Data collection: Information related to study variables will be captured on the data capture sheet by the investigator or a trained field worker (see attached data sheet). Data entered onto the data capture sheet from the patient charts will be compared to the PMTCT register for confirmation and to add any missing information. All data will be captured onto an SPSS worksheet for processing and analysis.

Statistical methods: Descriptive statistics specifically the measures of central tendency will be used for all points of the care cascade. In addition for the analytic component of the study, a two sided one sample t-test will be used.

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Appendix 1: List of abbreviations

ANC	antenatal clinics
ART	antiretroviral therapy
AZT	zidovudine
CD4	cluster of differentiation 4
HIV	human immunodeficiency virus
MTCT	mother-to-child transmission
PMTCT	preventing mother-to-child transmission
SPSS	statistical package, originally used as a Statistical Package for the Social Sciences
TB	tuberculosis
WHO	World Health Organisation

Title of study:

Diagnosis and management of HIV infection in women attending antenatal clinics in the eThekwini Municipality in 2011.

Aim of study

The aim of this study is to establish the uptake and management of human immunodeficiency virus (HIV) counseling and testing in pregnant women attending antenatal clinics (ANC) within the eThekwini Municipality in 2011.

Specific objectives:

Data on HIV counselling in pregnancy will be collected. The study will include information on both HIV counselling and follow up management of two groups of women, women living with HIV and women diagnosed as HIV uninfected at their first antenatal clinic visit.
The objectives for women who were found to be HIV infected at the initiation of ANC were to determine:

a) the median gestational age at diagnosis of HIV infection;
b) the distribution of CD4 counts;
c) the median gestational age at initiation of which antiretroviral treatment (ART); and
d) Screening practices for tuberculosis and opportunistic infections.

The objectives for women who were found to be HIV uninfected at initiation of ANC were to determine:

a) the median gestational age at initial and repeat HIV test;
b) the proportion who seroconvert during pregnancy.

Background and literature

Women and girls account for over half of the estimated number of people living with HIV globally.[1] The highest burden of disease is concentrated in women in the reproductive age group. The contribution of the HIV epidemic to morbidity and mortality in pregnancy has been well

documented.[2,3] In South Africa, the Saving Mothers Report documents the outcomes of the confidential enquiry into maternal deaths and HIV was identified as the biggest single cause of maternal deaths, at 44% in the most recent report.[4] More than 90% of childhood HIV infections are due to mother-to-child transmission (MTCT). An estimated 2.5 million children (estimated range of 1.7 million-3.4 million) were living with HIV and 260 000 children died from AIDS-related illnesses at the end of 2009.[1]

Despite this overwhelming impact on maternal and child health globally, only 18 to 21% of women accessed counseling and testing for HIV in pregnancy and an average of 33 to 45% accessed an intervention aimed at preventing mother-to-child transmission (PMTCT) thereafter.[1] Successful PMTCT programmes in high income countries have reduced the MTCT rate to 1%; however MTCT remain high in low income countries at 15 to40%.[1,5] Provider initiated HIV counseling and testing in a number of health care facilities was recommended in an attempt to improve health outcomes within this expanding HIV epidemic.[6]

Antenatal clinics are often the first point of contact with health care for many females living with HIV. Testing for HIV infection at ANC facilitates access to HIV management in pregnancy which improves both maternal and neonatal outcomes.[7] Provider initiated HIV testing in pregnancy is therefore identified as a key objective in the South African National HIV and AIDS and STI Strategic Plan.[8] KwaZulu-Natal had the highest ANC HIV prevalence at 39% in 2009.[9] Information is available from routine surveillance data on the uptake of the antenatal counselling and testing services for HIV. However, limited information is available in three key areas: firstly, gestational age at initiation of the relevant antiretroviral therapy; secondly, implementation of TB screening processes in pregnant women living with HIV; and thirdly, follow up (HIV) testing in uninfected pregnant women.

This study therefore aims to explore the implementation of care for pregnant women living with HIV, specifically initiation of antiretroviral therapy and the TB screening process. Further, the study aims to determine follow up HIV testing in women who are uninfected at their first antenatal visit.

Definitions:

Preventing mother–to-child transmission (PMTCT) [10]**: T**here are four elements to the national PMTCT policy. These include primary prevention of HIV, especially among women of child-bearing age; integration of PMTCT interventions with basic antenatal care, sexual and reproductive health, child and adolescent health and TB services; strengthening postnatal care for the mother-baby pair and provision of an expanded package of PMTCT services. The scope of this study allows capturing of information related to the second and fourth elements.

Antiretroviral therapy is a combination of three antiretroviral drugs. National PMTCT antiretroviral guidelines currently recommend a fixed dose combination of lamivudine or emtracitabine, tenofovir and efavirenz, provided that there are no contra indications to any of the drugs. **[10]**

Study methods

6.1 Study location

The study will be conducted at clinics within the eThekwini Municipality offering antenatal care. A random sample of clinics will be selected for the purposes of this study.

6.2 Study setting

Offering an HIV test to all pregnant women is standard of care at all antenatal clinics. Women identified as first time attendees receive group counselling on the benefits and possible outcomes of an HIV test. Rapid HIV testing is then individually performed by the clinic nurses on women who consent to testing. The result of the test is then disclosed to the woman with the relevant advice. The attending clinician or senior nurse at the clinic will document the gestational age based on the date of the last normal menstrual period, perform a clinical examination and if required, an ultrasound investigation. In women living with HIV, WHO clinical staging of disease and CD4 assays are recommended at this first visit.

The current PMTCT guidelines advise that all pregnant women are initiated on ART irrespective of their CD4 count. Fixed dose combinations have been made available and are to be initiated on site on the day of HIV diagnosis.

6.3 Study population

The study population will be those women attending the ANC between 32 and 36 weeks gestation for the current pregnancy. The management of both women living with HIV and those that are HIV uninfected, will be documented according to the objectives outlined above. The target population for the study will then be attendees at antenatal clinics within the eThekwini Municipality.

Study design

7.1 Type of research

This study can be categorized as health systems research.

7.2 Study design

An exploratory, observational, cross-sectional study design presenting both descriptive and analytic statistics will be used.

7.3 Study period

The data for the retrospective review will be collected over a period of one year months between June 2013 and June 2014. Analysis and write up will occur over the following year. The total period for data collection and analysis will thus be 18 months.

7.4 Inclusion and exclusion criteria

The inclusion criteria for the study include:

7.4.1. Pregnant women over the age of 18 years attending ANC in eThekwini district clinics;

7.4.2. Pregnant women between 32 and 36 week gestational age; and

7.4.3. Women who accept the offer for an HIV test.

The exclusion criteria include:

7.4.4. Women whose first ANC visit occurs after 32 weeks;

7.4.5. Women who delivered prior to 32-36 weeks gestation/ pre term labour; and

7.4.6. Women whose HIV status was known prior to the current pregnancy.

7.5 Sampling strategy and sample size

Two data sets from antenatal clinics within the eThekwini municipality were obtained from the Department of Health. The variable of interest for sampling of clinics in this protocol was the number of clients attending the facility for the following visits:

- First antenatal visit,
- First antenatal visit occurring at 20 weeks or later,
- First antenatal visit occurring before 20 weeks, and
- Follow up (antenatal) visits.

Data for monthly antenatal attendance between and including January 2012 to December 2012 was reviewed. Further data on the other three factors listed above was only available between and including January 2012 to September 2012.

A total of 154 clinics within the eThekwini municipality offered antenatal care during this time frame. Clinics with an average of less than 10 clients per month were excluded from the sampling frame (n=54). In addition clinics in which attendance totals did not tally, were also excluded (n=5). A total of 95 clinics were therefore included in the sampling frame.

A two stage cluster sampling of 30 X 7 strategy is being proposed for the selection of clinics from the eligible clinics. The clinics were stratified into three categories depending on the average monthly number of antenatal attendees presenting for first time antenatal visits. Fifty four clinics had less than 50 attendees, 28 clinics had between 50-99 attendees and 12 clinics had a 100 or more attendees. A total of 30 clinics were then proportionally sampled to achieve representativeness. Seventeen clinics from the first stratum, nine from the second and four from the third stratum were then selected for data collection.

If we assume pregnant women present in random order to the clinics chosen, consecutive sampling of this population will generate a representative sample of the population in that area. For the descriptive purposes of this study, the sample will be constrained by the number of women between 32 to 36 weeks gestation that present to the chosen clinic on that day. All charts will be reviewed for eligibility and data will be captured as outlined.

Data on seven HIV infected and seven uninfected women (based on the 30X7 sampling frame) will be captured.

Data collection methods and tools

Women attending the ANC for the first time are issued an ANC card at that visit. Relevant information is recorded in this card and includes:

- Demographic data;
- The date of the first offer of an HIV test;
- The result of the (rapid) HIV test;
- The date and result of the CD4 count; and
- The initiation date of the antiretroviral therapy intervention.

The clinic has a PMTCT register which also captures this information.

Information related to study variables outlined in section 9 will be captured on the data capture sheet by the investigator or a trained field worker (see attached data sheet). Data entered onto the data capture sheet from the patient charts will be compared to the PMTCT register for confirmation and to add any missing information.

Data from the data capture sheets will be entered onto an SPSS worksheet for processing and analysis.

Statistical planning (variables)

List of variables for collection:

- Age
- Parity
- Gestational age at first ANC visit and number of subsequent antenatal visits
- Gestational age at which HIV test done in current pregnancy
- Result of HIV rapid tests
- Gestational age at which CD4 count taken
- Gestational age at which CD4 count results received
- Results of CD4 assays
- Gestational age at which (first) diagnosed uninfected
- Gestational age at which a second HIV test offered and performed

- Result of second HIV test
- TB symptom checklist administered in those women living with HIV
- Outcome of TB symptom checklist
- Initiation of antiretroviral therapy occurred at the clinic or referral to local hospital for antiretroviral therapy initiation
- Antiretroviral therapy initiated by nurse or doctor

Measures to improve validity:

Multiple sources of data collection will be used to verify information collected. The patient file will be the primary source of data and the accuracy of this information will be checked against the clinic registers and the PMTCT registers.

Measures to reduce bias:

Selection bias will be overcome by consecutive sampling of all eligible antenatal attendees.
Information bias will be addressed by training of field workers on use of data collection form and understanding of the PMTCT register to extract data.

Data quality, storage and safety

Multiple sources of data will help improve data quality.
Once data has been extracted all the data capture sheets will be completed and kept in a locked cupboard. Data will be shared among members of the research team and for the purposes of a report, otherwise data will be handled as confidential.

Data analysis techniques

The analytic component of the study will be derived from measuring the data collected against the standard of care outlined in National PMTCT Guidelines.

Statistical analysis

Data capturing and statistical analysis will be performed using SPSS version 18. Descriptive statistics specifically the measures of central tendency will be used for all points of the care

cascade. The mean gestational age, the median CD4 count and median time to antiretroviral therapy initiation, the proportion screened for TB and the proportion of HIV uninfected women who seroconvert with a seroconversion rate per unit time are some of the statistics that will be reported. In addition, a two-sided one sample t-test will be used to test for the analytic component; specifically the lag time to implementation of ART intervention as compared to the timelines outlined in the National PMTCT Guidelines.

15. Limitations of the study

15.1 There may be missing data in the patient charts and PMTCT register. This is a limitation of using a retrospective chart review. However, by using multiple data sources, minimisation of missing data should result. Further laboratory results can be tracked by the investigator on the laboratory data management system if necessary.

15.2 Antenatal clinics schedule repeat antenatal visits on a specific day of the week. Sampling would have to occur on these days and might introduce a bias since these attendees may not adhere to appointment days and the sample may then have women who are being managed differently.

16. Ethical considerations

No additional harm will result from participation in this study. The routine antenatal data from each clinic will be collected and analysed. There will be no immediate benefit to the participants of the study; however, there may be an operational systems benefit for future ANC attendees depending on the results from the study.

Ethical approval for this study will be sought from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal. Further permission will be obtained from the national and provincial departments of health to conduct the study at the clinics.

17. Budget:

The budget will be related to travel costs incurred on travel to the clinics sampled, to the administrative costs and to reimbursements of the field workers that will assist with collection of data.

18. Key references:

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APPENDIX ONE

Original version

DIAGNOSIS AND MANAGEMENT OF HIV INFECTION IN WOMEN ATTENDING THE ANTENATAL CLINICS IN THE eTHEKWINI MUNICIPALITY IN 2011

Submitted to:
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

For:
In Partial Fulfilment of the Requirement for the
Master of Public Health
Contributes 50% towards the qualification

Munira Khan
Student number: 913480931
HPCSA number 0473758

Supervisor:
Dr A Voce

2011

Summary

Background: The contribution of the HIV epidemic to morbidity and mortality in pregnancy has been well documented. Despite the overwhelming impact on maternal and child health globally, less than a quarter of women accessed counseling and testing for HIV in pregnancy and less than half accessed an intervention aimed at preventing mother-to-child transmission (PMTCT) following counseling and testing. Provider initiated HIV counseling and testing in a number of health care facilities including antenatal clinics, was recommended in an attempt to improve health outcomes within the expanding HIV epidemic.

Purpose: The study aims to explore the implementation of care for pregnant women living with HIV, specifically initiation of short course antiretroviral therapy for the purposes of PMTCT in women who do not meet eligibility criteria for antiretroviral therapy, initiation of antiretroviral therapy when indicated on clinical or immunological basis, and the tuberculosis screening process. Further, the study aims to determine follow up HIV testing in women who are uninfected at their first antenatal visit.

Objectives: The objectives for women living with HIV are to determine the median gestational age at which HIV infection is diagnosed, describe the distribution of CD4 counts, determine the median gestational age at initiation of antiretroviral treatment and to determine the TB screening practices. The objectives in those women who are HIV uninfected are to determine the median gestational age at initial and repeat HIV testing and to describe the proportion who seroconvert.

Study design: An exploratory, observational, cross-sectional study design with descriptive and analytic statistics will be used.

Setting: The study will be conducted at a sample of clinics within the eThekwini Municipality offering antenatal care. Offering an HIV test to all pregnant women is standard of care at all antenatal clinics.

Study population and study sample: The study population will be review of records of those women attending the ANC between 32-36 weeks gestation for the current pregnancy. The

management of both women living with HIV and those that are HIV uninfected, will be documented according to the objectives outlined above.

Data collection: Information related to study variables will be captured on the data capture sheet by the investigator or a trained field worker (see attached data sheet). Data entered onto the data capture sheet from the patient charts will be compared to the PMTCT register for confirmation and to add any missing information. All data will be captured onto an SPSS worksheet for processing and analysis.

Statistical methods: Descriptive statistics specifically the measures of central tendency will be used for all points of the care cascade. In addition for the analytic component of the study, a two sided one sample t-test will be used.

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Appendix 1: List of abbreviations

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ART	antiretroviral therapy
AZT	zidovudine
CD4	cluster of differentiation 4
HIV	human immunodeficiency virus
MTCT	mother-to-child transmission
PMTCT	preventing mother-to-child transmission
SPSS	statistical package, originally used as a Statistical Package for the Social Package
TB	tuberculosis
WHO	World Health Organisation

1. Title of study:

Diagnosis and management of HIV infection in women attending antenatal clinics in the eThekwini Municipality in 2011.

2. Aim of study

The aim of this study is to establish the uptake and management of human immunodeficiency virus (HIV) counseling and testing in pregnant women attending antenatal clinics (ANC) within the eThekwini Municipality in 2011.

3. Specific objectives:

Data on HIV counselling in pregnancy will be collected. The study will include information on both HIV counselling and follow up management of two groups of women, women living with HIV and women diagnosed as HIV uninfected at their first antenatal clinic visit.

The objectives for women living with HIV are to:

a) Determine the gestational age at which women are diagnosed with HIV infection;
b) Describe the distribution of CD4 counts;
c) Determine the gestational age at which the appropriate antiretroviral (ART) intervention is initiated; and
d) Determine the proportion of pregnant women living with HIV who are screened for tuberculosis (TB) at the visit at which HIV infection is diagnosed.

The objectives in HIV uninfected women are to:

a) Determine the gestational age at which women are diagnosed uninfected;
b) Determine the gestational age at which a second HIV test is offered to women; and
c) Describe the seroconversion rate in pregnant women following an initial HIV negative test.

4. Background and literature

Women and girls account for over half of the estimated number of people living with HIV globally.[1] The highest burden of disease is concentrated in women in the reproductive age group. The contribution of the HIV epidemic to morbidity and mortality in pregnancy has been well documented.[2,3] In South Africa, the Saving Mothers Report documents the outcomes of the confidential enquiry into maternal deaths and HIV was identified as the biggest single cause of maternal deaths, at 44% in the most recent report.[4] More than 90% of childhood HIV infections are due to mother-to-child transmission (MTCT). An estimated 2.5 million children (estimated range of 1.7 million-3.4 million) were living with HIV and 260 000 children died from AIDS-related illnesses at the end of 2009.[1]

Despite this overwhelming impact on maternal and child health globally, only 18 to 21% of women accessed counseling and testing for HIV in pregnancy and an average of 33 to 45% accessed an intervention aimed at preventing mother-to-child transmission (PMTCT) thereafter.[1] Successful PMTCT programmes in high income countries have reduced the MTCT rate to 1%; however MTCT remain high in low income countries at 15 to40%.[1,5] Provider initiated HIV counseling and testing in a number of health care facilities was recommended in an attempt to improve health outcomes within this expanding HIV epidemic.[6]

Antenatal clinics are often the first point of contact with health care for many females living with HIV. Testing for HIV infection at ANC facilitates access to HIV management in pregnancy which improves both maternal and neonatal outcomes.[7] Provider initiated HIV testing in pregnancy is therefore identified as a key objective in the South African National HIV and AIDS and STI Strategic Plan.[8] KwaZulu-Natal had the highest ANC HIV prevalence at 39% in 2009.[9] Information is available from routine surveillance data on the uptake of the antenatal counselling and testing services for HIV. However, limited information is available in three key areas: firstly, gestational age at initiation of the relevant antiretroviral therapy; secondly, implementation of TB screening processes in pregnant women living with HIV; and thirdly, follow up (HIV) testing in uninfected pregnant women.

This study therefore aims to explore the implementation of care for pregnant women living with HIV, specifically initiation of short course antiretroviral therapy for the purposes of PMTCT in women who do not meet eligibility criteria for antiretroviral therapy, initiation of antiretroviral therapy when indicated on clinical or immunological basis, the TB screening process. Further, the study aims to determine follow up HIV testing in women who are uninfected at their first antenatal visit.

Definitions:

Appropriate antiretroviral treatment: According to National PMTCT guidelines [10], a course of zidovudine (AZT) should be commenced from 14 weeks gestation onwards in women living with HIV with CD4 counts above 350 cells/ mm^3. Ideally this should be commenced upon diagnosis of HIV infection and discontinued upon receipt of CD4 count results below 350 cells/ mm^3. Women with CD4 counts below 350 cells/ mm^3 irrespective of World Health Organisation (WHO) clinical staging for HIV qualify for initiation of antiretroviral therapy within two weeks ('fast tracking').

Preventing mother–to-child transmission (PMTCT) [10]: There are four elements to the national PMTCT policy. These include primary prevention of HIV, especially among women of child-bearing age; integration of PMTCT interventions with basic antenatal care, sexual and reproductive health, child and adolescent health and TB services; strengthening postnatal care for the mother-baby pair and provision of an expanded package of PMTCT services. The scope of this study allows capturing of information related to the second and fourth elements.

Antiretroviral therapy is a combination of three antiretroviral drugs. National PMTCT antiretroviral guidelines currently recommend a combination of lamivudine, tenofivir and nevaripine. [10]

5. Study methods

5.1 Study location

The study will be conducted at clinics within the eThekwini Municipality offering antenatal care. The referral system within the municipality links clinics within a certain geographic region to a dedicated district- level hospital. An average of 10 to 14 clinics are linked to a district- level hospital and for the purposes of this study, a single referral stream of clinics will be selected.

5.2 Study setting

Offering an HIV test to all pregnant women is standard of care at all antenatal clinics. Women identified as first time attendees receive group counselling on the benefits and possible outcomes of an HIV test. Rapid HIV testing is then individually performed by the clinic nurses on women who consent to testing. The result of the test is then disclosed to the woman with the relevant advice. The attending clinician or senior nurse at the clinic will document the gestational age based on the date of the last normal menstrual period, perform a clinical examination and if required, an ultrasound investigation. In women living with HIV, WHO clinical staging of disease and CD4 assays are recommended at this first visit.

The follow up of women living with HIV involves a review of the CD4 count within the week in keeping with a one-week turn around time for CD4 count results. Additionally, those with WHO clinical stage 3 or 4, co-infected with TB or with CD4 counts below 350 cells/ mm^3 require initiation of antiretroviral therapy within two weeks. In women who do not meet these criteria, prophylaxis with zidovudine is recommended from 14 weeks gestation.

5.3 Study population

The study population will be records of those women attending the ANC between 32 and36 weeks gestation for the current pregnancy. The management of both women living with HIV

and those that are HIV uninfected, will be documented according to the objectives outlined above. The target population for the study will then be attendees at antenatal clinics within the eThekwini Municipality.

6. Study design

6.1 Type of research

This study can be categorized as health systems research.

6.2 Study design

An exploratory, observational, cross-sectional study design will be used.

6.3 Study period

The data for the retrospective review will be collected over a period of six months between July 2011 and December 2011. Analysis and write up will occur over the following year. The total period for data collection and analysis will thus be 18 months.

6.4 Inclusion and exclusion criteria

The inclusion criteria for the study include:

6.4.1. Pregnant women over the age of 18 years attending ANC in eThekwini district clinics;

6.4.2. Pregnant women between 32 and 36 week gestational age; and

6.4.3. Women who accept the offer for an HIV test.

The exclusion criteria include:

6.4.4. Women whose first ANC visit occurs after 32 weeks;

6.4.5. Women who delivered prior to 32-36 weeks gestation/ pre term labour; and

6.4.6. Women whose HIV status was known prior to the current pregnancy.

6.5 Sampling strategy and sample size

A multi stage sampling process will be used. Referral systems will be identified and a single referral system will be chosen at random. On average 10 to14 clinics refer to one district- level hospital. The number of attendees at these clinics is documented in the District Health Information System. All clinics within this one referral system will be

sampled for two groups of women: those living with HIV either requiring AZT prophylaxis or antiretroviral therapy and those uninfected at their first ANC visit.

A specific clinic will be visited on one randomly chosen day of the week to review charts and documents for that day to identify all women between 32 and 36 weeks gestation who accepted an HIV test at their first ANC visit.

If we assume pregnant women present in random order to the clinics chosen, consecutive sampling of this population will generate a representative sample of the population in that area. For the descriptive purposes of this study, the sample will be constrained by the number of women between 32 to 36 weeks gestation that present to the chosen clinic on that day. All charts will be reviewed for eligibility and data will be captured as outlined. Data on the maximum number of patients that can be obtained within a specific timeframe will be captured.

For the analytic component, the sample size calculation was based on a provincial HIV prevalence of 39%. With the null hypothesis of time to ART initiation being 14 days and the alternate hypothesis being 20 days, a total of 45 women would be needed to achieve 80% power in order to detect a difference of -6.0 between the hypothesis mean of 14 and the alternate hypotheses mean of 20 with an estimated standard deviation of 14.0 and with a significance level (alpha) of 0.05 using a two sided one sample t- test.

Therefore the sample size needed for a sample of women living with HIV would be 100, with 50 women that meet eligibility criteria for antiretroviral therapy and 50 women that require AZT prophylaxis. The sample size required for the uninfected women will be 150 using the correlation to the HIV prevalence of 39%, the correlated HIV uninfected pregnant women in KwaZulu- Natal would be 61%. Therefore the total sample size required will be 250.

7. Data collection methods and tools

Women attending the ANC for the first time are issued an ANC card at that visit. Relevant information is recorded in this card and includes:

- Demographic data;
- The date of the first offer of an HIV test;
- The result of the (rapid) HIV test;

- The date and result of the CD4 count; and
- The initiation date of the appropriate antiretroviral therapy intervention.

The clinic has a PMTCT register which also captures this information.

Information related to study variables outlined in section 9 will be captured on the data capture sheet by the investigator or a trained field worker (see attached data sheet). Data entered onto the data capture sheet from the patient charts will be compared to the PMTCT register for confirmation and to add any missing information.

Data from the data capture sheets will be entered onto an SPSS worksheet for processing and analysis.

8. Statistical planning (variables)

List of variables for collection:

- Age
- Parity
- Marital status
- Level of education
- Gestational age at first ANC visit and number of subsequent antenatal visits
- Gestational age at which HIV test done in current pregnancy
- Result of HIV rapid tests
- Gestational age at which CD4 count taken
- Gestational age at which CD4 count results received
- Results of CD4 assays
- Gestational age at which AZT initiated in those with CD4 counts above 350 cells/ mm^3
- Gestational age at which antiretroviral therapy initiated in those with CD4 counts below 350 cells/ mm^3
- Gestational age at which (first) diagnosed uninfected
- Gestational age at which a second HIV test offered and performed
- Result of second HIV test
- TB symptom checklist administered in those women living with HIV
- Outcome of TB symptom checklist

- Initiation of antiretroviral therapy occurred at the clinic or referral to local hospital for antiretroviral therapy initiation
- Antiretroviral therapy initiated by nurse or doctor

9. Measures to improve validity:

Multiple sources of data collection will be used to verify information collected. The patient file will be the primary source of data and the accuracy of this information will be checked against the clinic registers and the PMTCT registers.

10. Measures to reduce bias:

Selection bias will be overcome by consecutive sampling of all eligible antenatal attendees.
Information bias will be addressed by training of field workers on use of data collection form and understanding of the PMTCT register to extract data.

11. Data quality, storage and safety

Multiple sources of data will help improve data quality.
Once data has been extracted all the data capture sheets will be completed and kept in a locked cupboard. Data will be shared among members of the research team and for the purposes of a report, otherwise data will be handled as confidential.

12. Data analysis techniques

The analytic component of the study will be derived from measuring the data collected against the standard of care outlined in National PMTCT Guidelines.

13. Statistical analysis

Data capturing and statistical analysis will be performed using SPSS version 18. Descriptive statistics specifically the measures of central tendency will be used for all points of the care cascade. The mean gestational age, the median CD4 count and median time to antiretroviral therapy initiation, the proportion screened for TB and the proportion of HIV uninfected women who seroconvert with a seroconversion rate per unit time are some of the statistics that will be reported. In addition, a two-sided one sample t-test will be used to test for the analytic

component; specifically the lag time to implementation of ART intervention as compared to the timelines outlined in the National PMTCT Guidelines.

14. Limitations of the study

14.1 There may be missing data in the patient charts and PMTCT register. This is a limitation of using a retrospective chart review. However, by using multiple data sources, minimisation of missing data should result. Further laboratory results can be tracked by the investigator on the laboratory data management system if necessary.

14.2 Only one district-level hospital with its referral stream of clinics can be studied which might result in selection bias.

14.3 Antenatal clinics schedule repeat antenatal visits on a specific day of the week. Sampling would have to occur on these days and might introduce a bias since these attendees may not adhere to appointment days and the sample may then have women who are being managed differently.

15. Ethical considerations

No additional harm will result from participation in this study. The routine antenatal data from each clinic will be collected and analysed. There will be no immediate benefit to the participants of the study; however, there may be an operational systems benefit for future ANC attendees depending on the results from the study.

Ethical approval for this study will be sought from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal. Further permission will be obtained from the national and provincial departments of health to conduct the study at the clinics.

16. Budget:

The budget will be related to travel costs incurred on travel to the clinics sampled, to the administrative costs and to reimbursements of the field workers that will assist with collection of data.

17. Key references:

1. UNAIDS/ World Health Organisation (2010). *UNAIDS report on the global epidemic-* December 2010. UNAIDS/10.11E. Geneva: UNAIDS.
2. Khan M, Pillay T, Moodley JM, Connolly CA. Maternal mortality associated with tuberculosis-HIV-1 co-infection in Durban, South Africa. *AIDS* 2001; 15: 1857- 1863.
3. Bicego G, Boerma JT, Ronsmans C. The effect of AIDS on maternal mortality in Malawi and Zimbabwe. *AIDS* 2002; 16: 1078- 1081.
4. National Committee on Confidential Enquiries into Maternal Deaths (2007). *Saving Mothers 2005-2007: Fourth Report on Confidential Enquiries into Maternal Deaths in South Africa.* Government Printer, Pretoria: Department of Health.
5. European Collaborative Study. The mother- to- child HIV transmission epidemic in Europe: evolving in the East and established in the West. *AIDS* 2006; 20: 1419- 1427.
6. Centres for Disease Control and Prevention. Revised Recommendations for HIV testing of Adults, Adolescents and Pregnant women in Health Care Settings. *Morb Mortal Wkly Rep* 2006; 65: 1-17.
7. World Health Organisation. *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Recommendations for a Public Health Approach.* 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf. Accessed 5 May 2011.
8. Department of Health (2008). *HIV and AIDS and STI Strategic Plan for South Africa.* Available at: http://www.info.gov.za/otherdocs/2007/aidsplan07.pdf. Accessed 5 May 2011.
9. Department of Health (2010). *National Antenatal Sentinel HIV and Syphilis prevalence survey in South Africa, 2009.* Pretoria: Department of Health.
10. Department of Health (2010). *Clinical Guidelines: PMTCT (Prevention of Mother- to- Child Transmission), 2010.* Pretoria: Department of Health.

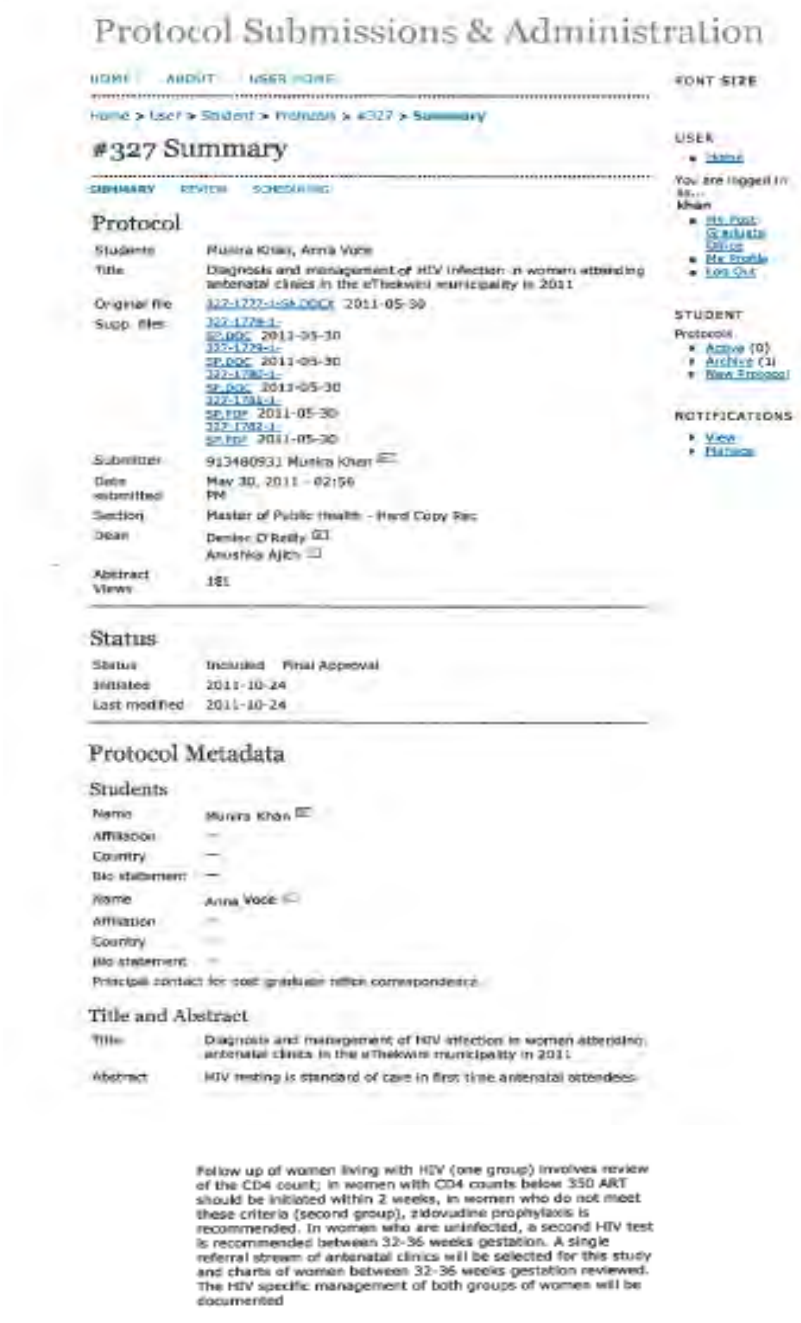
APPENDIX TWO

DATA COLLECTION TOOL

CLINIC NAME	
PARTICIPANT INITIALS	
PARTICIPANT IDENTITY NUMBER	
RACE (tick correct option):	☐ Black ☐ Indian ☐ Coloured ☐ White ☐ Other
DATE OF BIRTH _____	**AGE (years)** _____
PARITY 1 2 3 4 **(circle appropriate number)**	**GRAVIDA** 1 2 3 4 **(circle appropriate number)**
1st day of LNMP *(dd/mmm/yyyy)* _____	**EDD** *(dd/mmm/yyyy)* _____
MARITAL STATUS (tick correct option):	☐ Single/ widowed ☐ Single in stable relationship ☐ Married ☐ Divorced
GESTATIONAL AGE AT FIRST ANC VISIT	_____ weeks *(dd/mmm/yyyy)*_____
HIV SPECIFIC INFORMATION:	
1. Agreeable to an HIV test	☐ Yes ☐ No
2. Result of HIV test	☐ infected ☐ uninfected
3. If infected, result of CD4 count	_____cells/ mm^3
4. In those infected, record *date* for the following:	**NOT APPLICABLE** ☐
a. HIV infection diagnosed	☐☐/☐☐/☐☐☐☐
b. CD4 count taken	☐☐/☐☐/☐☐☐☐
c. CD4 count results received at clinic	☐☐/☐☐/☐☐☐☐
d. HAART initiated	☐☐/☐☐/☐☐☐☐ _____ weeks
5. In women requiring HAART:	
a. Site at which initiation occurred	☐ Clinic ☐ ☐ Referred to hospital
b. Staff member responsible for initiation	☐ Nurse ☐ Doctor
6. In those infected, with regards to TB:	
a. was a TB symptom questionnaire administered?	☐ Yes ☐ No *If yes*
b. was TB suspected?	☐ Yes ☐ No
c. was the patient referred for investigation?	☐ Yes ☐ No
7. In those uninfected, record *date* for the following:	**NOT APPLICABLE** ☐
a. HIV status noted	☐☐/☐☐/☐☐☐☐ _ _____ weeks
b. Offer of second test	☐☐/☐☐/☐☐☐☐ _____ weeks
c. Result of second test in women who tested uninfected at FIRST TEST	☐ Infected ☐ Remains uninfected

APPENDIX THREE

POSTGRADUATE APPROVAL



Protocol Submissions & Administration

HOME | ABOUT | USER HOME

Home > User > Student > Protocols > #327 > Summary

#327 Summary

SUMMARY | REVIEW | SCHEDULING

Protocol

Students	Munira Khan, Anna Voce
Title	Diagnosis and management of HIV infection in women attending antenatal clinics in the eThekwini municipality in 2011
Original file	327-1777-1-SR.DOCX 2011-05-30
Supp. files	327-1778-1-SD.DOC 2011-05-30 333-1779-1-SP.DOC 2011-05-30 327-1780-1-SP.DOC 2011-05-30 327-1781-1-SP.PDF 2011-05-30 327-1782-1-SP.PDF 2011-05-30
Submitter	913480931 Munira Khan
Date submitted	May 30, 2011 - 02:56 PM
Section	Master of Public Health - Hard Copy Rec
Dean	Denise O'Reilly Anushka Ajith
Abstract Views	181

Status

Status	Included Final Approval
Initiated	2011-10-24
Last modified	2011-10-24

Protocol Metadata

Students

Name	Munira Khan
Affiliation	—
Country	—
Bio statement	—
Name	Anna Voce
Affiliation	—
Country	—
Bio statement	—

Principal contact for post graduate office correspondence

Title and Abstract

Title	Diagnosis and management of HIV infection in women attending antenatal clinics in the eThekwini municipality in 2011
Abstract	HIV testing is standard of care in first time antenatal attendees.

Follow up of women living with HIV (one group) involves review of the CD4 count; in women with CD4 counts below 350 ART should be initiated within 2 weeks, in women who do not meet these criteria (second group), zidovudine prophylaxis is recommended. In women who are uninfected, a second HIV test is recommended between 32-36 weeks gestation. A single referral stream of antenatal clinics will be selected for this study and charts of women between 32-36 weeks gestation reviewed. The HIV specific management of both groups of women will be documented

FONT SIZE

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Protocols
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- Archive (3)
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APPENDIX FOUR

BREC APPROVALS

UNIVERSITY OF
KWAZULU-NATAL
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YAKWAZULU-NATALI
RESEARCH OFFICE
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

16 August 2012

Dr. M Khan
Department of Public Health Medicine
Nelson R. Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Khan

PROTOCOL: Diagnosis and management of HIV infection in women attending antenatal clinics in the eThekwini municipality in 2011. REF: BE096/11

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 02 June 2011.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 30 July 2012 to queries raised on 08 December 2011 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 16 August 2012.

This approval is valid for one year from **16 August 2012.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **11 September 2012.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

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Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

29 November 2013

Dr. M Khan
Department of Public Health Medicine
Nelson R. Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Khan

PROTOCOL: Diagnosis and management of HIV infection in women attending antenatal clinics in the eThekwini municipality in 2011. REF: BE096/11

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved: 16 August 2013
Expiration of Ethical Approval: 15 August 2014

I wish to advise you that your application for Recertification dated 19 November 2013 for the above protocol has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

BREC has condoned the lapse period of certification.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The approval will be ratified by the Committee at a meeting to be held on 10 December 2013.

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

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Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: [illegible]
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

12 September 2014

Dr. M Khan
Department of Public Health Medicine
Nelson R. Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Khan

PROTOCOL: Diagnosis and management of HIV infection in women attending antenatal clinics in the eThekwini municipality in 2011. REF: BE096/11

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	16 August 2014
Expiration of Ethical Approval:	15 August 2015

I wish to advise you that your application for Recertification received on 04 August 2014 for the above protocol has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The approval will be ratified by the Committee at a meeting to be held on 14 October 2014.

Yours sincerely

Ms A Marimuthu
Senior Administrator: Biomedical Research Ethics

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Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

19 June 2014

Dr. M Khan
Department of Public Health Medicine
Nelson R. Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Khan

PROTOCOL: Diagnosis and management of HIV infection in women attending antenatal clinics in the eThekwini municipality in 2011. REF: BE096/11

We wish to advise you that your letter dated 03 June 2014 requesting approval of Amendments due to minor changes in the PMTCT guidelines and statistical sampling for the above study has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee.

The following have been noted and approved:

- Letter dated 02 June 2014 with amendments to protocol.

This approval will be ratified at the next BREC meeting to be held on 24 June 2014.

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

APPENDIX FIVE

PROVINCIAL AND MUNICIPAL APPROVALS

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : **HRKM20/12**
Enquiries : **Mrs G Khumalo**
Telephone : 033 – 3953189

27 March 2012

Dear Dr M Khan

Subject: Approval of a Research Proposal

1. The research proposal titled '**Diagnosis and management of HIV infection in women attending the antenatal clinics in the eThekwini Municipality in 2011'** was reviewed by the KwaZulu-Natal Department of Health.

The proposal is hereby **approved** for research to be undertaken at selected clinics in eThekwini District.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mrs G Khumalo on 033-3953189.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
KwaZulu-Natal Department of Health
Date: 28/03/2012

ETHEKWINI MUNICIPALITY

HEALTH UNIT

9 Archie Gumede Place, Durban, 4001
P O Box 2443, Durban, 4000
Tel: 031 311 3523, Fax: 031 311 3530
www.durban.gov.za

Dear Munira Khan

28 May 2014

Subject: Approval of a research proposal.

The research proposal titled: **Diagnosis and Management of HIV Infection in Women Attending the Antenatal Clinics in the EThekwini Municipality in 2014,** was reviewed by the eThekwini Municipal Health Unit Research Committee. The study is hereby **approved for the eThekwini Municipality clinics.**

The following to be noted:

- Submission of the indemnity form obtainable from the EThekwini Municipality Health Unit before commencement of the study.
- Prior arrangements to be made with the facility and an assurance that all services will not be disrupted.
- No staff member should be used for collecting data for the researchers.
- **Progress reports to be provided and the final report of the study to the eThekwini Municipality Health Unit or emailed to: grace.mufamadi@durban.gov.za**
- Obtain permission from the eThekwini municipality Health Unit for press releases and release of results to communities/stakeholders.
- The Unit has to receive recognition for the assistance given.
- Any amendment to the study to be communicated with the eThekwini Municipality Health Unit and the relevant amendment form obtainable from the unit to be submitted.
- Withdrawal of permission to conduct research will be left to the discretion of the eThekwini Municipality Health Unit.

Yours faithfully

Dr Thando Ndimande

Signature: _____

Deputy Head for Health Unit

Date: 09/06/14

APPENDIX SIX

INSTRUCTIONS TO AUTHORS FOR SELECTED JOURNAL

BMC Health Services Research

BMC Health Services Research is an open access, peer-reviewed journal that considers articles on all aspects of health services research, including delivery of care, management of health services, assessment of healthcare needs, measurement of outcomes, allocation of healthcare resources, evaluation of different health markets and health services organizations, international comparative analysis of health systems, health economics and the impact of health policies and regulations.

BMC Health Services Research is part of the BMC series which publishes subject-specific journals focused on the needs of individual research communities across all areas of biology and medicine. We offer an efficient, fair and friendly peer review service, and are committed to publishing all sound science, provided that there is some advance in knowledge presented by the work.

Submission process

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

Please note that *BMC Health Services Research* levies an article-processing charge on all accepted Research articles; if the submitting author's institution is a BioMed Central member the cost of the article-processing charge may be covered by the membership (see About page for detail). Please note that the membership is only automatically recognised on submission if the submitting author is based at the member institution.

To facilitate rapid publication and to minimize administrative costs, *BMC Health Services Research* prefers online submission.

Files can be submitted as a batch, or one by one. The submission process can be interrupted at any time; when users return to the site, they can carry on where they left off.

See below for examples of word processor and graphics file formats that can be accepted for the main manuscript document by the online submission system. Additional files of any type, such as movies, animations, or original data files, can also be submitted as part of the manuscript.

During submission you will be asked to provide a cover letter. Use this to explain why your manuscript should be published in the journal, to elaborate on any issues relating to our editorial policies in the 'About *BMC Health Services Research*' page, and to declare any potential competing interests. You will be also asked to provide the contact details (including email addresses) of potential peer reviewers for your manuscript. These should be experts in their field, who will be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past five years, should not be current collaborators, and should not be members of the same research institution. Suggested reviewers will be considered alongside potential reviewers recommended by the Editorial team, Editorial Advisors, Section Editors and Associate Editors.

Assistance with the process of manuscript preparation and submission is available from BioMed Central customer support team.

We also provide a collection of links to useful tools and resources for scientific authors on our Useful Tools page.

File formats

The following word processor file formats are acceptable for the main manuscript document:

- Microsoft word (DOC, DOCX)

- Rich text format (RTF)
- Portable document format (PDF)
- TeX/LaTeX (use BioMed Central's TeX template)
- DeVice Independent format (DVI)

TeX/LaTeX users: Please use BioMed Central's TeX template and BibTeX stylefile if you use TeX format. During the TeX submission process, please submit your TeX file as the main manuscript file and your bib/bbl file as a dependent file. Please also convert your TeX file into a PDF and submit this PDF as an additional file with the name 'Reference PDF'. This PDF will be used by internal staff as a reference point to check the layout of the article as the author intended. Please also note that all figures must be coded at the end of the TeX file and not inline.

If you have used another template for your manuscript, or if you do not wish to use BibTeX, then please submit your manuscript as a DVI file. We do not recommend converting to RTF.

For all TeX submissions, all relevant editable source must be submitted during the submission process. Failing to submit these source files will cause unnecessary delays in the publication procedures.

Publishing Datasets

Through a special arrangement with LabArchives, LLC, authors submitting manuscripts to BMC Health Services Research can obtain a complimentary subscription to LabArchives with an allotment of 100MB of storage. LabArchives is an Electronic Laboratory Notebook which will enable scientists to share and publish data files in situ; you can then link your paper to these data. Data files linked to published articles are assigned digital object identifiers (DOIs) and will remain available in perpetuity. Use of LabArchives or similar data publishing services does not replace preexisting data deposition requirements, such as for nucleic acid sequences, protein sequences and atomic coordinates.

Instructions on assigning DOIs to datasets, so they can be permanently linked to publications, can be found on the LabArchives website. Use of LabArchives' software has no influence on the editorial decision to accept or reject a manuscript.

Authors linking datasets to their publications should include an Availability of supporting data section in their manuscript and cite the dataset in their reference list.

Preparing main manuscript text

General guidelines of the journal's style and language are given below.

Overview of manuscript sections for Research articles

Manuscripts for Research articles submitted to *BMC Health Services Research* should be divided into the following sections (in this order):

- Title page
- Abstract
- Keywords
- Background
- Methods
- Results and discussion
- Conclusions
- List of abbreviations used (if any)
- Competing interests
- Authors' contributions
- Authors' information
- Acknowledgements
- Endnotes
- References
- Illustrations and figures (if any)
- Tables and captions

- Preparing additional files

The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

The databases for which we can provide direct links are: EMBL Nucleotide Sequence Database (EMBL), DNA Data Bank of Japan (DDBJ), GenBank at the NCBI (GenBank), Protein Data Bank (PDB), Protein Information Resource (PIR) and the Swiss-Prot Protein Database (Swiss-Prot).

You can download a template (Mac and Windows compatible; Microsoft Word 98/2000) for your article.

For reporting standards please see the information in the About section.

Title page

The title page should:

- provide the title of the article
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

Please note:

- the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"
- abbreviations within the title should be avoided

Abstract

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: **Background,** the context and purpose of the study; **Methods**, how the study was performed and statistical tests used; **Results**, the main findings; **Conclusions**, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. **Trial registration**, if your research article reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. **Trial registration**: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

Methods

The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

For studies involving human participants a statement detailing ethical approval and consent should be included in the methods section. For further details of the journal's editorial policies and ethical guidelines see 'About this journal'.

For further details of the journal's data-release policy, see the policy section in 'About this journal'.

Results and discussion

The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

Conclusions

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

Competing interests

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

When completing your declaration, please consider the following questions:

Financial competing interests

- In the past five years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.
- Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.
- Do you have any other financial competing interests? If so, please specify.

Non-financial competing interests

Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

If you are unsure as to whether you, or one your co-authors, has a competing interest please discuss it with the editorial office.

Authors' contributions

In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

According to ICMJE guidelines, An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; 3) have given final approval of the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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