The Impact of Revised PMTCT Guidelines: A View From a Public Sector ARV Clinic in Cape Town, South Africa

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Abstract

Background: In April 2010, revised Prevention of Mother-to-Child Transmission guidelines were implemented in South Africa, advising fast-tracked lifelong highly active antiretroviral therapy (HAART) initiation at a higher CD4 count (≤350 cells per microliter). This study describes the impact of these changes on the management of pregnant women who initiated HAART at Tygerberg Hospital, Cape Town.

Methods: We conducted a retrospective review of all women who initiated HAART in pregnancy at the Tygerberg Hospital between January 2008 and December 2010. Year cohorts were compared.

Results: Two hundred and fifty HIV-infected women were included in the study and stratified by HAART initiation year: 2008:N = 82, 2009:N = 71, 2010:N = 97. There were no differences between the groups in age or parity. Median booking CD4 count was 155 cells per microliter [interquartile range (IQR) 107–187], 157 cells per microliter (IQR 104–206) and 208 cells per microliter (IQR 138–270), respectively ($P < 0.001$). Median gestation at HAART initiation was 31 weeks (IQR 27–35), 30 weeks (IQR 26–34), and 25 weeks (IQR 21–31; $P < 0.001$). HIV transmission rates were 3/65 (4.6%), 4/57 (7.0%), and 0/90 (0.0%; $P = 0.021$). Women <8 weeks on HAART before delivery were more likely to transmit than women ≥8 weeks [odds ratio 9.69; 95% confidence interval 1.66 to 56.58; $P = 0.017$]. Ninety-four (37.6%) women were lost to follow-up, 18.4% within 28 days of delivery.

Conclusions: The positive impact of the new Prevention of Mother-to-Child Transmission program is evident. A longer duration of HAART before delivery was associated with less transmission. However, the lost to follow-up rates remain concerning. Further research is needed to better understand the reasons for nonadherence and mechanisms to improve support for these women.

Keywords: HIV; antenatal; antiretroviral therapy; mother-to-child transmission; South Africa

INTRODUCTION

With an estimated 5.6 million (5.4 million–5.8 million) HIV-infected people, South Africa continues to have the world's largest HIV epidemic.[1] In 2010, the overall HIV prevalence among pregnant women attending antenatal clinics in South Africa was 30.2%. It is estimated that in 2010, there were 260,280 women in need of Prevention of Mother-to-Child Transmission (PMTCT) services, and 54,000 new infections occurred among children under 14 years of age. In the Cape Town Metro, the HIV prevalence among pregnant women attending antenatal services was 20.2% [95% confidence interval (CI) 15.7 to 25.6].[2] This figure is comparable with the HIV prevalence among women delivering at Tygerberg Hospital, which was 19% in 2010 (Tygerberg Delivery PMTCT Register).

Since April 2003, several PMTCT interventions have been implemented at all public sector antenatal service facilities in the Western Cape, South Africa, ensuring all pregnant women with a low CD4 count eligible for lifelong highly active antiretroviral therapy (HAART). In the 2008 Western Cape PMTCT guidelines HAART was advised in cases with CD4 counts <250 cells per microliter or World Health Organization (WHO) Stage 4. Cases with higher CD4 counts were, according to National PMTCT guidelines, provided with PMTCT prophylaxis, consisting of Zidovudine monotherapy from 28 weeks gestation until delivery, adding single dose Nevirapine (NVP) at the time of delivery. HIV-exposed infants received single dose NVP and Zidovudine monotherapy for 7 or 28 days depending on the duration of maternal PMTCT prophylaxis or HAART.[3] In April 2010, revised PMTCT guidelines were implemented, proposing fast-tracked HAART initiation within 2 weeks of diagnosis for all women with CD4 counts ≤350 cells per microliter or WHO stage 3 or 4 disease. Dual therapy is advised at earlier gestation, from 14 weeks onwards. HIV-exposed infants receive a minimum of 6 weeks of NVP.[4]

In the developed world, HIV transmission rates can be minimized to 0%–2.9% when HAART is initiated early in pregnancy.[5,6] Limited cohort data are available that report the performance of the ART services in the public sector in South Africa. The national PMTCT evaluation survey reported an overall MTCT rate of 3.9% (1.9–5.8) in the Western Cape in 2010.[7] A recent study from a community-based clinic in Cape Town described a rate of 5.1% in women initiated on HAART before delivery.[8] This study describes the cohort of pregnant women who initiated HAART at Tygerberg Infectious Diseases (ID) Clinic and describes the annual MTCT outcomes to evaluate the impact of the new guidelines.

METHODS

The Tygerberg ID Clinic is based in Tygerberg Academic Hospital and provides tertiary level infectious diseases specialist care to half of the Western Cape Province and primary level ART care to the population living in Tygerberg subdistrict. Pregnant women requiring HAART are referred from the Tygerberg High Risk Antenatal Care Clinic (ANC) and several community-based ANC clinics in the subdistrict that have no ART facilities. We conducted a retrospective cohort study and reviewed all women who initiated HAART in pregnancy at Tygerberg ID Clinic between January 2008 and December 2010. Clinical data of all patients referred to Tygerberg are routinely collected on a prospectively maintained clinic database in the Tygerberg ID Clinic, supported by funding from the President's Emergency Plan for AIDS Relief. Indicators extracted for the study were baseline CD4 count, gestation at booking, first ART clinic visit, HAART initiation and delivery, duration of HAART before delivery and before lost to follow-up (LTFU) and concurrent comorbidities including WHO clinical HIV staging. Neonatal outcomes were verified with the Tygerberg Delivery PMTCT Register and the regional laboratory polymerase chain reaction (PCR) test database.

Data were captured on a customized MS Excel spread sheet and analyzed using Statistica version 10 (Statsoft, Tulsa, OK). Descriptive statistics were performed per year cohort, using medians and standard deviations to include their measure of spread. Mann–Whitney *U* tests were used to compare medians. Contingency tables were constructed and Fisher exact, and χ^2 tests were done to determine significant differences between proportions. Two-tailed $P < 0.05$ were considered statistically significant. Odds ratios (ORs) were calculated to determine the risk of vertical transmission. The study was approved by the University of Stellenbosch Health Research Ethics Committee (N11/04/132).

RESULTS

During the 3-year study period, 250 pregnant women initiated lifelong HAART at Tygerberg ID Clinic. The majority of this cohort (69%) presented with uncomplicated WHO stage I HIV infection. A total of 256 live births were reported, including 12 pairs of twins. The study group was stratified per initiation year: 2008 N = 82 patients, 2009 N = 71 patients, 2010 N = 97 patients. Patient demographics are presented in Table 1. Baseline characteristics of the 3 groups were comparable, with no statistical difference in median age, parity, and gestation at delivery. Besides an expedited HAART initiation after booking, no other significant differences were found comparing the 2009 cohort to the 2008 cohort. Median CD4 count at the first antenatal clinic visit was significantly different in 2010 compared with that in 2009 {208 cells per microliter [interquartile range (IQR) 138–270] vs. 157 cells per microliter [IQR 104–206], $P < 0.001$} and in association with the proportion of patients presenting with WHO stage 3 or 4 clinical disease was significantly different in 2010 as well (11.3% vs. 23.9%, $P = 0.030$). Also, median gestation at the first antenatal clinic visit [17 weeks (IQR 14–25) vs. 23 weeks (IQR 16–27), $P = 0.026$] and median gestation at HAART initiation [25 weeks (IQR 21–31) vs. 30 weeks (IQR 26–34), $P < 0.001$] were significantly different in 2010 compared with that in 2009. The percentage of women receiving >8 weeks of HAART before delivery increased significantly from 47.8% in 2009 to 73.7% in 2010 ($P < 0.001$).

Table 1 Demographics of Study Cohort

Maternal Characteristics Total initiations	N	Overall 250	2008 82	2009 71	*P**	2010 97	*P*†
Age (yrs)	Median (IQR)	28 (25–32)	28 (25–32)	27 (25–32)	0.356	29 (25–33)	0.186
Parity	Median (IQR)	1 (0–2)	1 (1–2)	1 (0–1)	0.089	1 (0–2)	0.105
Gestation at delivery (wks)	Median (IQR)	39 (37–40)	39 (38–40)	39 (37–40)	0.238	39 (37–40)	0.740
Baseline CD4 count (cells per microliter)	Median (IQR)	176 (112–218)	155 (107–187)	157 (104–206)	0.460	208 (138–270)	< 0.001
CD4 count <200 cells per microliter	N (%)	160 (64.0)	67 (81.7)	52 (73.2)	0.209	41 (42.3)	< 0.001
WHO stage 3 or 4	N (%)	44 (17.6)	16 (19.5)	17 (23.9)	0.506	11 (11.3)	0.030
Gestation at booking (wks)	Median (IQR)	20 (15–26)	21(15–26)	23 (16–27)	0.378	17 (14–25)	0.026
Gestation at HAART initiation (wks)	Median (IQR)	29 (24–34)	31 (27–35)	30 (26–34)	0.321	25 (21–31)	< 0.001
Duration HAART before delivery (wks)	Median (IQR)	9.0 (5.1–14.1)	8.0 (4.7–11.6)	7.4 (3.9–12.0)	0.995	13.1 (7.7–17.9)	< 0.001
HAART ≥8 wks before delivery	N (%)	143 (58.8)	41 (50.6)	32 (47.8)	0.729	70 (73.7)	< 0.001
Duration booking till initiation (wks)	Median (IQR)	6.7 (4.6–11.4)	8.9 (6.0–13.1)	7.0 (4.3–11.0)	0.023	5.1 (3.7–9.0)	0.173
Duration first visit till initiation (wks)	Median (IQR)	1.9 (1.0–3.0)	2.1 (1.0–3.1)	2.0 (0.8–3.8)	0.940	1.1 (1.0–2.0)	0.030

*Comparison between 2008 and 2009.
†Comparison between 2009 and 2010.

We compared the first antenatal clinic visit with first visit date at our facility and HAART initiation date. The median time between the first antenatal visit and the actual HAART initiation did not differ between 2009 and 2010 ($P = 0.173$). The median time between first clinic attendance at our facility and HAART initiation however was significantly different in 2010 compared with that in 2009 [1.1 weeks (IQR 1.0–2.0) vs. 2.0 weeks (IQR 0.8–3.8), $P = 0.030$].

Neonatal outcomes are presented in Table 2. Out of a total of 256 live births, 212 (82.8%) follow-up neonatal HIV PCR results were found. There was a significant improvement in the availability of PCR results from 57/75 (76.0%) in 2009 to 90/99 (90.9%) in 2010 ($P = 0.016$).

HIV transmission rates per year cohort were 4.6% (n = 3), 7.0% (n = 4), and 0.0% (n = 0), which were significantly lower in 2010 compared with 2009 ($P = 0.021$). The duration of HAART before delivery was known in 242 (96.8%) cases, of which 211 had a known PCR result (Table 3). Women on HAART for <8 weeks before delivery were more likely to transmit than women who were on HAART for >8 weeks [OR 9.69 (95% CI 1.66 to 56.58, $P = 0.017$)]. No significant association was found between maternal age, maternal parity, booking CD4 count, WHO staging, booking gestation or delivery gestation, and HIV transmission.

Table 2 Neonatal Outcomes by Year of HAART Initiation

Neonatal Outcomes		Overall	2008	2009	P*	2010	P†
Total initiations	N	250	82	71		97	
Delivery method unknown	N (%)	44 (17.6)	8 (9.8)	12 (16.9)	0.233	24 (25.3)	0.248
Vaginal delivery	N (%)	139 (55.6)	52 (63.4)	38 (53.5)	0.215	49 (51.6)	0.700
Cesarean section	N (%)	65 (26.0)	22 (26.8)	21 (29.6)	0.706	22 (23.2)	0.312
Intrauterine death	N	4	3	1		0	
Miscarriage	N	0	0	0		0	
Mother/fetus death	N	1	0	0		1	
Termination of pregnancy	N	1	0	0		1	
Early neonatal death	N	5	2	2		1	
Twins	N	12	3	5		4	
Total live births	N	256	82	75		99	
Positive PCR	N	7	3	4		0	
Negative PCR	N	205	62	53		90	
Unknown PCR	N	44	17	18		9	
Total known PCR results	N (%)	212 (82.8)	65 (79.3)	57 (76.0)	0.876	90 (90.9)	0.016
Pos babies/live babies tested	N (%)	7/212 (3.3)	3/65 (4.6)	4/57 (7.0)	0.704	0/90 (0.0)	0.021

*Comparison between 2008 and 2009.
†Comparison between 2009 and 2010.

Table 3 Neonatal HIV Status by Maternal Characteristics

Maternal Characteristics and Neonatal Outcomes		Positive PCR	Negative PCR	OR	95% CI	P
Total HAART duration <8 wks*	N	6	78	9.69	1.66–56.58	0.017
Total HAART duration ≥8 wks*	N	1	126			
Booking CD4 count <100 cells per microliter	N	2	38	1.76	0.34–9.22	0.619
Booking CD4 count ≥100 cells per microliter	N	5	167			
Delivery gestation <37 wks	N	2	32	2.16	0.42–11.20	0.312
Delivery gestation ≥37 wks	N	5	173			

*In one case the duration of HAART could not be ascertained.

Of 250 women initiated, 99 were LTFU of whom 46 (18.4%) within 28 days of delivery and 94 (37.6%) within a year of HAART initiation (Table 4). LTFU numbers per initiation year were 26 (31.7%), 39 (54.9%), and 34 (35.1%), with 46/99 (46.5%) of all LTFU occurring within the first 8 weeks after HAART initiation. LTFU rates were higher in 2009 compared with those in 2008 but improved again in 2010. LTFU women who were initiated on 36 weeks of gestation and later were significantly more likely to become LTFU within 4 weeks of initiation [7/27 (25.9%), vs. 23/223 (10.3%), $P = 0.028$].

Table 4 Mothers Lost to Follow-Up by Year of HAART Initiation

Lost to Follow-Up Total initiations	N	Overall 250	2008 82	2009 71	P*	2010 97	P†
LTFU <1 yr after initiation	N (%)	94 (37.6)	25 (30.5)	36 (50.7)	0.011	34 (35.1)	0.042
LTFU ≤ 8 wks after initiation	N (%)	46 (18.4)	13 (15.8)	20 (28.2)	0.065	13 (13.4)	0.017
LTFU within 28 d of delivery	N (%)	46 (18.4)	16 (19.5)	20 (28.2)	0.208	10 (10.3)	0.003

*Comparison between 2008 and 2009.
†Comparison between 2009 and 2010.

DISCUSSION

We describe the characteristics of a cohort of pregnant women who initiated lifelong HAART during pregnancy in an urban public ART clinic in the Western Cape, South Africa, over 3 consecutive years.

When comparing the 2010 cohort with the 2009 cohort, we found that the median CD4 count at the first antenatal visit increased significantly. We also found that the median gestation at first antenatal visit and median gestation at HAART initiation had decreased. Not surprisingly, there was also a significant increase in the duration of HAART until delivery. This is in line with the revision of the national PMTCT protocol in April 2010,[4] ensuring that more pregnant women are eligible for HAART referral by increasing the cutoff CD4 count from 250 to 350 cells per microliter and recommending fast-tracked HAART initiation within 2 weeks of diagnosis, from 14-week gestation. Compared with a study from Cape Town describing a cohort of HIV-infected pregnant women from 2005 with a median gestation at HAART initiation of 32 weeks,[9] our cohort showed an earlier gestation at initiation from 31 weeks in 2008 to 25 weeks in 2010. As a consequence of this, the percentage of women receiving HAART for >8 weeks before delivery increased from 48.1% in 2008 (comparable with the 2005 rate in that study) to 73.7% in 2010. Thus, the new guideline has impacted the earlier initiation of therapy at higher CD4 count, an important factor in reducing MTCT.

Gestation at the first antenatal visit, HAART initiation, and delivery has been verified with antenatal records where possible. However, only 63% of the study participants booked before 24 weeks of gestation, and no accurate estimation of gestation by ultrasound can be established thereafter. Although booking gestation improved significantly in 2010 with a median of 17 weeks, still 9.2% of women booked at or after 30 weeks of gestation. Overall booking gestation is still late in pregnancy, limiting the window of opportunity for successful HAART initiation before delivery. Women should be encouraged to book early in pregnancy. Further research is needed to identify factors causing delays in booking.

The changes in the guideline do not seem to have expedited the referral process for HAART initiation. Although improvement was found in the median time between booking and actual HAART initiation in 2009, no further improvement was found after the introduction of the guideline in 2010, with the median time still >5 weeks. It is therefore clear that fast-tracking HAART initiation itself was not responsible for the reduction in MTCT, but rather that earlier HAART initiation at a higher CD4 count was the main contributor to this outcome.

Greater improvements might still be achievable by eliminating delays in the referral process for HAART initiation. In 2010, only 4.1% of pregnant women were initiated within the stipulated time period of 2 weeks after HIV diagnosis as per PMTCT guideline. This clearly identifies the current bottleneck of the referral system and poor integration of services. The median time between the first visit and HAART initiation at our facility was significantly shorter in 2010 at a median of 1.1 weeks, indicating that most treatment delay occurs during referral to our facility. Generally, delay is caused by awaiting laboratory results. Whether on-site rapid CD4 count measurement could shorten referral delay for pregnant women should be investigated, as this would minimize the time to establish HAART eligibility. Baseline blood could be drawn in the ANC facility upon referral, enabling ART clinicians with access to regional laboratory results to initiate HAART at the first visit if desired. Referral delay from the ANC facility to the ART facility might be caused by limited booking capacity for new referrals at the ART facility and requires investigation. Expansion of ART sites in the community with fast-track appointment slots for pregnant women is recommended. Integration of services with ANC health workers initiating and monitoring HAART is proposed, as this would eliminate the referral process entirely. Health policy changes toward universal HAART initiation for all HIV-positive pregnant women regardless of CD4 count would both reduce MTCT and simplify the initiation process.

The HIV transmission rate has decreased significantly with no transmission detected in 2010, compared with 7.0% in 2009. In 2010, the vertical HIV transmission rate at Tygerberg ID Clinic was comparable with the rates achieved in developed countries, which is an important milestone. Further studies are needed to show the impact on maternal health of starting therapy at higher CD4 counts. Our study confirmed that a longer duration of HAART in pregnancy was associated with decreased HIV transmission. No significant association was found between maternal age, maternal parity, booking CD4 count, booking gestation or delivery gestation, and HIV transmission. These findings are in agreement with previous reported data from a similar cohort in Cape Town.[8]

The availability of neonatal PCR results had significantly improved in 2010, with only 9.1% of PCR results unknown compared to 24% in 2009. Several factors contribute to the unavailability of neonatal PCR results, such as early neonatal death, migration, LTFU, errors in personal detail registration at the National Health Laboratory Service or Community Health Clinic, and lack of feedback systems between ART site and ANC and baby Community Health Clinics. Due to the retrospective nature of the study, information and selection bias may have occurred. As a result of the high number of LTFU after delivery, a number of baby birth dates and names could not be verified. This contributed to 17% of PCR results being unknown, possibly leading to the underestimation of transmission rates.

LTFU rates were unacceptably high at 37.6% within 1 year of initiation, with 18.4% of all LTFU occurring within 28 days of delivery date, which is generally within 8 weeks of initiation. Women initiating HAART in pregnancy are significantly more likely to become LTFU than are nonpregnant women initiating HAART.[10,11] Interestingly, those women who were more established on therapy had a lower risk of LTFU. Several reasons could contribute to the poor retention in care around delivery, such as poor maternal health, fast-tracked initiation with too little time to come to terms with recent HIV diagnosis, inadequate support with no regular contact with health care services related to the pregnancy, poor socioeconomic circumstances undermining transport and childcare availability, relocation to family homesteads and multiple appointments at postnatal and baby clinics at different locations. Further research is needed to better understand how retention in care after delivery can be improved to optimize the healthcare status of these vulnerable women and neonates. A possible intervention could be the provision of a >1 month prescription at the last predelivery visit to bridge the stressful time around delivery and the early postnatal period.

The LTFU date was recorded as the date of the last clinic or pharmacy attendance without recorded transfer out procedures. We may have underestimated the time to actual nonadherence, as patients might have adhered until the very end of their provided medication, which is generally 28 days. It is also possible that women have self-referred to alternative ART sites to obtain further medication, without requesting clinical notes. Likewise, it is uncertain if women who have been transferred to other clinics did in fact end up attending these facilities, as no feedback system is in place between ART sites. It is however reasonable to assume that most women who have not returned for planned follow-up appointments have at least experienced some period of treatment interruption, as only the exact amount of needed medication till the next follow-up date is dispensed and ART is not readily available in local primary clinics or other ART sites without referral letters. Therefore, the magnitude of reported LTFU remains of great concern, especially as treatment interruption during breastfeeding might increase the transmission risk. Emphasis on retention in care should be promoted by developing efficient referral feedback systems between community ANC and baby clinics and strengthening patient tracing capacity.

The Tygerberg ID clinic functions predominantly as a community-based primary level ART care facility for those women in need of HAART who live in the local catchment area. However, as central referral hospital, the clinic also manages more complicated patients who are referred

from other antenatal, ART or specialist clinics with specific comorbidity. The impact of these referred patients, together with the greater infrastructure at the Tygerberg ID clinic, interact in a complex way and limit the extrapolation of the data to other community-based ART clinics in South Africa.

CONCLUSIONS

Since the institution of the 2010 National PMTCT guideline, women initiated HAART earlier in pregnancy, and less MTCT of HIV transmission was evident. Longer duration of HAART before delivery was associated with a reduced risk of HIV transmission.

However, women are still initiating therapy relatively late in pregnancy and retention in care remains poor with unacceptable LTFU rates. With earlier access to PMTCT for pregnant women, the focus should now shift toward educating women of the benefits of early booking to effect immediate referral to ART facilities after HIV diagnosis and ensuring women remain in care in the postnatal period.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Sr Anneke Theron for collecting obstetric data, Justin Harvey for statistical support, Kathryn Stinson for her valuable comments on the manuscript, and the dedicated staff of the Tygerberg Infectious Diseases Clinic.

SPONSORSHIP

M. V. S., M. D. Z., and M. L. G. are funded by the Anova Health Institute's Share Care program through the US President's Emergency Plan for AIDS Relief (PEPFAR) grant and the US Agency for International Development (USAID) under Cooperative Agreement no. 674-A-00-08-00,009-00. M. I. A. is funded by Wellcome Trust grant (reference no. 087859).

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