UNIVERSITY OF CAPE TOWN

Tuberculosis and Hospitalization Incidence Postpartum among Women Living with HIV in Gugulethu, Western Cape, South Africa

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Contents

PREAMBLE

Declaration

I, Kelechi Francisca Njoku (NJKKEL001) hereby declare that the work on which this dissertation is based on is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being or is to be submitted for another degree in this University of Cape Town (UCT) or any other university.

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Abstract

Background: Knowledge of the incidence of tuberculosis (TB) and hospitalization postpartum could reduce maternal morbidity and mortality. TB infections are prevalent in pregnant women living with Human immunodeficiency virus (HIV) compared to women not living with HIV in South Africa. Adherence to Antiretroviral Therapy (ART) is poor among pregnant and postpartum women living with HIV (WLHIV), thus making WLHIV at a higher risk of hospitalization postpartum, due to the increased risk of Cesarean delivery (CD) and obstetric conditions as a result of HIV. The prevalence of TB among pregnant and postpartum women is poorly defined including in high prevalence TB and HIV locations, indicating limited evidence. The aim is to explore the incidence of TB and hospitalization within four years postpartum among WLHIV, including associated risk factors.

Methodology: The study population is from phase 2 of the Maternal and Child Health-Antiretroviral Therapy (MCH-ART) study. It is a single-arm observational cohort study of 628 WLHIV who attended antenatal care (ANC). Enrolment into phase 1 began in March 2013, the final deliveries from phase 2 were in December 2014, and the final follow-up visits were completed in 2016. MCH-ART is an ongoing study with global approval examining strategies for providing HIV care and treatment to HIV-infected women who initiate ART during pregnancy and their HIV-exposed infants. This study took place at the Midwife-Obstetric Unit (MOU) at Gugulethu Community Health Centre, Western Cape South Africa. It consists of three connected study designs and three phases through the antenatal and postnatal periods. Phase 1 is a cross-sectional study, phase 2 is a cohort study and phase 3 is a randomized trial. Kaplan-Meier survival analysis was used to assess the incidence of TB and hospitalization over time among

WLHIV up to four years postpartum and Cox regression was used to measure the effect of risk factors on the incidence of TB and hospitalization.

Results: Thirty-five (35) WLHIV developed TB postpartum at a total person-time of 2365.1 woman-years. The incidence rate (IR) of developing TB among WLHIV postpartum was 1.48 (95% CI=1.03-2.06) cases per 100 woman-years from 2013 to 2018. Twenty-three (23) WLHIV was hospitalized postpartum and a total person-time of 552.8 woman-years was spent. The IR of hospitalization among WLHIV postpartum was 4.16 (95% CI=2.64-6.24) cases per 100 woman-years from 2013 to 2018. The IR of TB and hospitalization among WLHIV postpartum is statistically significant. Adjusting, for other risk factors, the history of diabetes at ANC, the history of TB at ANC and CD4 count (200 - <500) cells/mm^3 at ANC significantly increased the incidence of TB postpartum. Also, WLHIV were hospitalized for obstetrics reasons and 4(0.65%) died postpartum.

Conclusions: The incidence of TB and hospitalization increases significantly postpartum among WLHIV. Having a history of diabetes, TB or CD4 count (200 - <500) cells/mm3 at ANC also significantly increases the incidence of TB postpartum, whereas, obstetric reasons is associated with the hospitalization of WLHIV.

Keywords: TB, hospitalization, postpartum, WLHIV, Kaplan-Meier survival analysis, Cox regression

List of abbreviations

AIDS	Acquired immune deficiency syndrome
ANC	Antenatal care
ART	Antiretroviral therapy
CD	Cesarean delivery
CI	Confidence interval
dob	Date of birth
EDD	Expected date of delivery
EM	Emergency medicine
GCHC	Guguletu CHC
GFJH	GF jooste hospital
GM	General medicine
GS	General surgery
GSH	Groote schuur hospital
GYN	Gynecology
HIV	Human immunodeficiency virus
HR	Hazard ratio
IR	Incidence rate
LCL	Lower confidence limit
LH	Laingsburg hospital
MCH-ART	Maternal and Child Health-Antiretroviral Therapy
MMH	Mowbray maternity hospital
MOU	Midwife-Obstetric Unit
MPH	Mitchells plain hospital
MTCT	Mother-to-child-transmission
NSH	New somerset hospital
OBS	Obstetrics
ORT	Orthopedics
QoL	Quality of life
SA	South Africa
TB	Tuberculosis
UCL	Upper confidence limit
UNAIDS	The Joint United Nations Programme on HIV and AIDS
WHO	World health organization
WLHIV	Women living with HIV
β	Beta

PART A: PROTOCOL

Protocol synopsis

Background and rationale: Tuberculosis (TB) is a leading cause of death among people living with Human Immunodeficiency Virus (HIV). Adults in their productive years are mostly affected. TB increases significantly in postpartum and its symptoms are coinciding with other infectious diseases. Increased TB incidence is associated with postpartum maternal and infant death among women living with HIV (WLHIV). South Africa (SA) has one of the worst HIV associated TB epidemics and the prevalence of TB among pregnant and postpartum women is poorly defined.

Aim and objective: The overall aim of this study is to describe the incidence of TB (pulmonary TB and extra pulmonary TB) and hospitalization among WLHIV up to four years postpartum in the Western Cape of SA. Including, measuring the effects of risk factors on the incidence of TB and hospitalization.

Study design, population and sampling: This will be a retrospective cohort study of the second phase of the Maternal and Child Health-Antiretroviral Therapy (MCH-ART) study. MCH-ART is an ongoing study with global approval carried out to assess strategies for delivering HIV care and treatment services during the postpartum period to suitable HIV-infected women who initiate ART during pregnancy and their HIV- exposed infants. It consists of three connected study designs and three phases through the antenatal and postnatal periods. Phase 1 is a cross-sectional study, phase 2 is a cohort study and phase 3 is a randomized trial. Enrolment into phase 1 began in March 2013, the final deliveries from phase 2 were in December 2014, and the final follow-up visits were completed in 2016. Follow-up of phase 3 is ongoing. The final sample sizes are: 1554 women enrolled in phase 1, 628 women initiating ART from phase1 enrolled in phase 2, and 471 breastfeeding women enrolled postpartum from phase 2 into phase 3.

Background

TB is among the top 10 causes of death globally. It is a leading cause of death of people living with HIV. About 10 million people developed TB, among which 1.6 million people including 0.3 million people living with HIV died from the disease in 2017. People living with HIV are 20-30 times more likely to develop active TB, and although all age groups are at risk of developing TB, adults in their productive years are mostly affected [1]. It is very important to correctly diagnose and effectively treat active or latent TB in pregnancy and during postpartum, as failure to do so could lead to morbidity and mortality of mother and baby [2]. People living with HIV are strongly recommended for screening for TB, according to the World Health Organization (WHO) Guidelines on screening for latent TB [3]. Also, TB clinical manifestations are the same in pregnant as well as non-pregnant patients which include fever, fatigue, cough, chest pain, weight loss, dyspnea and night sweat [2]. It has been shown that TB increases significantly in postpartum, which implies an increased incidence of TB during pregnancy [4]. Also, TB was shown to be associated with postpartum maternal and infant death among WLHIV [5]. Developing countries have over 95% TB prevalence and deaths. SA is among the eight countries that accounted for two-thirds of 87% of the new cases of TB or HIV associated TB that occurred in 30 high burden countries in 2017 [1,3]. Globally, SA has one of the worst TB epidemics driven by HIV [6]. The prevalence of TB among pregnant and postpartum women is poorly defined, including in high prevalence TB and HIV locations [7,8], indicating limited evidence on the subject. The case report of TB infection in a South African neonatal unit demonstrates the need for prompt identification of TB in pregnant and postpartum women in TB-endemic countries [9]. In SA the risk of TB among WLHIV is increased slightly postpartum [10].

This study focuses on the incidence of TB and hospitalization up to four years postpartum among WLHIV in a community with a high prevalence of TB and HIV in Western Cape, South Africa.

Aim

The general aim of this study is to explore the occurrence of TB (pulmonary TB and extra pulmonary TB) and hospitalizations among WLHIV up to four years postpartum.

Objectives

The objectives of this study are as follows:

1. To describe the incidence of TB among WLHIV up to four years postpartum
2. To examine the risk factors for incidence TB in WLHIV up to four years postpartum
3. To describe the incidence of hospitalization among WLHIV up to four years postpartum
4. To examine the risk factors for hospitalization in WLHIV up to four years postpartum

Methods

The Maternal and Child Health-Antiretroviral Therapy (MCH-ART) study (Clinical Trials. gov NCT01933477), is an implementation science project which took place at the Midwife-Obstetric Unit (MOU) at Gugulethu Community Health Centre, Western Cape, South Africa. MCH-ART consists of three connected study designs and three phases through the antenatal and postnatal periods. The basic aim of the MCH-ART study is to assess strategies for delivering HIV care and treatment services during the postpartum period to suitable HIV-infected women who initiate ART during pregnancy and their HIV-exposed infants.

Phase 1 is a cross-sectional study of consecutively enrolled pregnant WLHIV seeking antenatal care. This phase permits the description of the health status of the population of pregnant WLHIV seeking care at the Gugulethu MOU and the services they receive. Phase 2 is an observational cohort study of all women in phase 1 who are suitable for initiation of ART according to local public sector guidelines, from their second antenatal clinic visit until their first postpartum clinic visit conducted within 7 days postpartum. This phase allows a detailed description of ART initiation and antenatal follow-up in the population of women who will be involved in the postnatal component of the MCH-ART study. Phase 3 is a randomized trial of strategies for delivering ART to women during the postpartum period. Women enrolled in phase 2 who are breastfeeding their infants regardless of infant HIV status, are asked to participate in the trial at the first routine postpartum clinic visit and consenting suitable women are randomized to 1 of 2 strategies to delivering ART:

1. Referral to general adult ART services from approximately 4-8 weeks postpartum, which is the local standard of care, or,

2. Continued receipt of ART in the antenatal clinic, as part of MCH-focused ART service that only refers women to general adult ART services after the end of breastfeeding [11].

Data from the MCH-ART study has been used by different researchers and this study uses the data to explore the incidence of TB and hospitalization up to four years postpartum among WLHIV enrolled in phase 2 of the MCH-ART study.

Study design

Retrospective cohort study design

Study population and sampling

This study will include WLHIV who are up to four years postpartum and developed TB or were hospitalized.

Exclusion criteria: This study excludes WLHIV who developed TB or were hospitalized during pregnancy or within seven days after delivery at the beginning of the study. It also excludes repeat pregnancies during the study and WLHIV who are more than four years postpartum.

Inclusion criteria: This study includes WLHIV who developed TB or were hospitalized after seven days from the day of delivery at the beginning of the study and are also within four years postpartum, excluding repeat pregnancies.

Data collection

A list of variables to be collected and used for the analysis in this study as provided by the MCH-ART study is given in Table A-1. The list of abbreviations on page x will facilitate the understanding of abbreviations in this table. Also, the variables listed will be used to generate other variables needed to achieve the objectives of this study.

Table A-1: Variable list

Variables	Type
Pid	Continuous
Phdc study patient dominant id	Continuous
Phdc study patient id	Continuous
Infant dob.	Date
Maternal age	Continuous (Years)
Episode short description	Categorical (Asthma or COPD, Breast Cancer, Diabetes Mellitus, Epilepsy, HIV positive, Hypertension, Lung Cancer, Mental Health, Pregnancy, TB positive)
Episode start date	Date
Date of death	Date
Encounter visit type	Categorical (CHW, Hospital Admission, Hospital OP Visit, PHC Visit, Self-enrolment)
Encounter start date	Date

Encounter end date	Date
Education	Categorical (Less than secondary, Completed secondary/any tertiary)
Employment	Categorical (Unemployed, Employed)
Poverty	Categorical (Most disadvantaged, Moderate disadvantage, Least disadvantage)
Socioeconomic status (SES)	Categorical (Lowest SES, Moderate SES, Highest SES)
Primigravida	Categorical (No, Yes)
Married	Categorical (Not married/cohabiting, Married/cohabiting)
Previous ART	Categorical (No, Yes)
History of hypertension at ANC booking	Categorical (No, Yes)
History of diabetes at ANC booking	Categorical (No, Yes)
History of TB at ANC booking	Categorical (No, Yes)
Final booking of CD4 count at ANC, cells/mm^3	Categorical (AIDS (<200), Low (200 - <500), Normal (≥500))
Specialty description	Categorical (GS, EM, GM, OBS, GYN, ORT)
Facility name	Categorical (MMH, GSH, MPH, GCHC, NSH, LH, GFJH)
Admission method	Categorical (Maternity booked, Emergency/trauma, Planned, Maternity unbooked)
Referred for Medical care in past 12months	Categorical (No, NA)
Referred for pregnancy related care	Categorical (No, Yes, NA)
Referred for other medical care	Categorical (No, Yes, NA)
Reason for referral	Categorical (Appendix, Blood pressure, Delivery, Exceeded EDD, Fetal distress, Caesarean, Previous Caesarean, High blood pressure, Hypertension, STI & Abdominal pains)
Facility referred to	Categorical (GCHC, MMH, GSH)

Data management and analysis

This study uses quantitative longitudinal data from routine medical service records, which is captured into a password-protected Microsoft Access database. Data will be checked for completeness and cleaned where necessary to make it suitable for analysis. Individuals with complete data will be analyzed. All statistical analysis will be done using R version 3.6.0 (2019-04-26). Median and interquartile ranges (IQR) or mean and confidence intervals (CI) will be used in the description of continuous variables, whereas frequency and percentages will be used to describe categorical variables in this study.

Kaplan-Meier survival analysis will be used to assess the incidence of TB and hospitalization over time among WLHIV up to four years postpartum. Furthermore, Cox regression will be used to measure the effect of risk factors on the incidence of TB and hospitalization. A p-value ≤ 0.05 indicates statistical significance and the inclusion of 1 in a 95% CI means non-significance.

Ethics

Ethical review

This study uses data from the MCH-ART study. Ethical approval for the MCH-ART study, including informed consent procedure was approved by the Human Research Ethics Committee of the University of Cape Town (UCT-HREC) Faculty of Health Sciences and the Columbia University Medical Centre Institutional Review Board. This study will request approval from the UCT-HREC.

Informed consent

The data for this study will be an extraction of a retrospective examination of routinely collected service data. Participants in this study gave their consent before their enrollment, thus we will not obtain any further consent from study participants.

Confidentiality

To minimize the risk of loss of confidentiality throughout this study, participants will be identified by an anonymous identification number on the database and the database will be password-protected. Besides, all identifying participant information will be removed.

Risks

Generally, this study is considered to be of low risk to participants. There is, however, a possible risk of loss to confidentiality in the data processing. But, as stated above, measures have been put in place to minimize this risk.

Benefits

Although this study holds no direct benefit to its participants, the knowledge gained will provide a better understanding of the incidence rate of TB and hospitalization postpartum among WLHIV in the Western Cape of South Africa; including increasing awareness of the risk factors and their effects on the incidence of TB and hospitalization postpartum especially in the Western Cape. This will assist the healthcare system to set up measures that will control these incidences.

Reporting and publications

Presentation or publication of results from this study will be decided upon in partnership with my supervisor.

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PART B: LITERATURE REVIEW

Introduction

High incidence of TB is associated with postpartum maternal and infant death among women living with HIV [1]. TB is among the top ten global causes of death. People living with HIV are 20 to 30 times more likely to develop active TB and adults in their productive years are commonly affected [2]. TB symptoms usually overlap with other infectious diseases, thus it is important to properly diagnose and effectively treat TB in pregnancy and postpartum [3,4]. Individuals living with HIV are strongly recommended for TB screening, according to the World Health Organization (WHO) Guidelines on screening for latent TB [5]. WLHIV are at a higher risk of hospitalization postpartum, due to the increased risk of CD as a result of HIV [6,7]. SA has one of the worst TB epidemics driven by HIV globally and its prevalence among pregnant and postpartum women is unclear [8,9,10].

Objectives

This dissertation investigates the occurrence of tuberculosis and hospitalizations in women living with HIV (WLHIV) up to four years postpartum.

The objectives of the literature review are:

- To explore the incidence of TB postpartum among WLHIV in Africa
- To identify the risk factors for developing TB postpartum among WLHIV
- To explore the incidence of hospitalization postpartum among WLHIV in Africa
- To identify the risk factors for hospitalization postpartum among WLHIV

Literature search strategy

Google scholar and existing literature were searched for relevant publications. Also, PubMed was searched using the terms tuberculosis, hospitalization, postpartum and women living with HIV. The search was restricted to English language publications. The titles and abstracts of these publications were reviewed, and the references of included studies were also searched.

Inclusion criteria

- TB in pregnancy and postpartum studies
- Postpartum hospitalization studies

Exclusion criteria

- TB treatment types
- TB drug trials studies
- TB cost-effectiveness studies
- TB screening studies
- Neonatal hospitalization studies

Summary of literature review

Incidence of TB postpartum among WLHIV in Africa

TB is the major cause of maternal-child mortality and it is most common during a woman's reproductive years [11]. The incidence of TB diagnosis increases significantly postpartum compared to periods outside postpartum [12]. Owing to changes in the maternal immune system during pregnancy, the increased risk of progression or reactivation of latent TB to active TB is expected [13,12]. Latent tuberculosis infection (LTBI) in pregnant WLHIV poses a high risk for

the development of active TB postpartum [14]. TB is among the top ten causes of death in sub-Saharan Africa [15], it increases the rate of maternal mortality and even more so in mothers co-infected with HIV [16,17,18]. Nearly half of the pregnant women who suffered from TB globally were from African origin [19]. In Kenya, WLHIV experienced a high incidence of TB within two years postpartum [15]. South Africa has some of the highest rates of HIV, TB and co-infection of HIV and TB cases [20]. TB infections are prevalent in pregnant WLHIV compared to women not living with HIV in South Africa [21].

Risk factors for developing TB postpartum among WLHIV

The risk factors for TB among WLHIV include a history of TB, history of isoniazid preventive therapy (IPT), close contact with TB, Contact with multidrug-resistant tuberculosis (MDR-TB), positive TB symptom screen, household contact with TB symptoms, a smoker in the house, close contact with an infected person and HIV infection [14,22]. HIV disease remains high in resource-limited settings in Africa, Asia and the Americas, affecting people of all age group, most especially women and children. It is evident in conditions of food insecurity, obesity, diabetes, cardiovascular risk, malaria, tuberculosis, enteric diseases [23,24]. Pregnancy is a crucial time for HIV care management and TB prevention [25]. WLHIV initiate life-long ART use during antenatal [26]. Early initiation and regular adherence to ART can effectively suppress viral load, reduce drug resistance as well as opportunistic infections [27,28,29]. However, the literature indicates that adherence is poor among pregnant and postpartum WLHIV [30,31]. Failure to initiate ART and suppress viral load are key barriers to the Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 goals by 2020 and 95-95-95 goals by 2030 [32,33].

Incidence of hospitalization postpartum among WLHIV in Africa

Women are unfairly affected by HIV in SA. Among the adults living with HIV 62.67% are women. Compared to young men aged 15-24 years, new HIV infections among young women is beyond double [34]. Many WLHIV desire to have children and are likely to get pregnant [35,36,37]. With the help of ART, young WLHIV reach reproductive age and become pregnant [6], however, sustaining adherence to ART is a challenge among pregnant WLHIV, thus putting them at a high risk of postpartum viraemia [38,39]. Compared to HIV negative women, WLHIV are at higher risk of hospitalization postpartum, due to the increased risk of Cesarean delivery (CD) as a result of HIV [6,7]. Performing CD before labour and before rupture of membranes in WLHIV reduces the risk of mother-to-child-transmission (MTCT) [40]. The outcome from a population-based, retrospective cohort study shows hospitalization within 60 days postpartum to be more likely among women with CD or assisted virginal delivery [41]. The incidence of hospitalization postpartum was shown to be increased among women with prolonged labour and those receiving blood transfusion [42]. There is 80% increased risk of hospitalization postpartum for appendicitis among women which is usually linked to infection in CD [43]. The risk of CD related complications is associated with viraemia among WLHIV [44]. The rate of CD is steadily increasing in SA, and it is shown to lower the quality of life (QoL) of WLHIV over six-months [45,46]. Regardless of the mode of delivery, WLHIV are still at increased risk of postpartum complications [47], however, several obstetric conditions with CD increase the incidence of hospitalization postpartum [48].

Risk factors for hospitalization postpartum among WLHIV

Infection of surgical obstetric wounds is usually the most common reason for hospitalization postpartum [7]. The risk of hospitalization postpartum is associated with the method of delivery. CD and assisted vaginal delivery increases significantly the incidence of hospitalization postpartum compared to spontaneous vaginal delivery. CD results in gallbladder disease, uterine infection, obstetrical surgical wound complications, morbidity, infection, excessive blood loss, possible repetition of CD, postoperative pain, cardiopulmonary and thromboembolic conditions. Whereas assisted virginal delivery results in pelvic injury, obstetrical surgical wound complications, postpartum haemorrhage and trauma [6,41,49].

The QoL of WLHIV is mostly affected post-CD, especially in SA as the rate of CD is progressively increasing [46]. Adherence to treatment and care during pregnancy decreases HIV-related CD [7]. Other risk factors associated with hospitalization postpartum includes newborn readmission, CD4 count, formula-feeding, age, primigravida, education, socioeconomic status, pneumonia, TB, respiratory infection, malaria, urinary incontinence, mental health, non-adherence to ART, obstetric infection and anaemia [50,46,51,52,53,54]. Blood transfusion and prolonged labour after vaginal delivery also increase the incidence of hospitalization postpartum [42].

Areas for further research

Further research on the incidence of and risk factors for hospitalization postpartum among WLHIV should be implemented, to reduce the event of readmission postpartum which will help WLHIV to be more available to their neonates and to fully participate in ART services for better maternal and child health care.

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PART C: MANUSCRIPT

Tuberculosis and Hospitalization Incidence Postpartum among Women Living with HIV in Gugulethu, Western Cape, South Africa

Short Title: Incidence of TB and hospitalization postpartum among women living with HIV

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Abstract

Background: Knowledge of the incidence of tuberculosis (TB) and hospitalization postpartum could reduce maternal morbidity and mortality. TB infections are prevalent in pregnant women living with Human immunodeficiency virus (HIV) compared to women not living with HIV in South Africa. Adherence to Antiretroviral Therapy (ART) is poor among pregnant and postpartum women living with HIV (WLHIV), thus making WLHIV at a higher risk of hospitalization postpartum, due to the increased risk of Cesarean delivery (CD) and obstetric conditions as a result of HIV. The prevalence of TB among pregnant and postpartum women is poorly defined including in high prevalence TB and HIV locations, indicating limited evidence. The aim is to explore the incidence of TB and hospitalization within four years postpartum among WLHIV, including associated risk factors.

Methodology: The study population is from phase 2 of the Maternal and Child Health-Antiretroviral Therapy (MCH-ART) study. It is a single-arm observational cohort study of 628 WLHIV who attended antenatal care (ANC). Enrolment into phase 1 began in March 2013, the final deliveries from phase 2 were in December 2014, and the final follow-up visits were completed in 2016. MCH-ART is an ongoing study with global approval examining strategies for providing HIV care and treatment to HIV-infected women who initiate ART during pregnancy and their HIV-exposed infants. This study took place at the Midwife-Obstetric Unit (MOU) at Gugulethu Community Health Centre, Western Cape South Africa. It consists of three connected study designs and three phases through the antenatal and postnatal periods. Phase 1 is a cross-sectional study, phase 2 is a cohort study and phase 3 is a randomized trial. Kaplan-Meier survival analysis was used to assess the incidence of TB and hospitalization over time among

WLHIV up to four years postpartum and Cox regression was used to measure the effect of risk factors on the incidence of TB and hospitalization.

Results: Thirty-five (35) WLHIV developed TB postpartum at a total person-time of 2365.1 woman-years. The incidence rate (IR) of developing TB among WLHIV postpartum was 1.48 (95% CI=1.03-2.06) cases per 100 woman-years from 2013 to 2018. Twenty-three (23) WLHIV was hospitalized postpartum and a total person-time of 552.8 woman-years was spent. The IR of hospitalization among WLHIV postpartum was 4.16 (95% CI=2.64-6.24) cases per 100 woman-years from 2013 to 2018. The IR of TB and hospitalization among WLHIV postpartum is statistically significant. Adjusting, for other risk factors, the history of diabetes at ANC, the history of TB at ANC and CD4 count (200 - <500) cells/mm^3 at ANC significantly increased the incidence of TB postpartum. Also, WLHIV were hospitalized for obstetrics reasons and 4(0.65%) died postpartum.

Conclusions: The incidence of TB and hospitalization increases significantly postpartum among WLHIV. Having a history of diabetes, TB or CD4 count (200 - <500) cells/mm3 at ANC also significantly increases the incidence of TB postpartum, whereas, obstetric reasons is associated with the hospitalization of WLHIV.

Keywords: TB, hospitalization, postpartum, WLHIV, Kaplan-Meier survival analysis, Cox regression

Introduction

The incidence of TB diagnosis increases significantly postpartum compared to periods outside postpartum [1]. Latent tuberculosis infection (LTBI) in pregnant WLHIV poses a high risk for the development of active TB postpartum [2]. TB infections are prevalent in pregnant WLHIV compared to women not living with HIV in South Africa [3]. South Africa has some of the highest rates of HIV, TB and co-infection of HIV and TB cases [4]. HIV disease remains high in resource-limited settings in Africa, Asia and the Americas, affecting people of all age group, most especially women and children. It is evident in conditions of food insecurity, obesity, diabetes, cardiovascular risk, malaria, tuberculosis, enteric diseases [5,6]. Adherence to ART is poor among pregnant and postpartum WLHIV, which is a barrier to the UNAIDS 90-90-90 goals by 2020 and 95-95-95 goals by 2030 [7,8,9,10]. WLHIV are at a higher risk of hospitalization postpartum, due to the increased risk of CD and obstetric conditions as a result of HIV [11,12,13].

It is important to understand the incidence and risk factors for TB and hospitalization in the South African context because it is a population that has the worst TB epidemic driven by HIV. Hence, the need to equip the healthcare system with evidence to assist in the setup of measures for possible control of the incidence and risk factors for TB and hospitalization.

Methods

Ethics statement

Ethical approval for the MCH-ART study (Clinical Trials. gov NCT01933477), including the informed consent procedure was approved by the Human Research Ethics Committee of the University of Cape Town (UCT-HREC) Faculty of Health Sciences and the Columbia University Medical Centre Institutional Review Board. This study is based on the secondary analysis of data from the MCH-ART study.

Setting and study population

The MCH-ART study is an implementation science project which took place at the Midwife-Obstetric Unit (MOU) at Gugulethu Community Health Centre, Western Cape, South Africa. The MCH-ART study consists of three connected study designs and three phases through the antenatal and postnatal periods. Phase 1 is a cross-sectional study, phase 2 is a cohort study and phase 3 is a randomized trial [14]. The study population is from phase 2 of the MCH-ART study. This is a cohort study of 628 WLHIV from the ages of about 18 to 45years who are attending ANC. Focus is on WLHIV who developed TB or were hospitalized after seven days from the day of delivery at the beginning of the study and are also within four years postpartum, excluding repeat pregnancies.

Data sources and data linkage

Information collected from the WLHIV in the cohort study includes but is not limited to, Infant dob., Maternal age, Episode short description, Episode start date, Date of death, Encounter visit type, Encounter start date, Encounter end date, Education, employment, poverty, Socioeconomic

status, Primigravida, married, Previous ART, History of hypertension at ANC booking, History of diabetes at ANC booking, History of TB at ANC booking, Final booking of CD4 count at ANC, Specialty description, facility name, admission method, Referred for Medical care in past 12months, Referred for pregnancy-related care, Referred for other medical care, Reason for referral and Facility referred to. This information is collected from different datasets. These datasets are joined to each other on the phdc_study_patient_id and using the pid where necessary, which is believed to represent the same individual. The datasets joined includes All_phase_2_TB_episodes, baseline_data_phase_2, link_file, encounters_new, infantdob_p2, referrals_lace, referrals_p23, referrals_p31, referrals_p32, referrals_p33, referrals_p34, referrals_p35 and referrals_p36. Some required information, such as person-time was also generated from the collected information.

Statistical analysis

Statistical analysis was performed in R version 3.6.0 (2019-04-26). Median and interquartile ranges (IQR) or mean and confidence intervals (CI) was used in the description of continuous variables, frequency and percentages were used to describe categorical variables, whereas incidence rate (IR) and CI was used to explore the incidence of TB and hospitalization in this study. Kaplan-Meier survival analysis was used to assess the incidence of TB and hospitalization over time among WLHIV up to four years postpartum. Also, Cox regression was used to measure the effect of risk factors on the incidence of TB and hospitalization. A p-value ≤ 0.05 indicates statistical significance and the inclusion of 1 in a 95% CI means non-significance. Reasons for hospitalization, speciality and facility referred to was also explored.

Results

Description of the cohort

There are 628 WLHIV at baseline in the cohort study, at phase 2 of the MCH-ART study which took place at the Midwife-Obstetric Unit (MOU) at Gugulethu Community Health Centre, Western Cape South Africa. WLHIV who did not develop TB before the postpartum period was 611 (97%) and 371 (59%) WLHIV were not hospitalized before the postpartum period. Postpartum starts at seven days after delivery at the beginning of the study and excludes repeat pregnancies during the study.

Incidence of TB

Table C-1: Incidence of TB in WLHIV Postpartum

Incidence of TB	Cases	Person time woman-years	Rate per 100 woman-years	95% CI per 100 woman-years (LCL;UCL)
Total population followed-up	35	2365.1	1.48	(1.03-2.06)
Postpartum, years				
0-1	9	604.2	1.49	(0.68-2.83)
>1-2	11	597.2	1.84	(0.92-3.30)
>2-3	9	586.1	1.54	(0.70-2.91)
>3-4	6	577.6	1.04	(0.38-2.26)
Age, years				
18-24	10	572.0	1.75	(0.84-3.22)
25-29	10	818.0	1.22	(0.59-2.25)
30-34	9	669.0	1.35	(0.62-2.55)
35-39	3	230.0	1.30	(0.27-3.81)
40+	3	75.5	3.97	(0.82-11.61)

Thirty-five (35) WLHIV developed TB postpartum and total person-time of 2365.1 woman-years was spent, (Table C-1). The incidence rate (IR) of developing TB among WLHIV postpartum

was 1.48 cases per 100 woman-years from 2013 to 2018. This rate is marginally statistically significant (95% CI=1.03-2.06) as the confidence interval (CI) does not include null (1).

The IR of developing TB among WLHIV who were >3-4 years postpartum was 1.04 cases per 100 woman-years from 2013 to 2018. The IR is lowest during this postpartum period compared to those who were less than three years postpartum, yet it is not statistically significant (95% CI=0.38-2.26) as the confidence intervals include null. The rate of developing TB across the years of postpartum is not statistically significant.

The IR of developing TB among WLHIV postpartum who are 40+ years in age was 3.97 cases per 100 woman-years from 2013 to 2018. The IR is highest in this age group compared to other age groups, however, it is not statistically significant (95% CI=0.82-11.61) because the confidence intervals include null. The rate of developing TB across the age groups is not statistically significant.

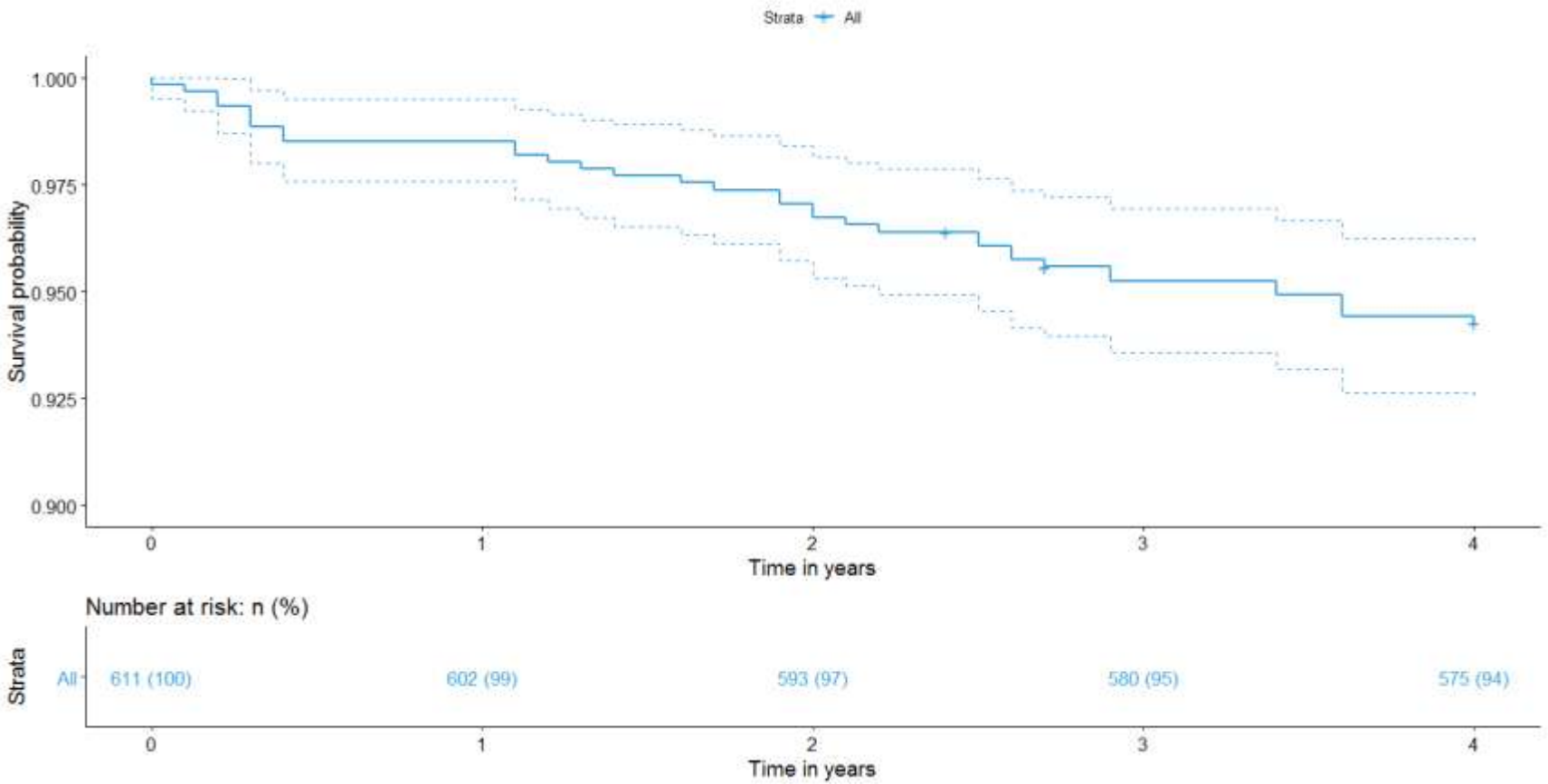

Figure C-1: Survival curve of overall incidence of TB in WLHIV up to four years postpartum

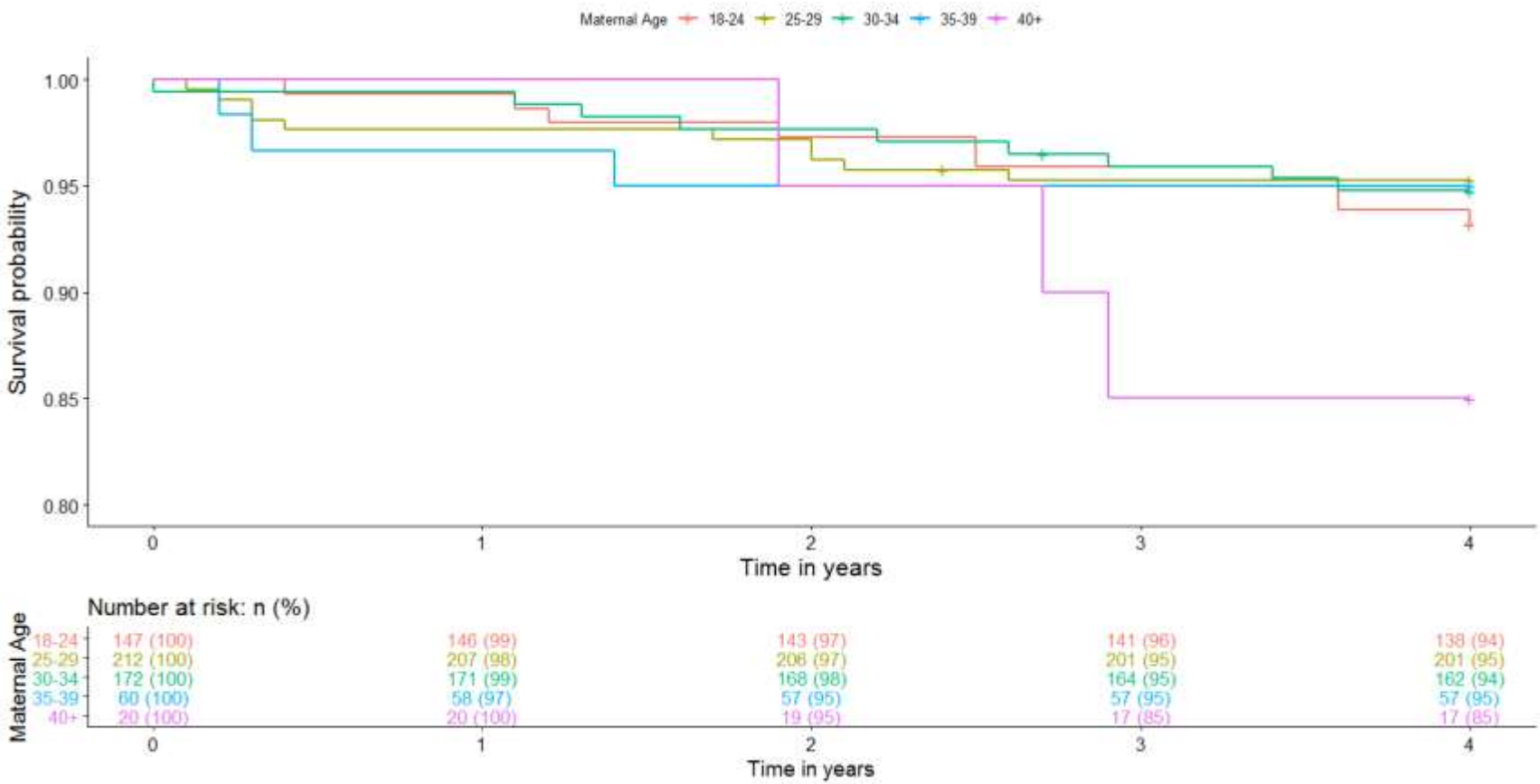

Figure C-2: Survival curve of the incidence of TB in WLHIV up to four years postpartum by maternal age

The incidence of TB in WLHIV is seen to increase between 0 and 3 years postpartum, (Figure C-1). The overall probability of developing TB postpartum is about 5% at four years postpartum. The median survival time was not reached.

WLHIV who are 40+ years in age experience a higher incidence of TB (Figure C-2), compared to other age groups. The probability of developing TB postpartum at 40 years and beyond is about 15% at four years postpartum and about 5% for other age groups. The occurrence of censoring was as a result of death 4(0.65%) and loss to follow-up. The median survival time was not reached.

Table C-2: Crude associations of risk factors and the incidence of TB in WLHIV Postpartum

Risk factors	**n**	**β**	**HR (95% CI)**	**p-value**
Maternal age, years	611			
18-24			1 (ref)	
25-29		-0.36	0.70 (0.29-1.68)	0.423
30-34		-0.26	0.77 (0.31-1.89)	0.568
35-39		-0.29	0.75 (0.21-2.71)	0.657
40+		0.81	2.26 (0.62-8.20)	0.216
Education	611			
Less than secondary			1 (ref)	
Completed secondary/any tertiary		-0.05	0.95 (0.44-2.02)	0.891
Employment	611			
Unemployed			1 (ref)	
Employed		-0.05	0.95 (0.48-1.90)	0.894
Poverty	611			
Most disadvantaged			1 (ref)	
Moderate disadvantage		-0.42	0.65 (0.27-1.58)	0.346
Least disadvantaged		0.23	1.26 (0.59-2.68)	0.550
Socioeconomic status (SES)	611			
Lowest SES			1 (ref)	
Moderate SES		-0.16	0.85 (0.37-1.97)	0.708
Highest SES		-0.06	0.94 (0.42-2.11)	0.889
Primigravida	611			
No			1 (ref)	
Yes		0.07	1.08 (0.47-2.46)	0.862
Married	611			
Not married/cohabiting			1 (ref)	
Married/cohabiting		-0.05	0.95 (0.48-1.87)	0.887

Previous ART	611			
No			1 (ref)	
Yes		1.09	2.97 (1.05-8.41)	0.041*
History of hypertension at ANC booking	527			
No			1 (ref)	
Yes		0.29	1.34 (0.41-4.39)	0.629
History of diabetes at ANC booking	527			
No			1 (ref)	
Yes		3.69	39.96 (5.23-305.5)	<0.001*
History of TB at ANC booking	527			
No			1 (ref)	
Yes		1.26	3.53 (1.08-11.58)	0.037*
Final booking of CD4 count at ANC, cells/mm^3	595			
(<200)			1 (ref)	
(200 - <500)		-0.94	0.39 (0.19-0.81)	0.012*
(≥500)		-1.22	0.30 (0.11-0.79)	0.015*

Reference category: ref; Significant: *; HR: Hazard Ratio

The following risk factors for developing TB postpartum among WLHIV according to literature (Table C-2), showed statistically significant ($p \leq 0.05$) crude associations with the incidence of TB: previous ART, history of diabetes at ANC booking, history of TB at ANC booking and final booking of CD4 count at ANC. Other risk factors: maternal age, education, employment, poverty score, SES score, primigravida, married and history of hypertension at ANC booking did not have statistically significant ($p > 0.05$) crude associations with the incidence of TB. Also, there is evidence of missing data in the recording of the history of hypertension, history of diabetes, history of TB and final booking of CD4 count at ANC.

There exists a strong relationship between previous ART and increased incidence of TB, p-value = 0.041 and HR (95% CI) = 2.97 (1.05-8.41). The incidence of TB increases by $\beta = 1.09$ per increase in previous ART use compared to no previous ART use.

The p-value for the history of diabetes at ANC booking is <0.001, with a HR (95%CI) = 39.96 (5.23-305.5), signifying a strong relationship between the history of diabetes at ANC booking

and increase in the incidence of TB. The incidence of TB increases by β = 3.69 per increase in the history of diabetes compared to no history of diabetes at ANC booking.

There is a strong association between the history of TB at ANC booking and increased incidence of TB, p-value = 0.037 and HR (95%CI) = 3.53 (1.08-11.58). The incidence of TB increases by β = 1.26 per increase in the history of TB compared to the absence of a history of TB at ANC booking.

The p-value for final booking of CD4 count (200 - <500) cells/mm^3 at ANC is 0.012 and CD4 count (≥500) cells/mm^3 at ANC is 0.015, with a HR (95%CI) = 0.39 (0.19-0.81) and 0.30 (0.11-0.79) respectively. This indicates a strong relationship between CD4 count and decrease in the incidence of TB. The incidence of TB decreases by β = -0.94 per cells/mm3 increase in CD4 count (200 - <500) cells/mm^3 and decreases by β = -1.22 per cells/mm3 increase in CD4 count (≥500) cells/mm^3 compared to final booking of CD4 count (<200) cells/mm^3 at ANC booking.

Table C-3: Adjusted associations of risk factors and the incidence of TB in WLHIV Postpartum

Risk factors (n=518)	**β**	**HR (95% CI)**	**p-value**
Previous ART (Yes)	0.51	1.67 (0.50-5.62)	0.406
History of diabetes at ANC booking (Yes)	4.03	56.11(7.04-447.28)	<0.001*
History of TB at ANC booking (Yes)	1.25	3.50 (1.05-11.64)	0.042*
Final booking of CD4 at ANC (200 - <500) cells/mm^3	-1.01	0.36 (0.17-0.80)	0.012*
Final booking of CD4 at ANC (≥500) cells/mm^3	-1.01	0.36 (0.13-1.00)	0.050*

Significant: *; Likelihood ratio test= 16.06, p= 0.007*; Wald test= 24.41, p= 2e-04*;
Score (logrank) test= 48.85, p= 2e-09*

Furthermore, the adjusted association of the statistically significant crude associations of risk factors for developing TB in WLHIV postpartum (Table C-3), indicates that the p-value for the overall tests (likelihood, Wald, and score) are all statistically significant (p≤0.05), signifying that the model is significant. Thus the hypothesis that all the betas (β) are zero is rejected.

The risk factors, history of diabetes, history of TB and final booking of CD4 count at ANC remains statistically significant ($p \leq 0.05$) and jointly impact on the incidence of TB. However, the risk factor, previous ART fails to remain statistically significant ($p > 0.05$).

Using the informal rule for the identification of confounders, that is a change in the β coefficient in the positive or negative direction by at least 10%, it can be observed that the adjusted association between previous art use and the incidence of TB, is ≥ 10% smaller (0.51 versus 1.09) after adjustment for other risk factors, although it is not statistically significant. Similarly, the association between the incidence of TB and final booking of CD4 count (≥500) cells/mm^3 at ANC is ≥ 10% smaller (-1.01 versus -1.22) after adjustment for other risk factors, however, it is statistically marginally significant. Therefore, part of the association between the incidence of TB postpartum among WLHIV and the risk factors: previous ART use and final booking of CD4 count (≥500) cells/mm^3 at ANC can be explained by the history of diabetes at ANC booking, history of TB at ANC booking and final booking of CD4 count (200 - <500) cells/mm^3 at ANC.

Assessing the validity of the Cox model

Table C-4: Testing proportional hazards assumption of the adjusted associations of risk factors and the incidence of TB in WLHIV Postpartum

Risk factors (n=518)	**rho**	**chisq**	**p-value**
Previous ART (Yes)	-0.13	0.57	0.449
History of diabetes at ANC booking (Yes)	0.12	0.50	0.481
History of TB at ANC booking (Yes)	0.18	1.10	0.294
Final booking of CD4 at ANC (200 - <500) cells/mm^3	-0.07	0.19	0.661
Final booking of CD4 at ANC (≥500) cells/mm^3	-0.26	2.45	0.118
Global	na	4.67	0.457

The proportional hazards (PH) assumption was checked using statistical tests based on the Schoenfeld residuals (Table C-4). The test is not statistically significant ($p > 0.05$) for each of the

covariates. Also, the relationship between residuals and time (global test) is not statistically significant (p>0.05). Hence, we assume the PH and support the validity of the Cox model.

Incidence of hospitalization

Table C-5: Incidence of hospitalization in WLHIV Postpartum

Incidence of hospitalization	Cases	Person time woman-years	Rate per 100 woman-years	95% CI per 100 woman-years (LCL;UCL)
Total population followed-up	23	552.8	4.16	(2.64-6.24)
Postpartum, years				
0-1	4	246	1.63	(0.44-4.16)
>1-2	8	158	5.06	(2.19-9.98)
>2-3	4	106.2	3.77	(1.03-9.64)
>3-4	7	42.6	16.43	(6.61-33.86)
Age, years				
18-24	9	146.0	6.16	(2.82-11.70)
25-29	6	181.0	3.31	(1.22-7.22)
30-34	5	159.0	3.14	(1.02-7.34)
35-39	2	43.9	4.56	(0.55-16.46)
40+	1	22.6	4.42	(0.11-24.65)

Twenty-three (23) WLHIV were hospitalized postpartum and a total person-time of 552.8 woman-years was spent (Table C-5). The IR of hospitalization among WLHIV postpartum was 4.16 cases per 100 woman-years from 2013 to 2018. This rate is statistically significant (95% CI=2.64-6.24) because the CI does not include null.

The IR of hospitalization among WLHIV who was 0-1 year postpartum was 1.63 cases per 100 woman-years from 2013 to 2018. The IR is least at this period compared to those who were more than one year postpartum. This incidence is not statistically significant (95%CI=0.44-4.16) because it includes the null. However, the incidence of hospitalization is statistically significant for WLHIV who are more than one year postpartum. Thus, the rate of becoming hospitalized postpartum for WLHIV increases as postpartum years increases.

The IR of hospitalization among WLHIV postpartum who was in the age group 18-24 years was 6.16 cases per 100 woman-years from 2013 to 2018. The rate of hospitalization is highest in this age group compared to other age groups. The IR is statistically significant (95% CI=2.82-11.70), including in age groups 25-29 and 30-34. However, it is not statistically significant in age groups 35-39 and 40+. Hence, the incidence of hospitalization reduces as the age of WLHIV increases.

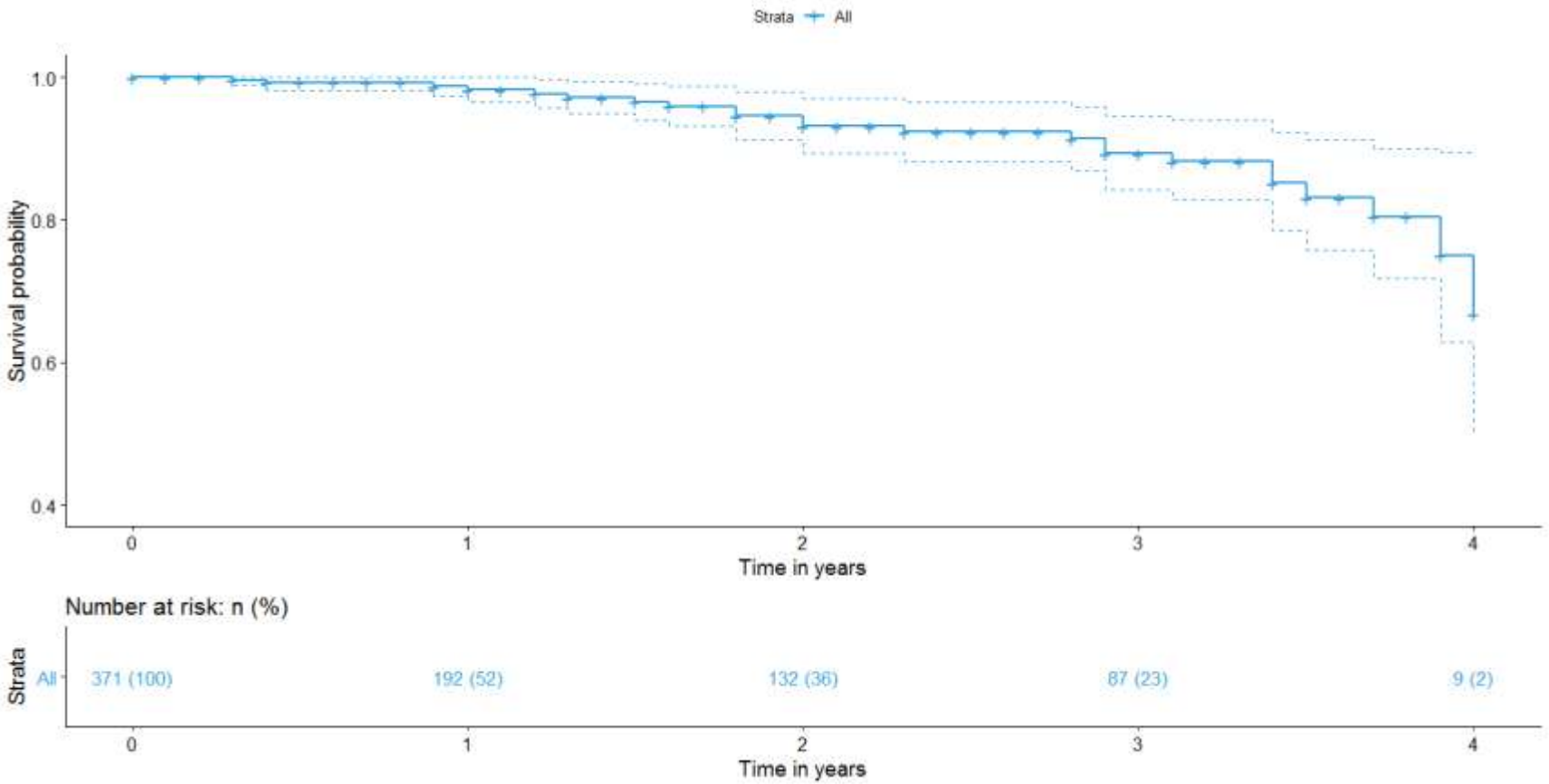

Figure C-3: Survival curve of overall incidence of hospitalization in WLHIV up to four years postpartum

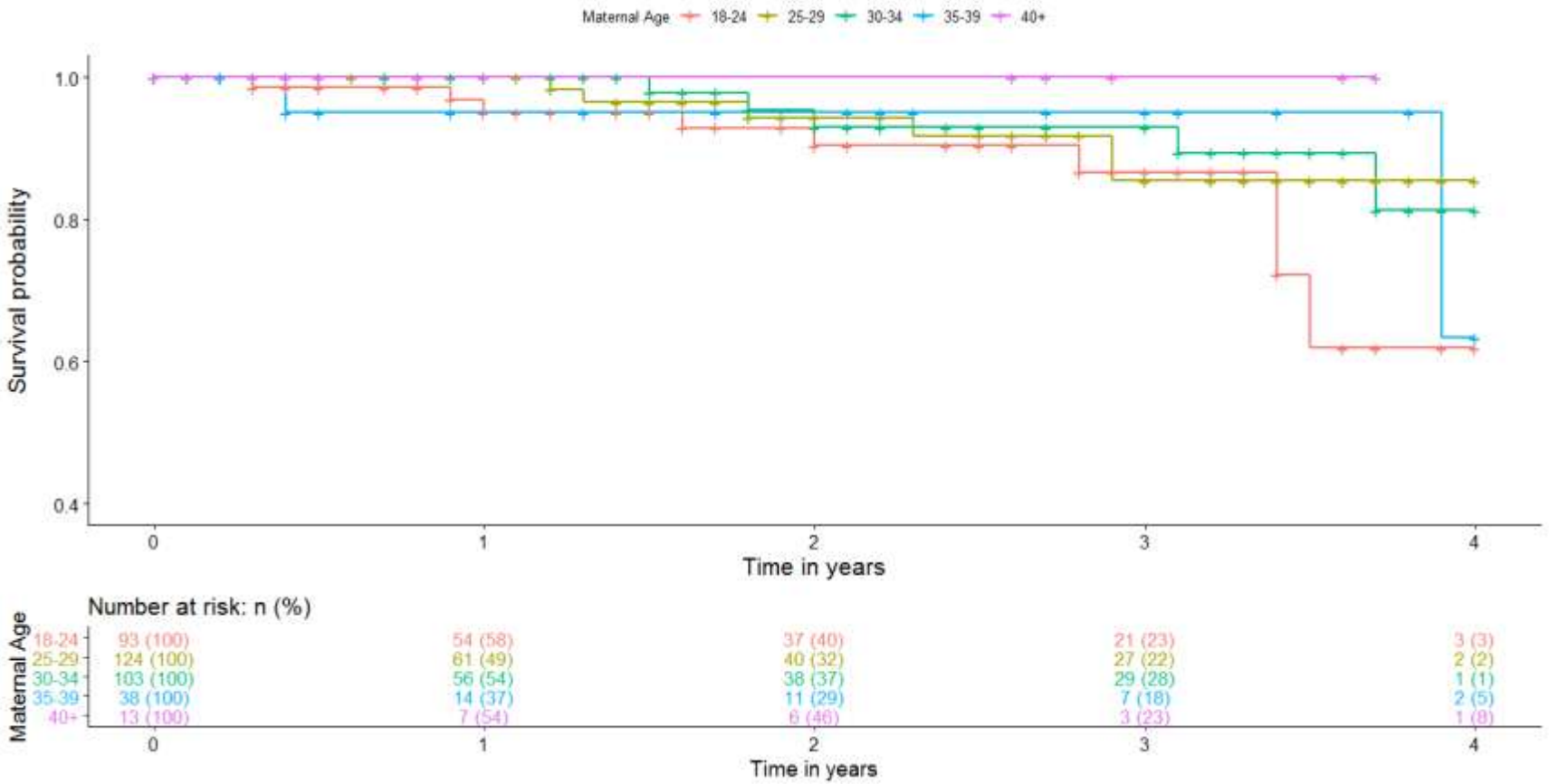

Figure C-4: Survival curve of the incidence of hospitalization in WLHIV up to four years postpartum by maternal age

The incidence of hospitalization in WLHIV is continually increasing across the postpartum years. The probability of hospitalization postpartum is about 40% at four years postpartum (Figure C-3). The median survival time was not reached.

WLHIV who are 18-24 years in age experience more incidence of hospitalization postpartum compared to other age groups. The probability of hospitalization is about 40% at four years postpartum (Figure C-4). The median survival time was not reached.

Table C-6: Crude associations of risk factors and the incidence of hospitalization in WLHIV Postpartum

Risk factors	**n**	**β**	**HR (95% CI)**	**p-value**
Maternal age, years	371			
18-24			1 (ref)	
25-29		-0.62	0.54 (0.19-1.51)	0.240
30-34		-0.70	0.49 (0.16-1.48)	0.209
35-39		-0.49	0.61 (0.13-2.85)	0.530
40+		-0.53	0.59 (0.07-4.67)	0.615
Education	371			
Less than secondary			1 (ref)	
Completed secondary/any tertiary		-0.46	0.63 (0.23-1.71)	0.367
Employment	371			
Unemployed			1 (ref)	
Employed		-0.03	0.97 (0.41-2.31)	0.951
Poverty	371			
Most disadvantaged			1 (ref)	
Moderate disadvantage		0.67	1.95 (0.70-5.40)	0.199
Least disadvantaged		0.35	1.42 (0.51-3.93)	0.497
Socioeconomic status (SES)	371			
Lowest SES			1 (ref)	
Moderate SES		0.38	1.47 (0.46-4.63)	0.514
Highest SES		0.59	1.80 (0.62-5.18)	0.277
Primigravida	371			
No			1 (ref)	
Yes		-0.90	0.41 (0.10-1.74)	0.225
Previous ART	371			
No			1 (ref)	
Yes		-16.04	0.00 (0.00-Inf)	0.997
History of TB at ANC booking	323			
No			1 (ref)	
Yes		-16.04	0.00(0.00-Inf)	0.997
Speciality description	22			
Emergency medicine			1 (ref)	

General medicine		-0.99	0.37 (0.06-2.38)	0.297
General surgery		23.76e+1	208 (0.00-Inf)	0.999
Gynecology		-0.77	0.46 (0.08-2.79)	0.400
Obstetrics		-0.40	0.67 (0.18-2.44)	0.541
Orthopedics		1.83	6.22 (0.46-84.82)	0.170
Final booking CD4 count at ANC, cells/mm^3	361			
(<200)			1 (ref)	
(200-500)		0.37	1.44 (0.40-5.14)	0.573
(≥500)		0.92	2.50 (0.64-9.80)	0.189

Reference category: ref; Significant: *

The risk factors for hospitalization postpartum among WLHIV according to literature (Table C-6) did not have statistically significant (p>0.05) crude associations. Therefore, the calculation of adjusted associations was unnecessary. Also, there is evidence of missing data in the recording of the history of TB and final booking of CD4 count at ANC. Including missingness in speciality description.

Table C-7: Description of hospitalization among WLHIV Postpartum

Participant ID	Speciality description	Facility name	Admission method	Referred for Medical care in past 12months	Referred for pregnancy related care	Referred for other medical care	Reason for referral	Facility referred to
1	GS	MMH		No	No	Yes	Appendix	GCHC
7	EM	MMH	Maternity booked	No	No	No	Unknown	Unknown
133	GM	GSH	Emergency/trauma	Unknown	No	No	Unknown	Unknown
423	OBS	MPH	Planned	No	No	No	Unknown	Unknown
437	OBS	MMH	Maternity booked	Unknown	Unknown	Unknown	Unknown	Unknown
522	OBS	MMH	Maternity booked	Unknown	No	No	Unknown	Unknown
559	OBS	MMH	Maternity booked	No	Yes	No	Blood pressure, Delivery	MMH
572	OBS	GCHC		No	No	No	Unknown	Unknown
582	GYN	MPH	Emergency/trauma	No	No	No	Unknown	Unknown
697	GS	NSH	Planned	No	No	No	Unknown	Unknown
698	GYN	NSH	Emergency/trauma	Unknown	No	No	Unknown	Unknown
746	OBS	MPH	Maternity booked	Unknown	Yes	No	Exceeded EDD	MMH
787	OBS	MMH	Maternity booked	No	No	No	Unknown	Unknown
797	OBS	MMH	Maternity booked	Unknown	Unknown	Unknown	Unknown	Unknown
855	OBS	MMH	Maternity booked	No	Yes	No	Fetal distress	MMH
1014	ORT	MPH	Planned	No	Yes	No	Caesarean	MMH
1116	GM	LH	Planned	Unknown	Yes	No	Previous Caesarean	MMH
1187	EM	GFJH	Planned	Unknown	No	No	Unknown	Unknown
1214	OBS	MMH	Maternity booked	No	Yes	No	High blood pressure	MMH, GSH
1224	OBS	MMH	Maternity booked	No	No	No	Unknown	Unknown
1253	EM	GFJH	Planned	No	No	No	Unknown	Unknown
1267	OBS	MMH	Maternity booked	No	Yes	No	Hypertension	MMH
1284	OBS	MPH	Maternity unbooked	Unknown	Yes	No	STI & Abdominal pains	GSH

Further description of the 23 incidences of hospitalization shows that the WLHIV were generally maternity booked, at the obstetrics department of Mowbray maternity hospital at the beginning of the study, (Table C-7). None of the WLHIV was referred for medical care at 12 months of postpartum. Five WLHIV were referred for pregnancy-related care at 18 months of postpartum, whereas one WLHIV was referred for other medical reason (appendix).

Discussion

This study is one of the few studies that have investigated the incidence of TB and hospitalization postpartum. It explored the incidence of TB and hospitalization up to four years postpartum among 628 WLHIV at the MOU in Gugulethu Community Health Centre in the Western Cape of South Africa, which is also a TB and HIV endemic area. Repeat pregnancies during the study are excluded and postpartum is stated to start seven days after delivery at the beginning of the study.

Regarding TB, the results indicate that the incidence of TB postpartum among WLHIV is marginally significant. Majority of the pregnancy-associated TB cases are usually confirmed postpartum [15]. This is usually as a result of immunological changes and also late diagnosis owing to the symptoms of TB being masked by the physiological changes associated with pregnancy [1,15]. The incidence of TB is significantly higher during postpartum but not during pregnancy or delivery [1]. TB infections are prevalent in pregnant WLHIV compared to women not living with HIV in South Africa [3]. The incidence of TB also increases with age and lower postpartum periods. Risk factors such as finance, diabetes, education, living in an urban area and cultural barriers can limit health status, and increase the likelihood of TB [16,17]. After adjustment for other risk factors, the history of diabetes at ANC, the history of TB at ANC and

CD4 count (200 - <500) cells/mm^3 at ANC significantly increases the incidence of TB postpartum. Whereas, previous ART use and CD4 count (≥500) cells/mm^3 at ANC are confounders. In addition, to being predisposed to TB, WLHIV are also prone to death postpartum. TB increases the rate of maternal mortality and even more so in mothers co-infected with HIV [18,19,20].

Regarding hospitalization, the results indicate that the risk of becoming hospitalized postpartum among WLHIV is statistically significant and increases as postpartum years increases. The duration of hospitalization postpartum is increased in WLHIV and also women co-infected with HIV/TB [21]. The incidence of hospitalization postpartum reduces as the age of WLHIV increases and although the risk factors for hospitalization postpartum among WLHIV in the data did not have statistically significant crude associations, however evidence shows that postpartum maternal readmission is signs of severe morbidity of which WLHIV are at a higher risk compared to women not living with HIV and socio-demographic factors account considerably for the difference [12]. Other risk factors for hospitalization include multiple gestations, postoperative complications and cesarean delivery (CD) [22,23]. Furthermore, results show that WLHIV were basically hospitalized for obstetrics reasons. CD is increasingly performed by obstetricians in South Africa [24]. Majority of readmission among WLHIV is attributable to obstetrical surgical wound infections as a result of CD [25,12].

WLHIV experience significant morbidity resulting from common infections especially respiratory infections, diarrhoea and TB which are among the top 10 causes of mortality in sub-Saharan Africa, and are increased by immune status or socioeconomic factors [26,27].

A major strength of this study is the good level of data completeness on most variables. However, there exist missing observations in some variables of interest such as the history of

hypertension at ANC booking, history of diabetes at ANC booking, history of TB at ANC booking, and final booking of CD4 count at ANC, which did not seem to affect the result.

The major limitation in this study is the incomplete information on hospitalization, which leads to a vague description of hospitalization and a less confident conclusion regarding reasons for hospitalization. Also, results from this cohort study may not be generalized because it focuses only on WLHIV at the Midwife-Obstetric Unit (MOU) at Gugulethu Community Health Centre, Western Cape, South Africa.

Encouraging adherence to ART for high CD4 count or low viral load among WLHIV in ANC and reducing the occurrence of comorbidities would reduce the likelihood of incidence of TB and hospitalization postpartum.

Conclusions

TB and hospitalization increase significantly postpartum among WLHIV at Gugulethu Community Health Centre in the Western Cape of South Africa. Having a history of diabetes, TB or CD4 count (200 - <500) cells/mm^3 at antenatal care also significantly increases the incidence of TB postpartum. Previous ART use and CD4 count (≥500) cells/mm^3 at antenatal care are confounding variables. The incidence of hospitalization postpartum increases for obstetric reasons and reduces as the age of WLHIV increases.

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PART D: APPENDICES

UNIVERSITY OF CAPE TOWN
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03 March 2020

HREC REF:101/2020

Prof L Myer
Epidemiology & Biostatistics
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Falmouth Building -FHS

Dear Prof Myer

PROJECT TITLE: TB AND HOSPITALIZATION INCIDENCE POSTPARTUM AMONG WOMEN LIVING WITH HIV IN WESTERN CAPE, SOUTH AFRICA (MASTERS-MISS K NJOKU)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

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

Approval is granted for one year until the 30 March 2021.

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

The HREC acknowledge that the student: Miss Kelechi Njoku will also be involved in this study.

Please quote the HREC REF in all your correspondence.

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

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

Yours sincerely

Signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 101/2020sa

NHREC-registration number: REC-210208-007

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

HREC 101/2020sa