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Cohort Profile: The Hlabisa pregnancy cohort, KwaZulu-Natal, South Africa

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ABSTRACT

Purpose: The Hlabisa pregnancy cohort was established to evaluate the effectiveness of Prevention of Mother-to-Child Transmission (PMTCT) guideline revisions. The objectives of the Hlabisa pregnancy cohort are to: (i) provide cohort-level information on pregnancy outcomes in a high HIV prevalence setting; (ii) evaluate aspects of PMTCT treatment and care that have policy relevance; and (iii) provide a platform for studies to test interventions designed to improve pregnancy outcomes.

Participants: The pregnancy cohort is located in primary health clinics in the Hlabisa sub-district of rural KwaZulu-Natal, South Africa. Baseline data collection between 2010 and 2014 has been completed, with the enrolment of 25 608 pregnancies; age ranged from 15-49 years. Pregnant women were assessed during routine antenatal visits: first visit, follow-up one week later, 32 week (HIV test), infant delivery and six weeks postpartum. Demographic, pregnancy, clinical, laboratory and HIV data were collected through Department of Health interviews, laboratory tests and routine data linkage. Treatment data for HIV-infected pregnant women were linked to the Africa Centre HIV Treatment and Care Programme for detailed ART history, baseline and follow-up laboratory tests.

Findings to date: While the retention of HIV-infected women on lifelong antiretroviral therapy (ART) was high (84.8%), approximately 32% of HIV-infected women not on ART were lost to follow-up. The majority of HIV-infected women were either on lifelong ART or ART prophylaxis during their pregnancy; ~ 12% of women were not on any ART. Pregnancy viral load monitoring was inadequate.

Future plans: This cohort will be used to: (1) determine HIV acquisition risk during pregnancy and postpartum, (2) determine the effect of HIV and ART on birth outcomes; (3) examine the effect of pregnancy on virologic response to ART; and (4) characterize the effect of sequential pregnancies on access to clinical care, response to prolonged ART and birth outcomes.

Strengths and limitations of this study

- The key characteristic of the Hlabisa pregnancy longitudinal cohort is size and ability to model the impact of the HIV programme on the community through linkage of Africa Centre’s population level data with clinical, pregnancy and HIV data.
- Despite its size, poor follow-up of HIV-infected mothers and infants is problematic, undermining infant HIV-free survival measurement at 18 months.
- Using linked population datasets, pregnancy outcomes of women not retained in care may be assessed, and through sensitivity analysis, factors related to poor attrition will be characterised.

INTRODUCTION

Prevention of mother-to-child transmission (PMTCT) of HIV using antiretroviral drugs can nearly eliminate vertical HIV transmission risk and increase maternal survival [1]. However, poor delivery of any of the sequential steps in PMTCT results in cumulative losses of pregnant women from services, raising HIV transmission risk to infants [2]. The PMTCT “cascade” highlights the sequence of steps for optimum PMTCT: HIV counselling and testing at the first antenatal visit; CD4⁺ measurement; antiretroviral therapy (ART) initiation and adherence; and early infant HIV testing [2], or after cessation of breastfeeding and final infant HIV test at 18 months [3].

The Hlabisa HIV Treatment and Care programme, described previously,[4] was a partnership between the South African Department of Health (DoH) and the Wellcome Trust funded Africa Centre for Population Health (Africa Centre), in rural KwaZulu-Natal. In January 2010, the Africa Centre established a pregnancy cohort in keeping with the HIV programme objectives to monitor the PMTCT cascade to provide feedback indicators to funders. A further objective is to use this cohort to determine clinical markers related to pregnancy and pregnancy outcomes in this setting with high HIV prevalence. The pregnancy cohort is linked with the Africa Centre Demographic Information System, which has demographic and health data through population-based longitudinal surveillance of approximately 90 000 people in 11 000 households. In doing so, the demographic and health factors related to the success of the PMTCT programme can be monitored.

Cohort description

The pregnancy cohort is located in the Hlabisa sub-district of UMkhanyakude in northern KwaZulu-Natal, South Africa with a population of approximately 228 000, of whom 28.6% are females aged 15-49 years [5]. From 1 January 2010 to September 2012, data pertaining to pregnant women accessing antenatal services in 17 DoH primary health care (PHC) clinics in Hlabisa were recorded, after which enrolment was limited to seven PHC clinics in the Africa Centre Demographic Surveillance Area due to funding changes. The pregnancy cohort is linked with data from the Africa Centre surveillance which spans 438km² (Figure 2). The surveillance area is predominantly rural with an urban township and

informal peri-urban settlements. Six of the DoH clinics and 40% of patients are located within the surveillance area. Household data surveillance began in January 2000, with nested annual population-based adult HIV surveillance since 2003. Routine household visits were conducted biannually, and since 2012 three-times a year, to collect information about births, deaths, and migrations. Socioeconomic data are collected annually. The overall HIV prevalence in the study area was ~ 29% in adults in 2011,[6] with an HIV incidence of 6.6 per 100 person-years from 2004 to 2011 for females aged 24 years [5]. Since 2000, overall fertility was steady in the surveillance area at ~ three children per woman,[7] with an average of 2200 live-births annually [8].

Ethics

Ethical approval from the University of KwaZulu-Natal Biomedical Research Ethics Committee was granted to allow linkage of routine patient data to Africa Centre’s Demographic Information System (E 134/06) and for retrospective analysis of routine data collected in Hlabisa and Mtubatuba local municipalities health centres (Ref BE066/07).

Who is in the cohort?

All pregnant women attending antenatal care for the first time at primary health clinics in the Hlabisa sub-district were eligible for inclusion in the cohort. Data was initially collected from all 17 primary health care clinics in the sub-district; since 2012 the focal point for data collection has primary health clinics within the Africa Centre surveillance area. The cohort has completed enrolment for 25 608 pregnancies recorded from 1 January 2010 until 31 December 2014 (Figure 1). A secure database system was developed to capture pregnancy, delivery and infant data on women from first antenatal visit through delivery and infant follow-up to 18 months of age.

Data from 7634 HIV-infected pregnant women has been linked with the Africa Centre Hlabisa HIV Treatment and Care Programme database to provide details on HIV treatment and monitoring, including postpartum follow-up status. Pregnancies of HIV-infected women were categorized according to ART initiation timing: (1) Initiation of ART during pregnancy; (2) Initiation of ART prior to pregnancy; and (3) Not on ART.

Clinical care and follow-up

Until 2013, pregnant women first testing HIV negative had repeat HIV testing recommended at or after 32 weeks gestation; the 2013 HIV guidelines recommend repeat HIV testing for uninfected pregnant women three monthly throughout breastfeeding [9]. The 2010 and 2013 PMTCT guidelines are summarized in Table 1.

Table 1: South African Prevention of Mother-to-Child Transmission guidelines

Regimen	2010 Guidelines	2013 Guidelines
PMTCT prophylaxis (CD4 ⁺ > 350 and WHO stage 1/2)	Antenatal Zidovudine (AZT) from 14 weeks; Intrapartum single-dose Nevirapine (sdNVP), 3 hourly AZT; Postpartum single dose of Tenofovir (TDF) + Emtracitabine (FTC)	TDF, 3TC/FTC, EFV to be initiated as soon as pregnancy is diagnosed (if no active psychiatric illness or history of renal disease) to be continued through the postnatal period until one week after complete cessation of breastfeeding
	<i>Infant regimen:</i> NVP at birth and then daily for six weeks continued as long as any breastfeeding; if formula fed infant NVP should stop at six weeks	<i>Infant regimen:</i> NVP at birth and then daily for six weeks; if the mother on AZT regimen, the infant should receive NVP at birth, then daily for six weeks to be continued till one week after complete cessation of breastfeeding
Lifelong ART (CD4 ⁺ ≤ 350 or stage 3/4)	TDF, 3TC/FTC, EFV	TDF, 3TC/FTC, EFV
	<i>Infant regimen:</i> NVP at birth and then daily for six weeks irrespective of feeding choice	<i>Infant regimen:</i> NVP at birth and then daily for six weeks

As per current standard guidelines (SA, 2015), pregnant women are asked to present for follow-up antenatally six weekly until delivery or more frequently for complicated pregnancy [10]. Women presenting in labour should be counselled and HIV tested during first stage of labour and offered routine PMTCT interventions. If not possible, counselling and testing should be offered postpartum. HIV-exposed infants should be initiated on NVP immediately and provided additional NVP for six weeks. The mother should be counselled on feeding practices and the infant should be tested. Further, women should be commenced on lifelong antiretroviral therapy before discharge and have creatinine and CD4⁺ count checked at the three to six day postpartum visit. Follow-up visits for HIV-exposed infants are structured around the South African immunization schedule starting at three to six days postpartum, then six, 10, and 14 weeks.

Infant HIV status is determined by DNA polymerase chain reaction (PCR) on dried blood spots (DBS Sample Collection Kit for Infant HIV PCR Tests – CCMT Program, Lasec, SA) collected from a heel prick at birth, six weeks (before 2015), and 10 weeks (from 2015). For breastfed infants, an additional PCR is performed six weeks after breastfeeding cessation. HIV-uninfected infants are offered a final test at 18 months using a rapid HIV antibody test (Determine HIV 1/2 Test Abbott Laboratories, Abbott Park, IL) and Sensa Tri-Line HIV 1/2/0 (Hitech Healthcare LTD, China).

What has been measured?

Data collection for the Hlabisa pregnancy cohort is paper-based with DoH staff collecting routine demographic, clinical and pregnancy data on women attending antenatal services (Table 2).

Table 2: Data collected for all pregnant women in the Hlabisa sub-district (2010-2014)

Data Fields	Variable list
Demographics	Name, national identity number, contact details, date of birth
	Date of visit, name of antenatal clinic, other antenatal clinic in close proximity,
Clinical visit data	TB screening, parity, gestational age at first antenatal visit
	Maternal HIV status at visit; if HIV-infected, prior PMTCT exposure, ART
HIV and related measures	initiation and monitoring bloods including CD4 ⁺ cell count and HIV viral load, full blood count, liver function tests, renal function tests
Medication history	If HIV-infected, date of start of ART, type of treatment, adherence
	Mode of delivery, infant prophylaxis after delivery; if HIV-infected, maternal
Delivery data	antiretroviral treatment or prophylaxis taken at delivery
	Birth weight, birth head circumference, birth length, feeding choice at birth, DNA
Infant data	PCR result at six weeks of age

Data is electronically captured at the Africa Centre. Data is collected at the following times during routine visits: first antenatal visit, follow-up one week after the first visit, week 32 (for repeat HIV testing), and at infant delivery. The following routine data on HIV care is collected: 1) CD4⁺; 2) HIV staging; 3) clinical screening for tuberculosis; and 4) initiation of ART prophylaxis or treatment.

Postpartum, data is collected at the six week infant visit. Data on treatment for HIV-infected pregnant women was linked to the Africa Centre HIV Treatment and Care Programme cohort, described previously, to determine detailed measures of timing of ART initiation, medication history, including adherence to ART, baseline and follow-up CD4⁺ and viral load levels [4]. All data, including monitoring laboratory tests for HIV-infected patients, were as per DoH antenatal and HIV guidelines. We report on

the CD4⁺ count according to the 2010 and 2013 HIV guideline eligibility for lifelong ART initiation at 350 cells/mm³ [3,9].

FINDINGS TO DATE

The Hlabisa pregnancy cohort consists of pregnant women attending antenatal care for the first time since January 2010. At the time of data censoring (31 December 2014), the database included 26 520 pregnancies, of whom 25 608 women (96.5%) had an HIV test result; 10 469 (40.8%) were HIV-infected, and 15 139 were HIV-uninfected (Figure 1).

There were 912 (3.4%) women with unknown HIV status excluded from this analysis (indeterminate, missing, or refused HIV test). Compared to included women, those excluded were more likely to attend PHC clinics late in pregnancy at or after 30 weeks ($p < 0.0001$). Further, included women were slightly younger at first visit (24 years; interquartile range (IQR) = 20–29 years) relative to women excluded (26 years; IQR = 22–31 years) from the study (data not shown).

HIV-uninfected women were younger (median age 22 years; IQR 19–26 years) than those HIV-infected (median age 27 years; IQR 23–31 years) and presented marginally later to PHC clinics for their first visit (median 28 weeks; IQR 20–38 weeks) versus 26 weeks in HIV-infected women (IQR 18–38 weeks). HIV-uninfected and -infected women had 7833 (51.7%) and 7287 (69.6%) live-born infants delivered at facilities in Hlabisa to date, respectively. Analysis of pregnancy outcomes is still being conducted.

Clinical characteristics of HIV-infected pregnant women

Of the 10 469 HIV-infected pregnant women, the data of 7634 (72.9%) were linked with the Hlabisa HIV Treatment and Care database,[4] to provide additional detailed information on pregnant women accessing HIV care. Of the 7634 women included in this HIV cohort, to date 972 (12.7%) had subsequent pregnancies recorded. The linkage with the remaining 27% of women was not possible as incomplete national identifying number data made probabilistic linkage between two databases unreliable.

One quarter of women (n = 1917; 25.1%) were already on lifelong ART at pregnancy diagnosis; and 1349 women (17.7%) started lifelong ART within six months of the first antenatal visit of current pregnancy (Table 3).

Table 3: Clinical Characteristics of 7634 HIV-infected women in the Hlabisa pregnancy cohort from 1 January 2010 to 31 December 2014

Characteristic	Initiated ART prior to incident pregnancy (N = 1917) (n %)	Initiated ART within six months of incident pregnancy (N = 1349) (n %)	Pregnant not on ART (N = 4368) (n %)
Median age, years (IQR)	30 (26 - 34)	26 (23 - 31)	25 (22 - 30)
Missing data	16 (0.83)	7 (0.52)	66 (1.51)
Gestation at first antenatal visit, weeks	26 (17 - 38)	20 (15 - 26)	24 (18 - 37)
Median baseline CD4 ⁺ count, cells/mm ³ (IQR)	171.0 (110.0-248.5)	265.0 (187.0 - 340.0)	449 (333.0-595.0)
Missing data	113 (5.9%)	134 (9.9)	1818 (41.6)
Baseline CD4 ⁺ cell count, cells/mm ³			
≤ 350	1692 (88.3)	955 (70.8)	716 (16.4)
> 350	112 (5.8)	260 (19.3)	1834 (42.0)
Missing	113 (5.9)	134 (9.9)	1818 (41.6)
On TB treatment at initiation			
No	1425 (74.3)	1112 (82.4)	-
Yes	187 (9.8)	16 (1.2)	-
Missing	305 (15.9)	221 (16.4)	-
Initiation drug regimen			
Tenofovir regimen	1040 (54.3)	1208 (89.5)	-
Stavudine regimen	788 (41.1)	19 (1.4)	-
Zidovudine regimen	50 (2.6)	85 (6.3)	-
Missing	39 (2.0)	37 (2.7)	-
Status (31 December 2014)			
Active	1636 (85.3)	1132 (83.9)	2628 (60.2)
Deceased	13 (0.7)	12 (0.9)	14 (0.3)
Loss to follow-up	223 (11.6)	184 (13.6)	1412 (32.3)
Transfer out	45 (2.4)	21 (1.6)	4 (0.09)
Missing	0 (0)	0 (0)	310 (7.1)

The majority of women started on ART during pregnancy received TDF-based regimens; women on ART before their pregnancy were initiated either on a stavudine-based or TDF-based regimen. There were a further 3449 women (45.2%) who received ART prophylaxis for PMTCT (either AZT, or short term triple therapy, or both). There were 12% of HIV-infected women (n = 919) who did not receive any ART during their pregnancy; of these, 716 women had $CD4^+ \leq 350$ cells/mm³ and were thus eligible for treatment. There may have been several reasons why these women were not commenced on ART: movement between antenatal clinics and not accessing results; movement out of the sub-district; or death (0.3%) due to disease progression.

The median maternal age of women not on ART or initiating ART within six months of the first visit was younger than women already on lifelong ART at pregnancy diagnosis. Overall, the median gestational age at first antenatal care (ANC) visit was 23 weeks (IQR 17–37 weeks). Women already on lifelong ART before pregnancy attended their first visit later than women who started ART following pregnancy or were not on lifelong ART. In general, women who commenced lifelong ART within six months of pregnancy were in better health at ART initiation with a higher median baseline $CD4^+$ and less tuberculosis than women who were on ART prior to pregnancy (Table 3). Viral load monitoring is inadequate during pregnancy, with only 24.2% (n = 739) of the women on lifelong ART having a viral load test recorded six months before or after first antenatal visit. Of those with viral loads, 12.0% (n = 89) had virologic failure (i.e. viral load 1000 copies/ml or greater within six months of their pregnancy).

While follow-up in the HIV programme was high in women on lifelong ART (n = 2768; 84.8%), postpartum, approximately 32% of women not on ART for their own health were lost to follow-up.

DISCUSSION

Data from the Hlabisa pregnancy cohort indicate the low proportion of women who attend their first ANC visit in the first trimester. Early antenatal attendance is particularly important given the current PMTCT guidelines to provide triple ART to all HIV-infected women from the first antenatal visit for their own and infant’s health. The younger age of HIV-uninfected pregnant women compared with those HIV-infected in this cohort is similar to a finding in a Sowetan study [11]. A possible explanation for this may

be that pregnancy rates decline with HIV disease progression [12]. However, given the expanded ART use in pregnant women which has been associated with higher pregnancy rates,[13] another likely scenario is that HIV-infected women may be accessing contraception and delaying pregnancy as they progress through the HIV treatment cascade as reported in a study using the Africa Centre's surveillance data [14].

Our finding that only 25% of the women had viral load testing highlights a common problem in resource poor settings [15] and encourages policy makers to seek strategies to overcome this challenge. Moreover, viral load monitoring during pregnancy may be improved since the latest HIV guideline release [10]. Virologic failure in pregnant women on ART underscores the importance of understanding the different pathways of pregnancy effect, including physiologic, hormonal, drug pharmacokinetics and behavioural factors,[16] as the risk of drug resistance increases as more women on ART become pregnant. Moreover, it is important to engage mothers as partners in their health since it is very clear that access to drugs does not translate to adherence where mothers are not empowered and engaged [17–20]. Caution needs to be exercised that budgets that spend enormous amounts on drugs do not get swamped resulting in diminished resources for the equally important psycho-social elements of management of HIV disease. The nature of health service provision, as well as social context, are equally important in improving programmes

We are currently conducting analyses in terms of birth outcomes. We also plan a series of analyses to: (1) determine the risk of HIV acquisition during pregnancy and postpartum, (2) determine the impact of HIV and ART on birth outcomes; (3) examine the impact of pregnancy on virologic response to ART; and (4) characterize the impact of sequential pregnancies on access to clinical care and response to prolonged ART and birth outcomes.

Strengths and limitations

The main strengths of this cohort include its size and the ability to model the impact of the HIV programme on the population due to detailed, longitudinal information available about the community and the linkage between clinical and population data. Accurate characterization of the cohort will provide an understanding of the determinants of pregnancy outcomes, and implications for service delivery in a

typical HIV hyperendemic rural setting, which is likely to be generalizable to other resource-limited settings in South Africa.

One of the main challenges common to all pregnancy cohorts is the attrition rate. Poor follow-up of HIV-infected mothers and their infants remain a major problem, undermining the delivery of maternal and infant ART; support of safe infant feeding practices; and measurement of infant HIV-free survival at 18 months. Using our linked population datasets, the pregnancy outcome of women not retained in care may be assessed, and through sensitivity analysis, factors related to poor attrition will be characterised. The clinical pregnancy data will also be utilized to validate the general health surveys on pregnancy and contraception in the surveillance area, providing sensitivity and specificity estimates of individual reporting of pregnancy and pregnancy outcomes within the Africa Centre surveillance area.

Collaboration

Requests for access to this pregnancy cohort should be directed to Africa Centre’s Helpdesk (help@afRICACentRE.ac.za) with “Research Dataset Request” in the subject line of the email. A data access agreement will be requested from the researcher and is submitted to the applicable data custodian. The data user will be notified once access approval is granted.

Contributors: TC contributed to the data collection and curation, performed the data analysis, and wrote the first draft. CT, FT, TB, and AC commented on the results and contributed to all subsequent drafts.

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district located within and around the surveillance area. The opinions expressed herein are those of the authors and do not necessarily reflect the views of USAID, or the United States Government, or the Department of Health, KwaZulu-Natal.

Competing interest: None declared

Ethics approval: University of KwaZulu-Natal Biomedical Research Ethics Committee

Provenance and peer review: Not commissioned; internally peer reviewed

Data sharing statement: Further information about the data can be obtained from the corresponding author (tchetty@afRICACENTRE.ac.za) or from the Africa Centre website (www.afRICACENTRE.ac.za). Access to the dataset is available with permission from the data team at the Africa Centre.

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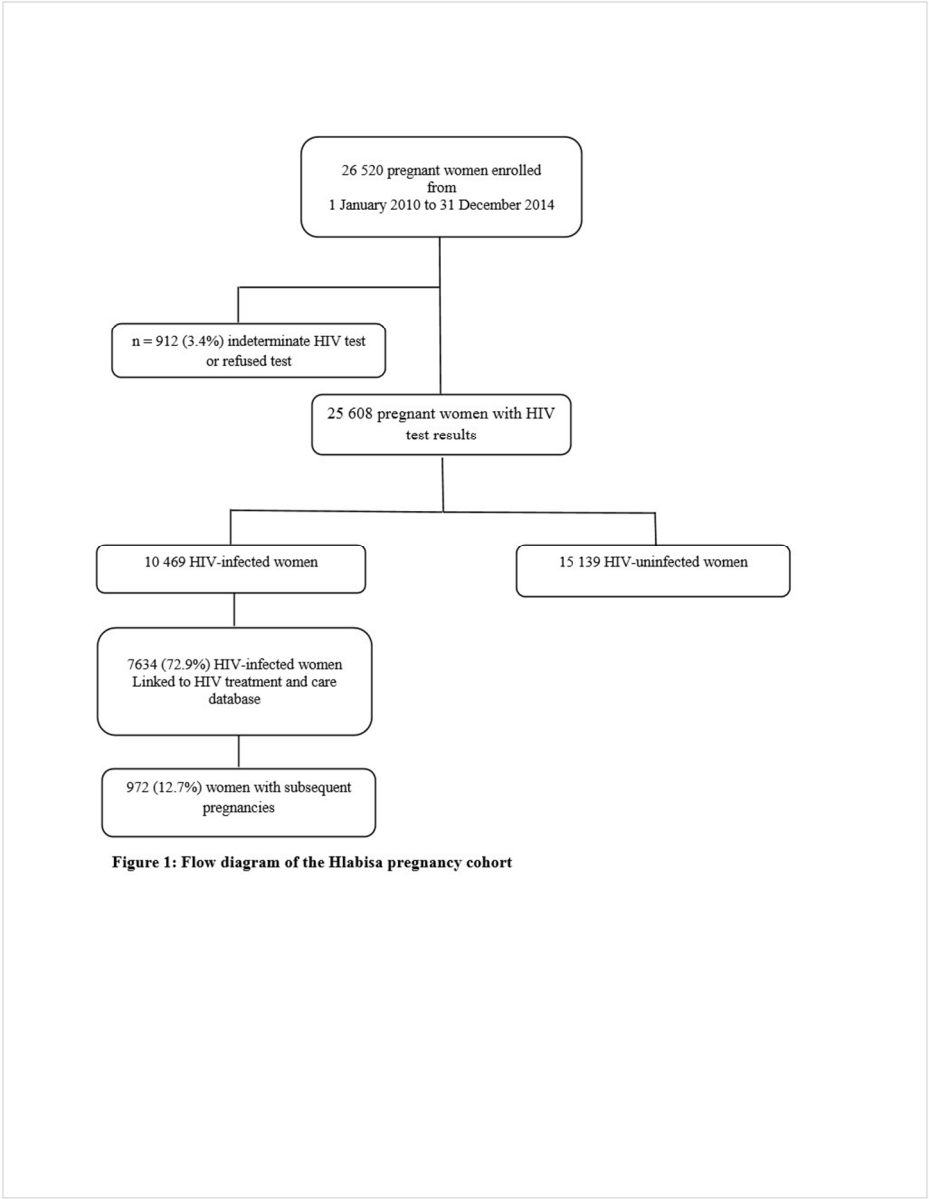


Figure 1: Flow diagram of the Hlabisa pregnancy cohort

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217x280mm (120 x 120 DPI)

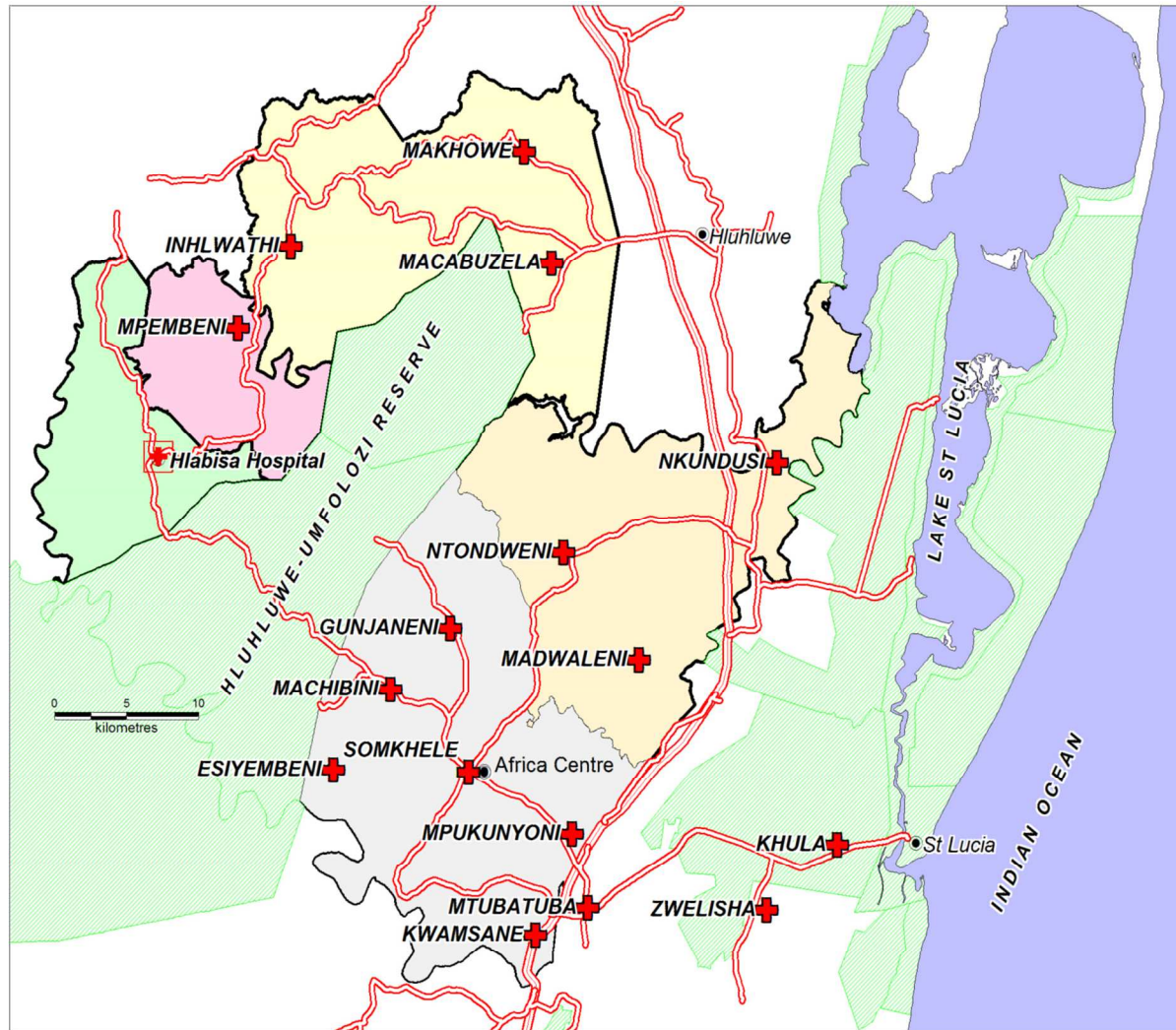


Figure 2: Africa Centre surveillance area showing the position of the Hlabisa Hospital with an on-site clinic and 16 peripheral clinics in the Hlabisa sub-district, KwaZulu-Natal, South Africa. The Hlabisa sub-district encompasses the area to the bottom-right of the map which includes Mtubatuba and Zwenelisha clinics.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2, 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 4,5
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	5, 9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A as we ran descriptive statistics only
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	N/A as we provide descriptive statistics only of the cohort.
		(b) Describe any methods used to examine subgroups and interactions	N/A

		(c) Explain how missing data were addressed	We report on missing data in covariates on page 10 (Table 3)
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	We report on the proportion of pregnant women lost to follow-up in the findings (page 11) and table 3 (page 10)
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, 9,10
		(b) Give reasons for non-participation at each stage	Figure 1 (separate from main text)
		(c) Consider use of a flow diagram	Figure 1 (separate)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	As we describe the cohort only, we did not provide person-time in this paper
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	9, 10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Cohort description only provided in Table 3 (page 10)
		(b) Report category boundaries when continuous variables were categorized	9
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A

Discussion				
Key results	18	Summarise key results with reference to study objectives		9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results		13
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Cohort Profile: The Hlabisa pregnancy cohort, KwaZulu-Natal, South Africa

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Cohort Profile: The Hlabisa pregnancy cohort, KwaZulu-Natal, South Africa

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ABSTRACT

Purpose: The Hlabisa pregnancy cohort was established to evaluate the effectiveness of Prevention of Mother-to-Child Transmission (PMTCT) guideline revisions. The objectives of the Hlabisa pregnancy cohort are to: (i) provide cohort-level information on maternal health up to six weeks postpartum in a high Human Immunodeficiency Virus (HIV) prevalence setting; and to (ii) evaluate aspects of PMTCT care that have policy relevance.

Participants: The pregnancy cohort is located in primary health clinics in the Hlabisa sub-district of rural KwaZulu-Natal, South Africa. Baseline data collection between 2010 and 2014 has been completed, with the enrolment of 25 608 pregnancies; age ranged from 15-49 years. Pregnant women were assessed during routine antenatal visits: first visit, follow-up one week later, 32 weeks (HIV test), infant delivery and six weeks postpartum. Demographic, pregnancy, clinical, laboratory and HIV data were collected through Department of Health interviews, laboratory tests and routine data linkage. Treatment data for HIV-infected pregnant women were linked to the Africa Centre Hlabisa HIV Treatment and Care Programme for detailed antiretroviral therapy (ART) history and laboratory tests.

Findings to date: The proportion of women initiated on ART post-2013 were higher (n=437; 100%) than pre-2013 (n=768; 84.2%). The proportion of women in care at six weeks (73.8%) was also higher post-2013 relative to earlier years (58.5%). The majority of HIV-infected pregnant women were either on lifelong ART or ART prophylaxis; pre-2013 ~ 9.6% of women were not on any ART. Pregnancy viral load monitoring was inadequate.

Future plans: This cohort will be used to: (1) determine HIV acquisition risk during pregnancy and postpartum, (2) determine the effect of HIV and ART on birth outcomes; (3) examine the effect of pregnancy on virologic response to ART; and (4) characterize the effect of sequential pregnancies on access to clinical care, response to prolonged ART and birth outcomes.

Strengths and limitations of this study

- The key characteristic of the Hlabisa pregnancy longitudinal cohort is size and ability to model the impact of the HIV programme on the community through linkage of Africa Centre’s population level data with clinical, pregnancy and HIV data; and
- Follow-up of HIV-infected mothers are crucial to monitor adherence to ART and disease progression.

For peer review only

INTRODUCTION

Prevention of mother-to-child transmission (PMTCT) of the Human Immunodeficiency Virus (HIV) using antiretroviral drugs can nearly eliminate vertical HIV transmission risk and increase maternal survival [1]. However, poor delivery of any of the sequential steps in PMTCT results in cumulative losses of pregnant women from services, raising infant HIV transmission risk [2]. The PMTCT “cascade” highlights the sequence of steps for optimum PMTCT: HIV counselling and testing at the first antenatal visit; CD4⁺ measurement; antiretroviral therapy (ART) initiation and adherence; and early infant HIV testing [2], or after cessation of breastfeeding and infant HIV test at 18 months [3].

The Hlabisa HIV Treatment and Care programme (HHTCP), described previously,[4] was a partnership between the South African Department of Health (DoH) and the Wellcome Trust funded Africa Centre for Population Health (Africa Centre). In January 2010, the Africa Centre established a pregnancy cohort in keeping with the HHTCP objectives to monitor the PMTCT cascade to provide feedback indicators to funders. A further objective is to use this cohort to determine clinical markers related to pregnancy in this high HIV prevalence setting. The pregnancy cohort can be linked with the Africa Centre Demographic Information System (ACDIS), which has demographic and health data through population-based longitudinal surveillance of approximately 90 000 people in 11 000 households, including accurate longitudinal HIV incidence, HIV prevalence and ART coverage estimates for this sub-population since 2003 [5,6]. In doing so, the demographic and health factors related to the success of the PMTCT programme can be monitored.

Cohort setting

The Hlabisa sub-district of uMkhanyakude in northern KwaZulu-Natal, South Africa is predominantly rural with a population of approximately 228 000 [5]. There are 17 nurse-led primary health care (PHC) clinics with a primary level district hospital (Hlabisa Hospital), which handles most of the deliveries. Six DoH clinics and 40% of patients are located within the surveillance area (Figure 1). Household surveillance began in January 2000. Routine household visits were conducted biannually, and since 2012 three-times a year, to collect information about births, deaths, and migrations. The sample of resident and

non-resident females aged 15 – 49 years in ACDIS from 2010 through 2014, were respectively: 65 454 (27.3%); 65 352 (27.5%); 65 889 (27.7%); 65 092 (27.8%); 62 705 (27.9%).

Ethics

Ethical approval from the University of KwaZulu-Natal Biomedical Research Ethics Committee was granted to allow linkage of routine patient data to ACDIS (E 134/06) and for retrospective analysis of routine data collected in Hlabisa and Mtubatuba local municipalities health centres (Ref BE066/07).

Due to the dynamic movement of patients within antenatal clinics with entry at varying times, including delivery, reliable written informed consent for pregnancy data linkage with the ACDIS was challenging. Additionally, consent from the ACDIS cohort is obtained at household level, with either the household head providing verbal consent for the survey to be conducted, or a proxy in the absence of the household head. We therefore requested a waiver of written informed consent for linkage of the pregnancy and ACDIS data from the University of KwaZulu-Natal Biomedical Research Ethics Committee (E134/06). Instead, women attending antenatal clinics gave verbal consent to link their details with ACDIS data.

Who is in the cohort?

From 1 January 2010 to December 2014, all pregnant women attending antenatal care (ANC) for the first time at PHC clinics in the sub-district entered the cohort automatically. Data was initially collected from all 17 PHC clinics in Hlabisa up to 2012; thereafter as funding was restricted, the data collection focal point became six PHC clinics within the surveillance and one clinic located just outside the surveillance due to the proximity to the national road.

The cohort has completed enrolment for 25 608 pregnancies recorded from 1 January 2010 until 31 December 2014 (Figure 2). A secure database system was developed to capture data on women from first antenatal visit through delivery and infant follow-up to 18 months of age.

Data from 7634 HIV-infected pregnant women has been linked with the Africa Centre HHTCP database to provide details on HIV treatment and monitoring, including postpartum follow-up [4]. All pregnant women were offered HIV counselling and testing at their first antenatal visit. Women who disclosed that

they were HIV-infected (i.e. known HIV status prior to pregnancy) were asked about prior PMTCT or ART exposure and if they had started lifelong ART.

Pregnancies of HIV-infected women were categorized according to ART initiation timing: (1) Already on lifelong ART prior to first antenatal visit; (2) Started lifelong ART within six months of the first antenatal visit; and (3) Not on lifelong ART during the pregnancy (as assessed at delivery). For those patients already on lifelong ART prior to the first antenatal visit, we report the ART regimen prescribed within six months of the first antenatal visit.

Clinical care and follow-up

Until 2013, pregnant women first testing HIV negative had repeat HIV testing recommended at or after 32 weeks gestation; the 2013 HIV guidelines recommend repeat HIV testing for -uninfected pregnant women three monthly throughout breastfeeding [7]. The 2010 and 2013 PMTCT guidelines are summarized in Table 1. Since 2015, South Africa has followed the World Health Organization (WHO) recommendation to initiate all pregnant HIV-infected women on lifelong ART, regardless of CD4⁺ count (Option B+) [8,9]. Before 2010, the first line regimen recommended for patients with a CD4⁺ count \leq 200 cells/mm³ or WHO stage 4 was Stavudine (d4T), Lamivudine (3TC), and either Efavirenz (EFV) or nevirapine (NVP) [10]. The 2010 ART adult guidelines recommended that patients already on a d4T-based regimen continue on this treatment if well tolerated, with early switch to tenofovir (TDF) with any toxicity [11]. Tenofovir was rolled out according to a phased implementation plan. Pregnant patients were prioritized if they were newly initiating ART in April 2010. By April 2011, d4T to TDF switches were prioritized, hence there was a lag with d4T regimen changes for patients that initiated prior to April 2010 if side effects were not severe [12]. The approximate proportion of patients on d4T regimens in the HHTCP were as follows: (1) by December 2012, approximately 20-30% of patients; (2) by the end of 2013, ~ 10-20%; and (3) by December 2014, ~5% [12].

Table 1: South African Prevention of Mother-to-Child Transmission guidelines

Regimen	2010 Guidelines	2013 Guidelines
PMTCT prophylaxis (CD4 ⁺ > 350 and WHO stage 1/2)	Antenatal Zidovudine (AZT) from 14 weeks; Intrapartum single-dose Nevirapine (sdNVP), 3 hourly AZT; Postpartum single dose of TDF + Emtracitabine (FTC)	TDF, 3TC/FTC, EFV to be initiated as soon as pregnancy is diagnosed (if no active psychiatric illness or history of renal disease) to be continued through the postnatal period until one week after complete cessation of breastfeeding (WHO Option B)[8]
	<i>Infant regimen:</i> NVP at birth and then daily for six weeks, continued as long as any breastfeeding; if formula fed infant NVP should stop at six weeks	<i>Infant regimen:</i> NVP at birth and then daily for six weeks; if the mother on AZT regimen, the infant should receive NVP at birth, then daily for six weeks to be continued till one week after complete cessation of breastfeeding
Lifelong ART (CD4 ⁺ ≤ 350 or WHO stage 3/4)	TDF, 3TC/FTC, EFV	TDF, 3TC/FTC, EFV
	<i>Infant regimen:</i> NVP at birth and then daily for six weeks irrespective of feeding choice	<i>Infant regimen:</i> NVP at birth and then daily for six weeks

As per 2015 guidelines, pregnant women are asked to present for follow-up antenatally six weekly until delivery or more frequently for complicated pregnancies [9]. Women presenting in labour should be counselled and HIV tested during first stage of labour and offered routine PMTCT interventions. If not possible, counselling and testing should be offered postpartum. The mother should be counselled on feeding practices and the infant should be tested. Further, women should be commenced on lifelong ART before discharge and have creatinine and CD4⁺ count checked at the three to six day postpartum visit. Follow-up visits are aligned with infant immunization schedule at six, 10 and, 14 weeks.

What has been measured?

Data collection for the Hlabisa pregnancy cohort is paper-based with DoH staff collecting routine demographic, clinical and pregnancy data on women attending antenatal services (Table 2). The database was designed as an early identification tool for pregnant women requiring further care and to inform clinics of the appropriate actions to be performed at each step in the PMTCT cascade. Data flow was not unidirectional as Africa Centre provided action lists, data issues, and tracking reports to DoH staff on a weekly basis. Additionally, routine PMTCT statistics were reported to clinics at least quarterly when the HHTCP was operational.

Patient monitoring in the HHTCP, including PMTCT care, were conducted as follows: (1) Africa Centre staff responsible for the PMTCT data telephoned nurses at the antenatal and HIV clinics to flag abnormal maternal and infant results (HIV tests, CD4⁺ and viral load results), to determine if the appropriate treatment had been provided, and if patients were in care; (2) Patients with abnormal blood results were telephoned and asked to return to the clinic for care (Africa Centre staff did not provided blood results telephonically or disclose confidential information); (3) Patients eligible for, or on lifelong ART, who did not return for care were referred to the HHTCP tracking team; and (4) Clinicians in the HHTCP followed up patients on lifelong ART with virologic failure, including pregnant women (latest viral load results above 1000 copies/ml after at least 12 months on a standard first line regimen), offering genotypic resistance testing as part of HIV Treatment Failure Clinic model and The Southern African Treatment and Resistance Network (SATuRN) [13–15], changing treatment according to DoH guidelines [7,11].

Table 2: Data collected for all pregnant women in the Hlabisa sub-district (2010-2014)

Data Fields	Variable list
Demographics	Name, national identity number, contact details, date of birth
	Visit date, Antenatal clinic name, other antenatal clinic in close proximity, TB
Clinical visit data	screening, parity, gestational age at first antenatal visit
	Maternal HIV status at visit; if HIV-infected, prior PMTCT exposure, ART
HIV and related measures	initiation and monitoring bloods including CD4 ⁺ cell count and HIV viral load, full blood count, liver function tests, renal function tests
Medication history	If HIV-infected, date of start of ART, type of treatment, adherence
	Mode of delivery, infant prophylaxis after delivery; if HIV-infected, maternal
Delivery data	antiretroviral treatment or prophylaxis taken at delivery
	Birth weight, birth head circumference, birth length, feeding choice at birth, DNA
Infant data	PCR result at six weeks of age

Data is electronically captured at the Africa Centre. Data is collected at the following times during routine visits: first antenatal visit, follow-up one week after the first visit, week 32 (for repeat HIV testing), and at infant delivery. The following routine data on HIV care is collected: 1) CD4⁺; 2) HIV staging; 3) clinical screening for tuberculosis; and 4) initiation of ART prophylaxis or treatment.

Postpartum, data is collected at the six week infant visit. Data on treatment for HIV-infected pregnant women was linked to the HHTCP cohort, described previously [4], to determine detailed measures of timing of ART initiation, medication history, including ART adherence, baseline and follow-up CD4⁺ and viral loads. All test results are collated into a laboratory database and then imported into the HHTCP database, allowing monitoring of the clinical disease progression of all patients initiated on ART [4].

All data, including monitoring laboratory tests for HIV-infected patients, were as per DoH antenatal and HIV guidelines. We report on the CD4⁺ count according to the 2010 and 2013 HIV guideline eligibility for lifelong ART initiation at 350 cells/mm³ [3,7].

Data linkage

Pregnancy data were linked to HHTCP data using name, surnames, and identity numbers, or dates of birth where identity numbers were missing. Additional information such as cellphone numbers and laboratory test dates were used to verify patient linkage. Trained data capturers linked pregnancy and HIV datasets at data capture into the pregnancy database, and through provision of monthly lists generated by a data manager. Data were password protected and known only to study investigators and the data team.

ACDIS Linkage

Individuals in ACDIS are assigned an alphanumeric 'External Identification Number (DSID)', which is linked to individual identifiers, including names and/or identity numbers. The 'External ID' is linked to an 'Internal ID' through a highly protected table, accessible only to the senior data manager. At data capture, an individual's 'Internal ID' replaces his 'External ID' in the database, anonymising all data. The "Internal ID" is added to the HHTCP and pregnancy databases for all patients in ACDIS. This 'Internal ID' provides the link between the ACDIS, HHTCP and pregnancy databases, allowing de-identified data to be extracted from across databases. An 'Internal ID' cannot be used to identify an individual on an ACDIS field questionnaires or lists.

FINDINGS TO DATE

The Hlabisa pregnancy cohort consists of women attending ANC for the first time since January 2010. At the time of data censoring (31 December 2014), the database included 26 520 pregnancies, of whom 25 608 women (96.5%) had HIV test results; 10 469 (40.8%) were HIV-infected, and 15 139 were HIV-uninfected (Figure 2).

There were 912 (3.4%) women with unknown HIV status excluded from this analysis (indeterminate, missing, or refused HIV test). Compared to included women, those excluded were more likely to attend

PHC clinics late in pregnancy at or after 30 weeks ($p < 0.0001$). Further, included women were slightly younger at first visit (24 years; interquartile range (IQR) = 20–29 years) relative to excluded women (26 years; IQR = 22–31 years) (data not shown).

HIV-uninfected women were younger (median age 22 years; IQR 19–26 years) than those HIV-infected (median age 27 years; IQR 23–31 years) and presented marginally later to PHC clinics for their first visit (median 28 weeks; IQR 20–38 weeks) versus 26 weeks in HIV-infected women (IQR 18–38 weeks). HIV-uninfected and -infected women had 7833 (51.7%) and 7287 (69.6%) live-born infants delivered at facilities in Hlabisa to date, respectively.

Clinical characteristics of HIV-infected pregnant women

Of the 10 469 HIV-infected pregnant women, the data of 7634 (72.9%) were linked with the HHTCP database [4], to provide detailed information on pregnant women accessing HIV care. Of the 7634 women included in this cohort, to date 972 (12.7%) had subsequent pregnancies recorded. The linkage with the remaining 27% of women was not possible as incomplete national identifying number data made probabilistic linkage between two databases unreliable.

Overall, 25.1% of women ($n = 1917$) were already on lifelong ART at their first ANC visit; 1349 women (17.7%) started lifelong ART within six months of the first antenatal visit of the current pregnancy.

Before 2013, most women who started on lifelong ART at their first antenatal visit received TDF-based regimens; women on lifelong ART before pregnancy were initiated either on a TDF-based or d4T-based regimen (Table 3). There were a further 2347 women (76.4%) who received AZT prophylaxis for PMTCT (Table 4). There were 9.6% of HIV-infected women ($n = 296$) who did not receive any ART during their pregnancy; of these, 82 women (27.7%) had $CD4^+ \leq 350$ cells/mm³ and were eligible for treatment. There may have been several reasons why these women were not commenced on ART: movement between clinics and not accessing results; transfer out of the sub-district; or death (0.4%) due to disease progression.

Post-2013, most women established on ART before their first antenatal visit were on TDF-based regimens. Further, the proportion of women who initiated on d4T regimens (13.7%) before their first visit were less than in prior years (25.9%), reflecting the phased implementation plan for ART, with pregnant women prioritized to start triple ART [16]. Moreover, relative to earlier years, there was an increase in the proportion of women on established ART before their first visit, and initiated on ART within six months of the first visit. All women who were newly initiated on ART within six months of their first antenatal visit were on TDF-based regimens. Of the 1298 women who were not on lifelong ART, most were started on the fixed dose combination of TDF+FTC+EFV; and 14% received AZT prophylaxis (Table 4). The proportion of pregnant women who did not receive ART prophylaxis or were missing data on treatment decreased post-2013 versus earlier years.

The median maternal age of women not on ART or initiating ART within six months of the first visit was younger than women already on lifelong ART at pregnancy diagnosis (Table 3). Overall, the median gestational age at first ANC visit was 23 weeks (IQR 17–37 weeks). Across the years and irrespective of ART initiation, a low proportion of women had a first antenatal visit before 12 weeks. Despite HIV guideline revisions emphasizing the importance of early antenatal attendance, over 15% of women attended their first antenatal visit in the third trimester at 25 to 36 weeks gestation. Unexpectedly, there were over 20% of women who were already on lifelong ART with a first antenatal visit after 37 weeks gestation, both pre- and post-2013; this may suggest women on lifelong ART had their pregnancy managed while attending the clinic for HIV treatment. However, this was not standard, and women on established lifelong ART were usually referred to the antenatal clinic for pregnancy care. While the proportion of women who newly initiated ART within six months of their pregnancy after 37 weeks fell post-2013, more women not on lifelong ART attended their first antenatal visit after 37 weeks relative to earlier years. This may be aligned with guideline revisions to start pregnant HIV-infected women on ART as soon as possible, or reflect an improvement in data collection with less missing data on gestational age post-2013.

In general, women who commenced lifelong ART within six months of pregnancy were in better health at ART initiation with a higher median baseline CD4⁺ count, particularly after guidelines revisions in 2013

(Table 3). Viral load monitoring was inadequate during pregnancy, with only 24.2% (n = 739) of the women on lifelong ART overall having a viral load test recorded six months before or after first antenatal visit. Of those with viral loads, 12.0% (n = 89) had virologic failure (i.e. viral load ≥ 1000 copies/ml) within six months of their first antenatal visit).

Overall, preliminary analysis suggests that follow-up in the HIV programme was over 80% in women on lifelong ART (n = 2768; 80%), at six weeks postpartum. Though the proportion of women not on lifelong ART who did not return for care declined in later years versus earlier years, and is likely to be an indicator of better adherence to triple ART prophylaxis post-2013, there were still over 15% of women not in care post-2013.

Table 3: Characteristics of 7634 HIV-infected pregnant women in Hlabisa from 1 January 2010 to 31 December 2014 by ART status

	Up to 2012			2013 and later		
	On lifelong ART before the first antenatal visit (N=1295)	Started lifelong ART within six months of the first antenatal visit (N=912)	Not on lifelong ART (N=3070)	On lifelong ART before the first antenatal visit (N=622)	Started lifelong ART within six months first antenatal visit (N=437)	Not on lifelong ART (N=1298)
Median age, years	30 (26-34)	27 (23-31)	25 (21-29)	31 (27-35)	25 (22-30)	26 (22-31)
Gestational age at first visit, weeks						
< 12	68 (5.3)	55 (6.0)	177 (5.8)	54 (8.7)	43 (9.8)	59 (4.6)
12-24	363 (28.0)	473 (51.9)	1108 (36.1)	214 (34.4)	240 (54.9)	415 (32.0)
25-37	209 (16.1)	165 (18.1)	631 (20.6)	98 (15.8)	78 (17.9)	200 (15.4)
>37	319 (24.6)	57 (6.3)	436 (14.2)	174 (28.0)	10 (2.3)	416 (32.1)
Missing	336 (26.0)	162 (17.8)	718 (23.4)	82 (13.2)	66 (15.1)	208 (16.0)
Median baseline CD4 ⁺ count (IQR), cells/mm	166 (105-233)	235 (162-300)	431 (321-568)	187 (125-274)	440 (299-629)	492 (357-656)
Missing	60	37	1290	53	80	340
Baseline CD4 ⁺ count						
≤ 350 cells	1179 (91.0)	827 (90.7)	532 (17.3)	513 (82.5)	132 (30.2)	184 (14.2)
> 350 cells	56 (4.3)	48 (5.3)	1244 (40.5)	56 (9.0)	225 (51.5)	774 (59.6)
Missing	60 (4.6)	37 (4.1)	1290 (42.0)	53 (8.5)	80 (18.3)	340 (26.2)
On TB treatment at initiation						
Latest drug regimen						
TDF based	872 (67.3)	768 (84.2)	-	480 (77.2)	437 (100)	-
Stavudine based	335 (25.9)	16 (1.8)	-	85 (13.7)	-	-
AZT based	50 (3.9)	79 (8.7)	-	23 (3.7)	-	-
Unknown	38 (2.9)	49 (5.4)	-	34 (5.5)	-	-
Status						
Active	1076 (83.1)	724 (79.4)	1670 (58.5)	560 (90.0)	408 (93.4)	958 (73.8)
Deceased	12 (0.9)	12 (1.3)	10 (0.4)	1 (0.2)	-	4 (0.3)
LTFU	169 (13.1)	155 (17.0)	1172 (41.0)	54 (8.7)	29 (6.6)	240 (18.5)
Transfer out	38 (2.9)	21 (2.3)	4 (0.1)	7 (1.1)	-	-
Missing			214			96 (7.4)

Table 4: PMTCT regimens of pregnant women in the Hlabisa sub-district who were not on lifelong ART from 1 January 2010 to 31 December 2014

ART prophylaxis	Up to 2012 (N=3070)	2013 and later (N=1298)
*AZT	2347 (76.4)	186 (14.3)
TDF+FTC+EFV	-	967 (74.5)
None	296 (9.6)	95 (7.3)
Missing	427 (13.9)	50 (3.9)

* Inclusive of either sd-NVP, sd-FTC or both

DISCUSSION

Data from the Hlabisa pregnancy cohort indicate the low proportion of women who attend their first ANC visit early in the first trimester. Early attendance is particularly important given the current PMTCT guidelines to provide triple ART to HIV-infected women from the first antenatal visit for their own and infant's health. The younger age of HIV-uninfected pregnant women compared with those HIV-infected in this cohort is similar to a finding in a Sowetan study [17]. A possible explanation for this may be that pregnancy rates decline with HIV disease progression [18]. However, given the expanded ART use in pregnant women which has been associated with higher pregnancy rates,[19] another likely scenario is that HIV-infected women may be accessing contraception and delaying pregnancy as they progress through the HIV treatment cascade as reported in a study using the Africa Centre's surveillance data [20].

The improvement in the PMTCT coverage and patient retention post-2013 supports the feasibility and acceptability of the 2013 PMTCT revisions. While Malawi reported an ART coverage increase of approximately 49% [21], the ART coverage progression in our study was more conservative. These findings should be contextualized by the successes within the HHTCP with high ART coverage; by July 2011 approximately 37% of all HIV-infected patients were on lifelong ART [6]; by 2012 over 50 000 patients were enrolled in the programme with 25 000 individuals initiated on lifelong ART [6,13]; our study indicates that over 65% of women were established on ART before pregnancy and newly initiated on ART within six months of the pregnancy pre-2013. These findings reinforce South Africa's commitment to reduce vertical HIV transmission and improve maternal health and child survival consistent with international priorities [22,23].

Prior studies before Option B was implemented have reported approximately 25-50% of patients of women on ART at delivery lost to care within six months postpartum [24–26]. While the proportion of women on lifelong ART retained in care in this study was high, the proportion of women initiated on interrupted triple ART prophylaxis post-2013 was higher than the attrition rate in the DREAM cohort of pregnant women in Cameroon initiated on Option B (92.6% at six months) [27], our study reports follow-up status at six weeks postpartum and it possible that retention may deteriorate over time. In Malawi, approximately 17% of pregnant women initiated on Option B+ were lost to care by six months; most

women were lost to follow-up at the day of HIV testing and ART initiation [28]. These results emphasize the importance of treatment literacy, particularly as pregnant women start ART on higher CD4⁺ counts.

Our finding that only 25% of the women had viral load testing highlights a common problem in resource poor settings [29] and encourages policy makers to seek strategies to overcome this challenge. While viral load monitoring during pregnancy may have improved since the latest HIV guideline release [9], monitoring of virologic failure is necessary to minimize PMTCT leakages that may prevent elimination of paediatric HIV. In population based survey of three countries, including South Africa, viral loads above 1000 copies/ml remained undiagnosed in pregnant and breastfeeding women [30]. Virologic failure in pregnant women on ART underscores the importance of understanding the different pathways of pregnancy effect, including physiologic, hormonal, drug pharmacokinetics and behavioural factors[31], as the risk of drug resistance increases as more women on ART become pregnant. Moreover, it is important to engage mothers as partners in their health since it is very clear that access to drugs does not translate to adherence where mothers are not empowered and engaged [32–35]. Caution needs to be exercised that budgets that spend enormous amounts on drugs do not get swamped resulting in diminished resources for the equally important psycho-social elements of management of HIV disease.

As South Africa has already expanded access to ART and implemented Option B+, it is likely that more women will conceive while on established ART. Strong routine information systems are required to ensure linkage to care, treatment and disease progression monitoring. In future studies, we will link data presented in this study to the Africa Centre surveillance system, providing us with an appropriate denominator for the pregnant population and minimizing the challenges posed by double counting in routine systems, necessary for utilizing routine data from PMTCT programmes for “HIV surveillance” as recommended by the WHO [36]. Additionally, as the pregnancy database was used for the active PMTCT care monitoring, we were able to inform DoH staff of the quality and effectiveness of their services and capacitate staff to improve their routine data. At a policy level, evidence-based decisions, including data from this study, can improve resource allocation and health care performance, particularly as South Africa expands access to Option B+. The centralized HIV and pregnancy database in this rural health setting, including routine data has allowed us to assess maternal HIV status and ART guidelines

over time, and is complementary to routine health information systems in South Africa, including the District Health Information System and the Three Interlinked Electronic Register (Tier.Net) to monitor ART provision. As Tier.Net evolves into an active monitoring system for HIV care, the lessons we have learned can advance understanding of data issues, patient challenges and possible solutions. Moreover, as the HHTCP includes directly imported laboratory data [4], the potential for information bias is lessened as we verify routine data of pregnant women in HIV care.

This cohort is generally representative of the Hlabisa sub-district with data on pregnant women attending all clinics in the area up to 2012, and thereafter still included two of busiest antenatal clinics in the sub-district. Moreover, the HIV prevalence reported in this study is comparable to the 2012 antenatal HIV prevalence in the uMkhanyakhude district (35.2%; 95% CI: 29.4–41.5) [37]. We are currently conducting analyses in terms of birth outcomes. We also plan a series of analyses to: (1) determine the risk of HIV acquisition during pregnancy and postpartum, (2) determine the impact of HIV and ART on birth outcomes; (3) examine the impact of pregnancy on virologic response to ART; and (4) characterize the impact of sequential pregnancies on access to clinical care and response to prolonged ART and birth outcomes.

Strengths and limitations

The main strengths of this cohort include its size and the ability to model the impact of the HIV programme on the population due to detailed, longitudinal information available about the community and the linkage between clinical and population data. Accurate characterization of the cohort will provide an understanding of the determinants of pregnancy outcomes, and implications for service delivery in a typical HIV hyperendemic rural setting, which is likely to be generalizable to other resource-limited settings in South Africa.

During the HHTCP, Africa Centre and DoH staff collaborated to follow-up patients lost to care. It is crucial to follow-up HIV-infected mothers in order to ensure effective delivery of maternal ART for their own and their infants' health; support safe infant feeding practices; and assess maternal adherence and disease progression. Using our linked population datasets, the pregnancy outcomes of women not

retained in care may be determined, and through sensitivity analysis, factors related to poor attrition will be characterised. The clinical pregnancy data will also be utilized to validate the general health surveys on pregnancy and contraception in the surveillance area, providing sensitivity and specificity estimates of reporting of pregnancy within the Africa Centre surveillance area.

Collaboration

Requests for access to this pregnancy cohort should be directed to the Africa Centre’s Helpdesk (help@afRICACentre.ac.za) with “Research Dataset Request” in the subject line of the email. A data access agreement will be requested from the researcher and is submitted to the applicable data custodian. The data user will be notified once access approval is granted.

Contributors: TC contributed to the data collection and curation, performed the data analysis, and wrote the first draft. CT, FT, TB, and AC commented on the results and contributed to all subsequent drafts.

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Competing interest: None declared

Ethics approval: University of KwaZulu-Natal Biomedical Research Ethics Committee

Provenance and peer review: Not commissioned; internally peer reviewed

Data sharing statement: Further information about the data can be obtained from the corresponding author (tchetty@afriacentre.ac.za) or from the Africa Centre website (www.afriacentre.ac.za). Access to the dataset is available with permission from the data team at the Africa Centre.

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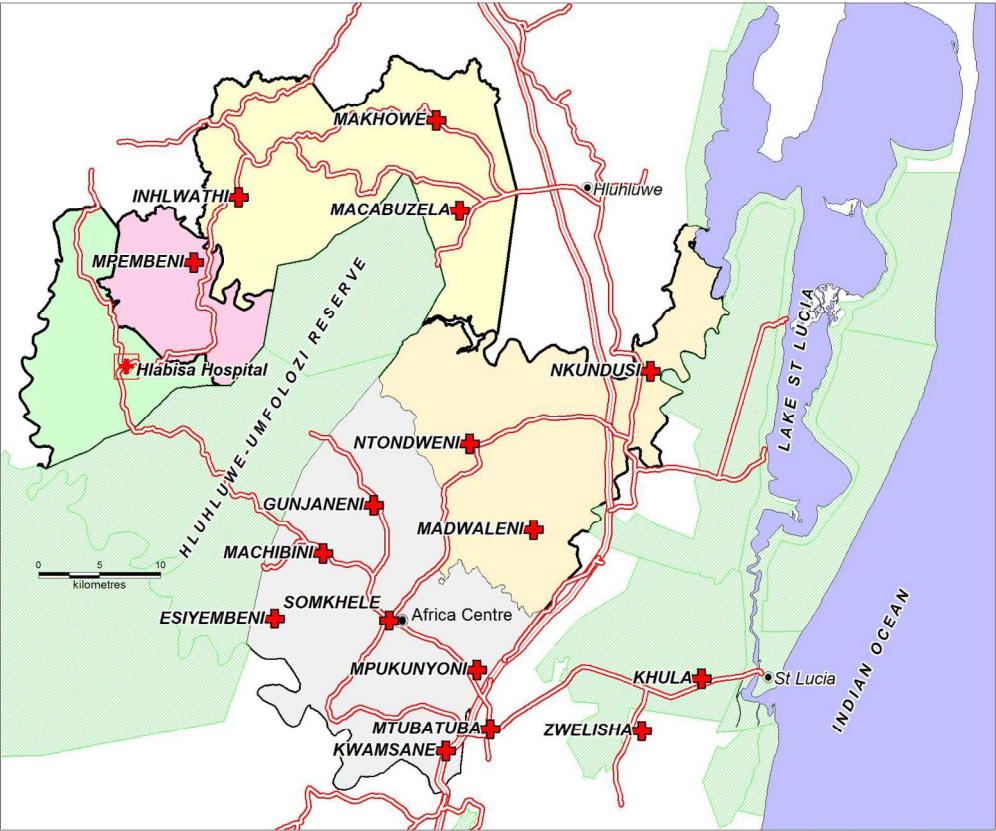


Figure 1: Africa Centre surveillance area showing the position of Hlabisa Hospital with an on-site clinic and 16 peripheral clinics in the Hlabisa sub-district, KwaZulu-Natal, South Africa. The Hlabisa sub-district encompasses the area to the bottom-right of the map which includes Mtubatuba and Zwenelisha clinics

185x154mm (300 x 300 DPI)

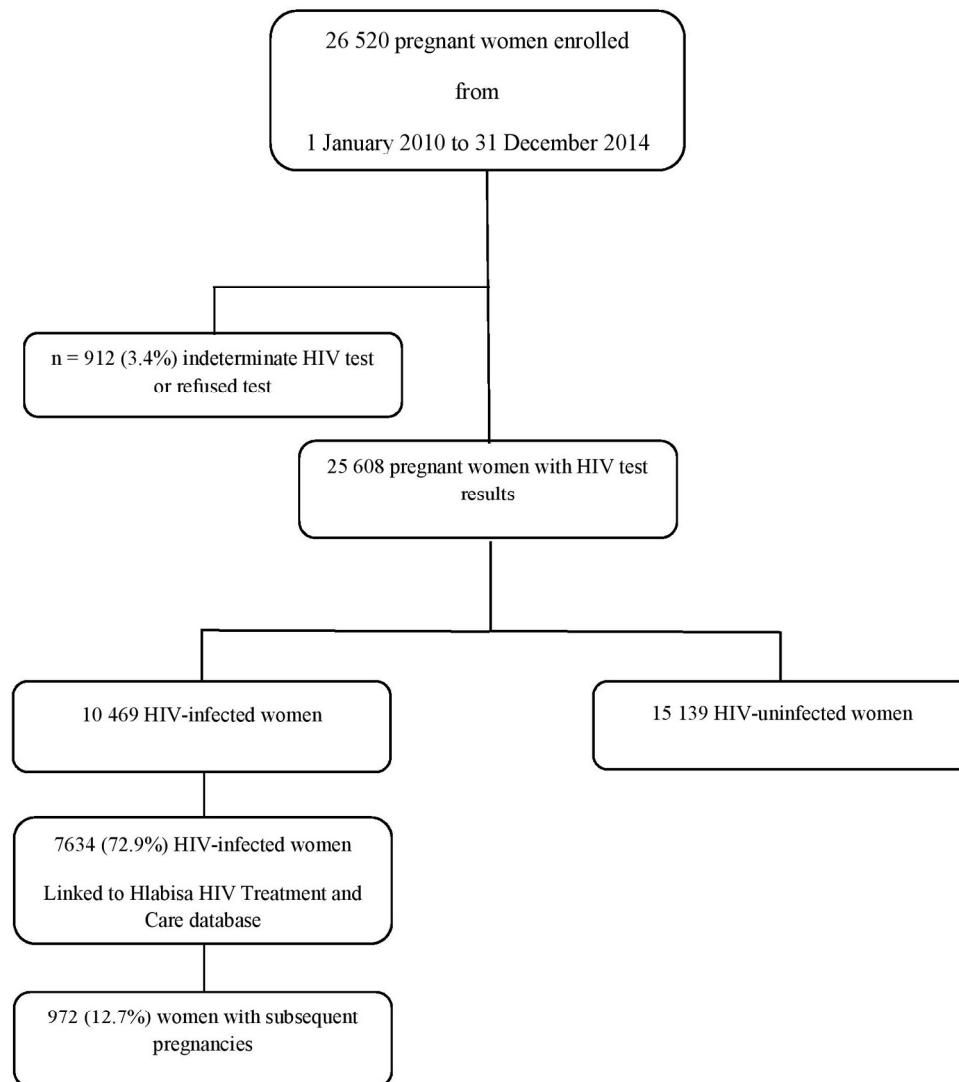


Figure 2: Flow diagram of the Hlabisa pregnancy cohort

165x187mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2, 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	2,4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 4,5,6
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,8,9
Bias	9	Describe any efforts to address potential sources of bias	9,10,13,14
Study size	10	Explain how the study size was arrived at	5, 10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A as we ran descriptive statistics only
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	N/A as we provide descriptive statistics only of the cohort.
		(b) Describe any methods used to examine subgroups and interactions	N/A

		(c) Explain how missing data were addressed	We report on missing data in covariates on page 14 (Table 3)
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	We report on the proportion of pregnant women lost to follow-up in the findings (page 13) and table 3 (page 14)
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, 9,10
		(b) Give reasons for non-participation at each stage	Figure 1 (separate from main text)
		(c) Consider use of a flow diagram	Figure 1 (separate)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	14
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	As we describe the cohort only, we did not provide person-time in this paper
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	13, 14
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Cohort description only provided in Table 3 (page 14)
		(b) Report category boundaries when continuous variables were categorized	14
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A

Discussion				
Key results	18	Summarise key results with reference to study objectives		10,11,12,13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results		18
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Cohort Profile: The Hlabisa pregnancy cohort, KwaZulu-Natal, South Africa

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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Public health, Epidemiology
Keywords:	pregnancy cohort, HIV & AIDS < INFECTIOUS DISEASES, antiretroviral therapy

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Cohort Profile: The Hlabisa pregnancy cohort, KwaZulu-Natal, South Africa

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Key words: pregnancy cohort, HIV, antiretroviral therapy

Word count: 3957

ABSTRACT

Purpose: The Hlabisa pregnancy cohort was established to evaluate the effectiveness of Prevention of Mother-to-Child Transmission (PMTCT) guideline revisions. The objectives of the Hlabisa pregnancy cohort are to: (i) provide cohort-level information on maternal health up to six weeks postpartum in a high Human Immunodeficiency Virus (HIV) prevalence setting; and to (ii) evaluate aspects of PMTCT care that have policy relevance.

Participants: The pregnancy cohort is located in primary health clinics in the Hlabisa sub-district of rural KwaZulu-Natal, South Africa. Baseline data collection between 2010 and 2014 has been completed, with the enrolment of 25 608 pregnancies; age ranged from 15-49 years. Pregnant women were assessed during routine antenatal visits: first visit, follow-up one week later, 32 weeks (HIV test), infant delivery and six weeks postpartum. Demographic, pregnancy, clinical, laboratory and HIV data were collected through Department of Health interviews, laboratory tests and routine data linkage. Treatment data for HIV-infected pregnant women were linked to the Africa Centre Hlabisa HIV Treatment and Care Programme for detailed antiretroviral therapy (ART) history and laboratory tests.

Findings to date: The proportion of women initiated on ART post-2013 were higher ($n=437$; 100%) than pre-2013 ($n=768$; 84.2%). The proportion of women in care at six weeks (73.8%) was also higher post-2013 relative to earlier years (58.5%). The majority of HIV-infected pregnant women were either on lifelong ART or ART prophylaxis; pre-2013 ~ 9.6% of women were not on any ART. Pregnancy viral load monitoring was inadequate.

Future plans: This cohort will be used to: (1) determine HIV acquisition risk during pregnancy and postpartum; (2) determine the effect of HIV and ART on birth outcomes; (3) examine the effect of pregnancy on virologic response to ART; and (4) characterize the effect of sequential pregnancies on access to clinical care, response to prolonged ART and birth outcomes.

Strengths and limitations of this study

- The key characteristic of the Hlabisa pregnancy longitudinal cohort is size and ability to model the impact of the HIV programme on the community through linkage of Africa Centre’s population level data with clinical, pregnancy and HIV data;
- Follow-up of HIV-infected mothers are crucial to monitor adherence to ART and disease progression; and
- Assessment of long-term maternal outcomes may be limited by high population mobility and use of routine health sector data.

INTRODUCTION

Prevention of mother-to-child transmission (PMTCT) of the Human Immunodeficiency Virus (HIV) using antiretroviral drugs can nearly eliminate vertical HIV transmission and increase maternal survival.[1] However, poor delivery of any of the steps in PMTCT results in cumulative losses of pregnant women, raising infant HIV transmission risk.[2] The PMTCT “cascade” highlights the optimum PMTCT sequence: HIV counselling and testing at the first antenatal visit; CD4⁺ measurement; antiretroviral therapy (ART) initiation and adherence; and early infant HIV testing,[2] or after cessation of breastfeeding and infant HIV test at 18 months.[3]

The Hlabisa HIV Treatment and Care programme (HHTCP), described previously,[4] was a partnership between the South African Department of Health (DoH) and the Wellcome Trust funded Africa Centre for Population Health (Africa Centre). In January 2010, the Africa Centre established a pregnancy cohort aligned with the HHTCP objectives to monitor PMTCT for feedback to funders. A further objective is to use this cohort to determine clinical markers related to pregnancy in this high HIV prevalence setting. The pregnancy cohort can be linked with the Africa Centre Demographic Information System (ACDIS), which has demographic and health data through population-based longitudinal surveillance of approximately 90 000 people in 12 000 households, including accurate longitudinal HIV incidence, HIV prevalence and ART coverage estimates for this sub-population since 2003.[5,6] Hence, demographic and health factors related to the PMTCT programme success can be monitored.

Cohort description

Setting

The predominantly rural Hlabisa sub-district of uMkhanyakude in northern KwaZulu-Natal, South Africa has a population of approximately 228 000.[5] There are 17 nurse-led primary health care (PHC) clinics with a primary level district hospital (Hlabisa Hospital), which handles most of the deliveries. Six DoH clinics and 40% of patients are located within ACDIS (Figure 1). Household surveillance began in January 2000. Routine household visits were conducted biannually, and since 2012 three-times a year, to collect information about births, deaths, and migrations. The sample of resident and non-resident females

aged 15 – 49 years in ACDIS from 2010 through 2014, were respectively: 65 454 (27.3%); 65 352 (27.5%); 65 889 (27.7%); 65 092 (27.8%); 62 705 (27.9%).

Ethics

Ethical approval from the University of KwaZulu-Natal Biomedical Research Ethics Committee was granted to allow linkage of routine patient data to ACDIS (E 134/06) and for retrospective analysis of routine data collected in Hlabisa and Mtubatuba local municipalities health centres (Ref BE066/07).

Due to the dynamic movement of patients within antenatal clinics with varying entry times, including delivery, reliable written informed consent for pregnancy data linkage with ACDIS was challenging. Additionally, ACDIS consent is at household level, with either the household head providing verbal consent for surveys to be conducted, or a proxy in the absence of the household head. We therefore requested a waiver of written informed consent for pregnancy and ACDIS data linkage from the University of KwaZulu-Natal Biomedical Research Ethics Committee (E134/06). Instead, women attending antenatal clinics gave verbal consent to link their details with ACDIS data.

Who is in the cohort?

From 1 January 2010 to December 2014, all pregnant women attending antenatal care (ANC) for the first time at PHC clinics in the sub-district entered the cohort automatically. Data was initially collected from all 17 PHC clinics in Hlabisa up to 2012; thereafter as funding was restricted, the data collection focal point became six PHC clinics within ACDIS and one clinic located just outside the surveillance due to the proximity to the national road.

The cohort has completed enrolment for 25 608 pregnancies recorded from 1 January 2010 until 31 December 2014 (Figure 2). A secure database system was developed to capture data on women from first antenatal visit through delivery up to 18-month infant follow-up.

Data from 7634 HIV-infected pregnant women has been linked with the Africa Centre HHTCP database to provide details on HIV treatment and monitoring, including postpartum follow-up.[4] All pregnant women were offered HIV counselling and testing at their first visit. Women who disclosed that they were

HIV-infected (i.e. known HIV status before pregnancy) were asked about prior PMTCT or ART and if they had started lifelong ART.

Pregnancies of HIV-infected women were categorized according to ART initiation timing: (1) Already on lifelong ART prior to first antenatal visit; (2) Started lifelong ART within six months of the first antenatal visit; and (3) Not on lifelong ART during pregnancy (as assessed at delivery). For those patients already on lifelong ART prior to the first antenatal visit, we report the ART regimen prescribed within six months of the first visit.

Clinical care and follow-up

Until 2013, pregnant women first testing HIV negative had repeat HIV testing recommended at or after 32 weeks gestation; the 2013 HIV guidelines recommend repeat HIV testing for -uninfected pregnant women three monthly throughout breastfeeding.[7] The 2010 and 2013 PMTCT guidelines are summarized in Table 1. Since 2015, South Africa has followed the World Health Organization (WHO) recommendation to initiate all pregnant HIV-infected women on lifelong ART, regardless of CD4⁺ count (Option B+).[8,9] Before 2010, the first line regimen recommended for patients with a CD4⁺ count ≤ 200 cells/mm³ or WHO stage 4 was Stavudine (d4T), Lamivudine (3TC), and either Efavirenz (EFV) or nevirapine (NVP).[10] The 2010 ART adult guidelines recommended that patients already on a d4T-based regimen continue on this treatment if well tolerated, with early switch to tenofovir (TDF) with any toxicity.[11] Tenofovir was rolled out according to a phased implementation plan. Pregnant patients were prioritized if they were newly initiating ART in April 2010. By April 2011, d4T to TDF switches were prioritized, hence there was a lag with d4T regimen changes for patients that initiated prior to April 2010 if side effects were not severe.(Naidu KK (HHTCP Lead, 2016))

The approximate proportion of patients on d4T regimens in the HHTCP were as follows: (1) by December 2012, approximately 20-30% of patients; (2) by December 2013, ~ 10-20%; and (3) by December 2014, ~5%.(Naidu KK (HHTCP Lead, 2016))

Table 1: South African Prevention of Mother-to-Child Transmission guidelines

Regimen	2010 Guidelines	2013 Guidelines
PMTCT prophylaxis (CD4 ⁺ > 350 and WHO stage 1/2)	Antenatal Zidovudine (AZT) from 14 weeks; Intrapartum single-dose Nevirapine (sdNVP), 3 hourly AZT; Postpartum single dose of TDF + Emtracitabine (FTC)	TDF, 3TC/FTC, EFV to be initiated as soon as pregnancy is diagnosed (if no active psychiatric illness or history of renal disease) to be continued through the postnatal period until one week after complete cessation of breastfeeding (WHO Option B)[8]
	<i>Infant regimen:</i> NVP at birth and then daily for six weeks, continued as long as any breastfeeding; if formula fed infant NVP should stop at six weeks	<i>Infant regimen:</i> NVP at birth and then daily for six weeks; if the mother on AZT regimen, the infant should receive NVP at birth, then daily for six weeks to be continued till one week after complete cessation of breastfeeding
Lifelong ART (CD4 ⁺ ≤ 350 or WHO stage 3/4)	TDF, 3TC/FTC, EFV	TDF, 3TC/FTC, EFV
	<i>Infant regimen:</i> NVP at birth and then daily for six weeks irrespective of feeding choice	<i>Infant regimen:</i> NVP at birth and then daily for six weeks

As per 2015 guidelines, pregnant women are asked to present for follow-up antenatally six weekly until delivery or more frequently for complicated pregnancies.[9] Women presenting in labour should be counselled and HIV tested during first stage of labour and offered routine PMTCT interventions. If not possible, counselling and testing should be offered postpartum. The mother should be counselled on feeding practices and the infant should be tested. Further, women should be commenced on lifelong ART before discharge and have creatinine and CD4⁺ count checked at the three to six day postpartum visit. Follow-up visits are aligned with infant immunization schedule at six, 10 and, 14 weeks.

What has been measured?

Data collection for the Hlabisa pregnancy cohort is paper-based with DoH staff collecting routine demographic, clinical and pregnancy data on women attending antenatal services (Table 2). The database was designed as an early identification tool for pregnant women requiring further care and to inform clinics of the appropriate actions at each step in the PMTCT cascade. Data flow was not unidirectional as Africa Centre provided action lists, data issues, and tracking reports to DoH staff weekly. Additionally, routine PMTCT statistics were reported to clinics at least quarterly when the HHTCP was operational.

Patient monitoring in the HHTCP, including PMTCT care, were as follows: (1) Africa Centre staff responsible for PMTCT data telephoned nurses at the antenatal and HIV clinics to flag abnormal maternal and infant results (HIV tests, CD4⁺ and viral loads), to determine if the appropriate treatment had been provided, and if patients were in care; (2) Patients with abnormal blood results were telephoned and asked to return to the clinic for care (Africa Centre staff did not provided blood results telephonically or disclose confidential information); (3) Patients eligible for, or on lifelong ART, who did not return for care were referred to the HHTCP tracking team; and (4) Clinicians in the HHTCP followed up patients on lifelong ART with virologic failure, including pregnant women (latest viral load results above 1000 copies/ml after at least 12 months on a standard first line regimen), offering genotypic resistance testing as part of HIV Treatment Failure Clinic model and The Southern African Treatment and Resistance Network (SATuRN), [12–14] changing treatment according to DoH guidelines. [7,11]

Table 2: Data collected for all pregnant women in the Hlabisa sub-district (2010-2014)

Data Fields	Variable list
Demographics	Name, national identity number, contact details, date of birth Visit date, Antenatal clinic name, other antenatal clinic in close proximity, TB
Clinical visit data	screening, parity, gestational age at first antenatal visit Maternal HIV status at visit; if HIV-infected, prior PMTCT exposure, ART
HIV and related measures	initiation and monitoring bloods including CD4 ⁺ cell count and HIV viral load, full blood count, liver function tests, renal function tests
Medication history	If HIV-infected, date of start of ART, type of treatment, adherence Mode of delivery, infant prophylaxis after delivery; if HIV-infected, maternal
Delivery data	antiretroviral treatment or prophylaxis taken at delivery Birth weight, birth head circumference, birth length, feeding choice at birth, DNA
Infant data	PCR result at six weeks of age

Data is electronically captured at the Africa Centre. Data is collected at the following times during routine visits: first antenatal visit, follow-up one week after the first visit, week 32 (repeat HIV testing), and infant delivery. The following routine data on HIV care is collected: 1) CD4⁺; 2) HIV staging; 3) clinical tuberculosis screening; and 4) ART prophylaxis or treatment initiation.

Postpartum, data is collected at the six week infant visit. Treatment data for HIV-infected pregnant women were linked to the HHTCP cohort, described previously,[4] to determine details of ART initiation timing, medication history, including ART adherence, baseline and follow-up CD4⁺ and viral loads. All test results are collated into a laboratory database and then imported into the HHTCP database, allowing monitoring of the clinical disease progression of all patients initiated on ART.[4]

All data, including monitoring laboratory tests for HIV-infected patients, were as per DoH antenatal and HIV guidelines. We report on the CD4⁺ count according to the 2010 and 2013 HIV guideline eligibility for lifelong ART initiation at 350 cells/mm³.^[3,7]

Data linkage

Pregnancy data were linked to HHTCP data using name, surnames, and identity numbers, or dates of birth when missing identity numbers. Additional information such as cellphone numbers and laboratory test dates were used to verify patient linkage. Trained data capturers linked pregnancy and HIV datasets at capture into the pregnancy database, and through provision of monthly lists generated by a data manager. Password protected data were known only to study investigators and the data team.

ACDIS Linkage

Individuals in ACDIS are assigned an alphanumeric 'External Identification Number (DSID)', which is linked to individual identifiers, including names and/or identity numbers. The 'External ID' is linked to an 'Internal ID' through a highly protected table, accessible only to the senior data manager. At data capture, an individual's 'Internal ID' replaces his 'External ID', anonymising all data. The "Internal ID" is added to the HHTCP and pregnancy databases for all ACDIS patients. This 'Internal ID' provides the link between the ACDIS, HHTCP and pregnancy databases, allowing de-identified data to be extracted from across databases. An 'Internal ID' cannot be used to identify individuals on ACDIS field questionnaires or lists.

FINDINGS TO DATE

The Hlabisa pregnancy cohort consists of women attending ANC for the first time since January 2010. At the time of data censoring (31 December 2014), the database included 26 520 pregnancies, of whom 25 608 women (96.5%) had HIV test results; 10 469 (40.8%) were HIV-infected, and 15 139 were HIV-uninfected (Figure 2).

There were 912 (3.4%) women with unknown HIV status excluded from this analysis (indeterminate, missing, or refused HIV test). Compared to included women, those excluded were more likely to attend

PHC clinics late in pregnancy at or after 30 weeks ($p < 0.0001$). Further, included women were slightly younger at first visit (24 years; interquartile range (IQR) = 20–29 years) relative to excluded women (26 years; IQR = 22–31 years) (data not shown).

HIV-uninfected women were younger (median age 22 years; IQR 19–26 years) than those HIV-infected (median age 27 years; IQR 23–31 years) and presented marginally later to PHC clinics for their first visit (median 28 weeks; IQR 20–38 weeks) versus 26 weeks in HIV-infected women (IQR 18–38 weeks). HIV-uninfected and -infected women had 7833 (51.7%) and 7287 (69.6%) live-born infants delivered at facilities in Hlabisa to date, respectively.

Clinical characteristics of HIV-infected pregnant women

Of the 10 469 HIV-infected pregnant women, the data of 7634 (72.9%) were linked with the HHTCP database,[4] to provide detailed information on pregnant women accessing HIV care. Of the 7634 included women, to date 972 (12.7%) had subsequent pregnancies recorded. The linkage with the remaining 27.1% of women was not possible as incomplete national identifying number data made probabilistic linkage between two databases unreliable.

Overall, 25.1% of women ($n = 1917$) were already on lifelong ART at their first ANC visit; 1349 women (17.7%) started lifelong ART within six months of the first visit of the current pregnancy.

Before 2013, most women who started on lifelong ART at their first antenatal visit received TDF-based regimens; women on lifelong ART before pregnancy were initiated either on a TDF-based or d4T-based regimen (Table 3). There were a further 2347 women (76.4%) who received AZT prophylaxis for PMTCT (Table 4). There were 9.6% of HIV-infected women ($n = 296$) who did not receive any ART during pregnancy; of these, 82 women (27.7%) had $CD4^+ \leq 350$ cells/mm³ and were eligible for treatment. There may have been several reasons why these women were not commenced on ART: movement between clinics and not accessing results; transfer out of the sub-district; or death (0.4%) due to disease progression.

Post-2013, most women established on ART before their first antenatal visit were on TDF-based regimens. Further, the proportion of women who initiated on d4T regimens (13.7%) before their first visit were less than in prior years (25.9%), reflecting the phased implementation plan for ART, with pregnant women prioritized to start triple ART.[15] Moreover, relative to earlier years, there was an increase in the proportion of women on established ART before their first visit, and initiated on ART within six months of the first visit. All women who were newly initiated on ART within six months of their first antenatal visit were on TDF-based regimens. Of the 1298 women who were not on lifelong ART, most were started on the fixed dose combination of TDF+FTC+EFV; and 14% received AZT prophylaxis (Table 4). The proportion of pregnant women who did not receive ART prophylaxis or were missing data on treatment decreased post-2013 versus earlier years.

The median maternal age of women not on ART or initiating ART within six months of the first visit was younger than women already on lifelong ART at pregnancy diagnosis (Table 3). Overall, the median gestational age at first visit was 23 weeks (IQR 17–37 weeks). Across the years and irrespective of ART initiation, a low proportion of women had a first antenatal visit before 12 weeks. Despite HIV guideline revisions emphasizing the importance of early attendance, over 15% of women attended their first antenatal visit in the third trimester at 25 to 36 weeks gestation. Unexpectedly, there were over 20% of women who were already on lifelong ART with a first antenatal visit after 37 weeks gestation, both pre- and post-2013; this may suggest women on lifelong ART had their pregnancy managed while attending the clinic for HIV treatment. However, this was not standard, and women on established lifelong ART were usually referred to the ANC for pregnancy care. While the proportion of women who newly initiated ART within six months of pregnancy after 37 weeks fell post-2013, more women not on lifelong ART attended their first antenatal visit after 37 weeks relative to earlier years. This may be aligned with guideline revisions to start pregnant HIV-infected women on ART as soon as possible, or reflect an improvement in data collection with less missing data on gestational age post-2013.

In general, women who commenced lifelong ART within six months of pregnancy were in better health at ART initiation with a higher median baseline CD4⁺ count, particularly after guidelines revisions in 2013 (Table 3). Viral load monitoring was inadequate during pregnancy, with only 24.2% (n = 739) of the

women on lifelong ART overall having a viral load test recorded six months before or after first antenatal visit. Of those with viral loads, 12.0% (n = 89) had virologic failure (i.e. viral load ≥ 1000 copies/ml) within six months of their first antenatal visit.

Overall, preliminary analysis suggests that follow-up in the HIV programme was over 80% in women on lifelong ART (n = 2768; 80%), at six weeks postpartum. Though the proportion of women not on lifelong ART who did not return for care declined in later years versus earlier years, and is likely to be an indicator of better adherence to triple ART prophylaxis post-2013, there were still over 15% of women not in care post-2013.

Table 3: Characteristics of 7634 HIV-infected pregnant women in the Hlabisa sub-district from 1 January 2010 to 31 December 2014 by ART status

	Up to 2012			2013 and later		
	On lifelong ART before the first antenatal visit (N=1295)	Started lifelong ART within six months of the first antenatal visit (N=912)	Not on lifelong ART (N=3070)	On lifelong ART before the first antenatal visit (N=622)	Started lifelong ART within six months first antenatal visit (N=437)	Not on lifelong ART (N=1298)
Median age, years	30 (26-34)	27 (23-31)	25 (21-29)	31 (27-35)	25 (22-30)	26 (22-31)
Gestational age at first visit, weeks						
< 12	68 (5.3)	55 (6.0)	177 (5.8)	54 (8.7)	43 (9.8)	59 (4.6)
12-24	363 (28.0)	473 (51.9)	1108 (36.1)	214 (34.4)	240 (54.9)	415 (32.0)
25-37	209 (16.1)	165 (18.1)	631 (20.6)	98 (15.8)	78 (17.9)	200 (15.4)
>37	319 (24.6)	57 (6.3)	436 (14.2)	174 (28.0)	10 (2.3)	416 (32.1)
Missing	336 (26.0)	162 (17.8)	718 (23.4)	82 (13.2)	66 (15.1)	208 (16.0)
Median baseline CD4 ⁺ count (IQR), cells/mm	166 (105-233)	235 (162-300)	431 (321-568)	187 (125-274)	440 (299-629)	492 (357-656)
Missing	60	37	1290	53	80	340
Baseline CD4 ⁺ count						
≤ 350 cells	1179 (91.0)	827 (90.7)	532 (17.3)	513 (82.5)	132 (30.2)	184 (14.2)
> 350 cells	56 (4.3)	48 (5.3)	1244 (40.5)	56 (9.0)	225 (51.5)	774 (59.6)
Missing	60 (4.6)	37 (4.1)	1290 (42.0)	53 (8.5)	80 (18.3)	340 (26.2)
On TB treatment at initiation						
Latest drug regimen						
TDF based	872 (67.3)	768 (84.2)	-	480 (77.2)	437 (100)	-
Stavudine based	335 (25.9)	16 (1.8)	-	85 (13.7)	-	-
AZT based	50 (3.9)	79 (8.7)	-	23 (3.7)	-	-
Unknown	38 (2.9)	49 (5.4)	-	34 (5.5)	-	-
Status						
Active	1076 (83.1)	724 (79.4)	1670 (58.5)	560 (90.0)	408 (93.4)	958 (73.8)
Deceased	12 (0.9)	12 (1.3)	10 (0.4)	1 (0.2)	-	4 (0.3)
LTFU	169 (13.1)	155 (17.0)	1172 (41.0)	54 (8.7)	29 (6.6)	240 (18.5)
Transfer out	38 (2.9)	21 (2.3)	4 (0.1)	7 (1.1)	-	-
Missing			214			96 (7.4)

Table 4: PMTCT regimens of pregnant women in the Hlabisa sub-district who were not on lifelong ART from 1 January 2010 to 31 December 2014

ART prophylaxis	Up to 2012 (N=3070)	2013 and later (N=1298)
*AZT	2347 (76.4)	186 (14.3)
TDF+FTC+EFV	-	967 (74.5)
None	296 (9.6)	95 (7.3)
Missing	427 (13.9)	50 (3.9)

* Inclusive of either sd-NVP, sd-FTC or both

Discussion

Data from the Hlabisa pregnancy cohort indicate the low proportion of women who attended their first ANC visit early in the first trimester. Early attendance is particularly important given the current PMTCT guidelines to provide triple ART to HIV-infected women from the first antenatal visit for maternal and infant health. The younger age of HIV-uninfected pregnant women compared with those HIV-infected in this cohort is similar to a Sowetan study.[16] A possible explanation may be that pregnancy rates decline with HIV disease progression.[17] However, given the expanded ART use in pregnant women which has been associated with higher pregnancy rates,[18] another likely scenario is that HIV-infected women may be accessing contraception and delaying pregnancy as they progress through the HIV treatment cascade as reported in another Africa Centre study using surveillance data.[19]

The improvement in PMTCT coverage and patient retention post-2013 supports the feasibility and acceptability of the 2013 PMTCT revisions. While Malawi reported an ART coverage increase of approximately 49%,[20] the ART coverage progression in our study was more conservative. These findings should be contextualized by successes within the HHTCP with high ART coverage; by July 2011 approximately 37% of all HIV-infected patients were on lifelong ART;[6] by 2012 over 50 000 patients were enrolled with 25 000 individuals initiated on lifelong ART.[6,12] Our study indicates that over 65% of women were established on ART before pregnancy and newly initiated on ART within six months of the pregnancy pre-2013. These findings reinforce South Africa's commitment to reduce vertical HIV transmission and improve maternal health and child survival consistent with international priorities.[21,22]

Prior studies before Option B implementation have reported approximately 25-50% of patients of women on ART at delivery lost to care within six months postpartum.[23–25] While the proportion of women on lifelong ART retained in care in this study was high, the proportion of women initiated on interrupted triple ART prophylaxis post-2013 was higher than the attrition rate in the DREAM cohort of pregnant women in Cameroon initiated on Option B (92.6% at six months),[26] our study reports follow-up status at six weeks postpartum and it possible that retention may deteriorate over time. In Malawi, approximately 17% of pregnant women initiated on Option B+ were lost to care by six months; most

women were lost to follow-up at the day of HIV testing and ART initiation.[27] These results emphasize the importance of treatment literacy, particularly as pregnant women start ART on higher CD4⁺ counts.

Our finding that 25% of women had viral load testing highlights a common problem in resource poor settings, [28] and encourages policy makers to seek strategies to overcome this challenge. While pregnancy viral load monitoring may have improved since the latest HIV guideline release,[9] monitoring of virologic failure is necessary to minimize PMTCT leakages that may prevent elimination of paediatric HIV. In population based survey including South African data, viral loads above 1000 copies/ml remained undiagnosed in pregnant and breastfeeding women.[29] Virologic failure in pregnant women on ART underscores the importance of understanding the different pathways of pregnancy effect, including physiologic, hormonal, drug pharmacokinetics and behavioural factors,[30] as the risk of drug resistance increases as more women on ART become pregnant. Moreover, it is important to engage mothers as partners in their health since it is clear that antiretroviral access does not translate to adherence where mothers are not empowered and engaged.[31–34] Caution needs to be exercised that budgets that spend enormous amounts on drugs do not get swamped resulting in diminished resources for the equally important psycho-social elements of management of HIV disease.

As South Africa has already expanded access to ART and implemented Option B+, it is likely that more women will conceive while on established ART. Strong routine information systems are required to ensure linkage to care, treatment and disease progression monitoring. In future studies, we will link data presented in this study to the Africa Centre surveillance system, providing us with an appropriate denominator for the pregnant population and minimizing the challenges posed by double counting in routine systems, necessary for utilizing routine data from PMTCT programmes for “HIV surveillance” as recommended by the WHO.[35] Additionally, as the pregnancy database was used for the active PMTCT care monitoring, we were able to inform DoH staff of the quality and effectiveness of their services and capacitate staff to improve their routine data. At a policy level, evidence-based decisions, including data from this study, can improve resource allocation and health care performance, particularly as South Africa expands access to Option B+. The centralized HIV and pregnancy database in this rural health setting, including routine data has allowed us to assess maternal HIV status and ART guidelines over

time, and is complementary to routine health information systems in South Africa, including the District Health Information System and the Three Interlinked Electronic Register (Tier.Net) to monitor ART provision. As Tier.Net evolves into an active monitoring system for HIV care, the lessons we have learned can advance understanding of data issues, patient challenges and possible solutions. Moreover, as the HHTCP includes directly imported laboratory data,[4] the potential for information bias is lessened as we verify routine data of pregnant women in HIV care.

This cohort is generally representative of the Hlabisa sub-district with data on pregnant women attending all clinics in the area up to 2012, and thereafter still included two of busiest antenatal clinics in the sub-district. Moreover, the HIV prevalence reported in this study is comparable to the 2012 antenatal HIV prevalence in the uMkhanyakhude district (35.2%; 95% CI: 29.4 –41.5).[36] We are currently conducting analyses in terms of birth outcomes. We also plan a series of analyses to: (1) determine HIV acquisition risk during pregnancy and postpartum; (2) determine the impact of HIV and ART on birth outcomes; (3) examine the effect of pregnancy on virologic response to ART; and (4) characterize the effect of sequential pregnancies on access to clinical care and response to prolonged ART and birth outcomes.

Strengths and limitations

The main strengths of this cohort include its size and the ability to model the impact of the HIV programme on the population due to detailed, longitudinal information available about the community and the linkage between clinical and population data. Accurate characterization of the cohort will provide an understanding of the determinants of pregnancy outcomes, and implications for service delivery in a typical HIV hyperendemic rural setting, which is likely to be generalizable to other resource-limited settings in South Africa.

One of the main challenges common to cohorts of HIV-infected pregnant women is the attrition rate. [24,37,38] High migration rates in the Hlabisa sub-district may limit postpartum assessment of long-term maternal outcomes in this cohort.[39] During the HHTCP, Africa Centre and DoH staff collaborated to follow-up patients lost to care. It is crucial to follow-up HIV-infected mothers in order to ensure effective

ART delivery for maternal and infant health; assess maternal adherence and disease progression; and support safe infant feeding. Using linked population datasets, the pregnancy outcomes of women not retained in care may be determined, and through sensitivity analysis, factors related to poor attrition will be characterised. The clinical pregnancy data will also be utilized to validate the general health surveys on pregnancy and contraception in the surveillance area, providing sensitivity and specificity estimates of reporting of pregnancy within the Africa Centre surveillance area. As routine data were collected, it is possible that pregnancy-related details may be incomplete resulting in information bias. Data discrepancies were queried with clinic and hospital staff prior to data entry. Pregnancy data collected by nurses and counsellors were also verified against antenatal and delivery registers at clinics and the hospital.

Collaboration

Requests for access to this pregnancy cohort should be directed to the Africa Centre’s Helpdesk (help@afRICACentre.ac.za) with “Research Dataset Request” in the subject line of the email. A data access agreement will be requested from the researcher and is submitted to the applicable data custodian. The data user will be notified once access approval is granted.

Footnotes

Contributors: TC contributed to the data collection and curation, performed the data analysis, and wrote the first draft. CT, FT, TB, and AC commented on the results and contributed to all subsequent drafts.

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Hlabisa sub-district located within and around the surveillance area. The opinions expressed herein are those of the authors and do not necessarily reflect the views of USAID, or the United States Government, or the DoH, KwaZulu-Natal.

Competing interest: None declared

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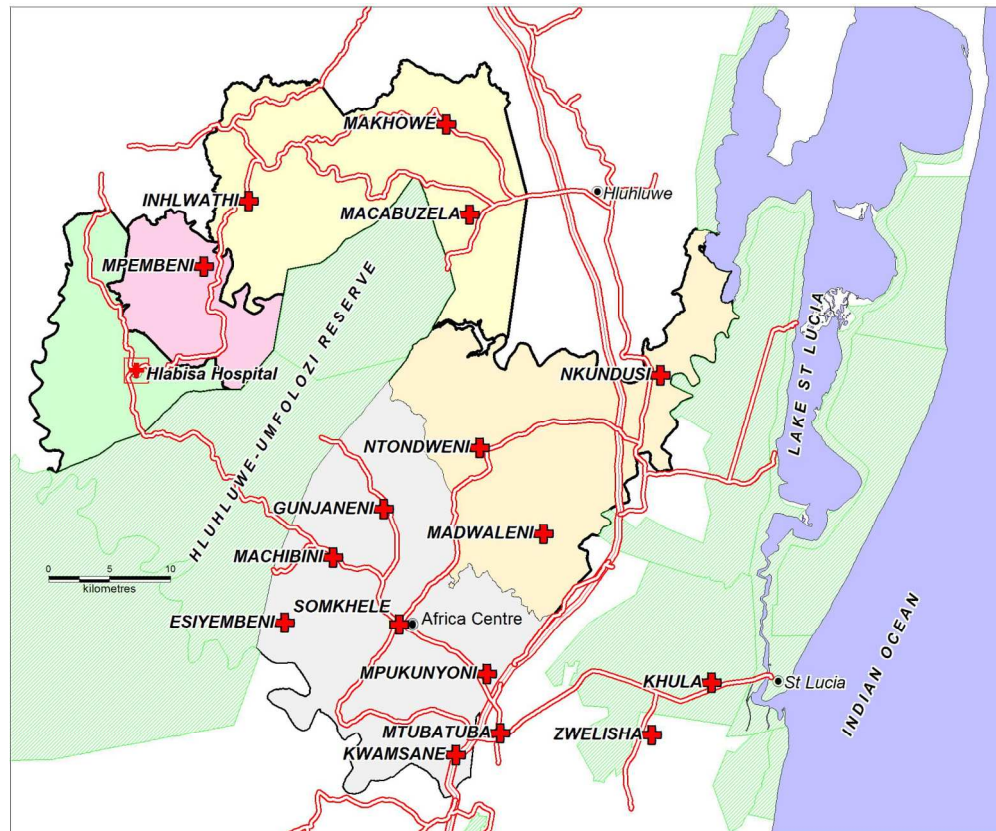


Figure 1: Africa Centre surveillance area showing the position of Hlabisa Hospital with an on-site clinic and 16 peripheral clinics in the Hlabisa sub-district, KwaZulu-Natal, South Africa. The Hlabisa sub-district encompasses the area to the bottom-right of the map which includes Mtubatuba and Zwelonisha clinics

185x154mm (300 x 300 DPI)

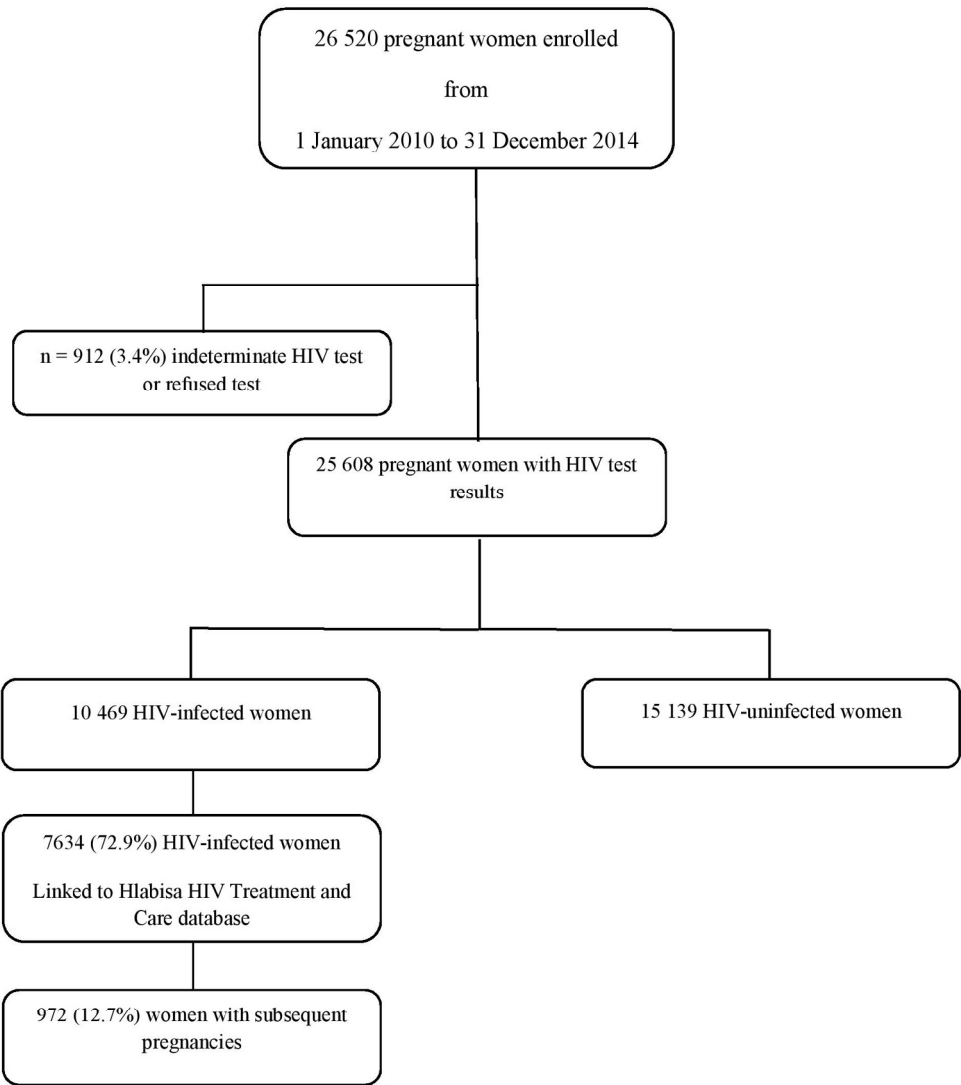


Figure 2: Flow diagram of the Hlabisa pregnancy cohort

165x187mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2, 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	2,4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2, 4,5,6
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8,9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,8,9
Bias	9	Describe any efforts to address potential sources of bias	9,10,13,14
Study size	10	Explain how the study size was arrived at	5, 10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A as we ran descriptive statistics only
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	N/A as we provide descriptive statistics only of the cohort.
		(b) Describe any methods used to examine subgroups and interactions	N/A

		(c) Explain how missing data were addressed	We report on missing data in covariates on page 14 (Table 3)
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	We report on the proportion of pregnant women lost to follow-up in the findings (page 13) and table 3 (page 14)
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5, 9,10
		(b) Give reasons for non-participation at each stage	Figure 1 (separate from main text)
		(c) Consider use of a flow diagram	Figure 1 (separate)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	14
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	As we describe the cohort only, we did not provide person-time in this paper
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	13, 14
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Cohort description only provided in Table 3 (page 14)
		(b) Report category boundaries when continuous variables were categorized	14
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A

Discussion				
Key results	18	Summarise key results with reference to study objectives		10,11,12,13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		18,19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results		18
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Cohort profile: the Hlabisa pregnancy cohort, KwaZulu-Natal, South Africa

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