RESEARCH ARTICLE

Maternal outcomes following introduction of antiretroviral therapy in the public sector:

A prospective study at a tertiary hospital in the Eastern Cape

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Background. Antiretroviral therapy (ART) has been available in the public sector since 2004, but limited published data exist on maternal outcomes in South Africa following its introduction.

Objectives. A prospective study of maternal outcomes after the introduction of ART at Frere Hospital, East London, E Cape.

Methods. Pregnant women with indications for lifelong ART were commenced on treatment, and followed up until 6 weeks after delivery. Baseline demographic details were collected, including details on the gestation and mode of delivery. The mothers and their infants were then referred to local ART centres for continued care. Maternal outcomes measured were maternal death, and predefined maternal morbidity. Results were analysed using Epi-info software version 3.3.2 (2005).

Results. Data on 385 women are presented. The women initiated ART at a median age of 28 years. Median gestation at commencement of ART was 30 weeks. The median CD4 count and HIV-1 RNA viral load (VL) were 173 cells/µl and 4.56 $\log_{10}$ copies/ml, respectively. Fifty-five (14.3%) and 19 women (4.9%) had World Health Organization (WHO) stage 3 and stage 4 disease, respectively. Twenty-five (6.5%) were concurrently on treatment for tuberculosis (TB) while 10% had other co-infections – meningitis, hepatitis, pneumonia and urinary tract infections. Immune reconstitution inflammatory syndrome (IRIS) occurred in 7.0% of cases, and pre-eclampsia developed in 7.5%. Median gestation at delivery was 39 weeks. Seven maternal deaths (1.8%) occurred in this cohort. All 7 women died in the postpartum period. Five women died within 5 weeks of commencing ART. Two women died of *Pneumocystis jirovecii* pneumonia (PCP) and another 2 died from liver failure – 1 death was presumed to be from lactic acidosis related to stavudine (d4T) toxicity. The 3 remaining deaths were due to PCP IRIS, meningitis and TB, respectively. The strongest predictor of maternal death was WHO stage 4 disease (p=0.0006). Maternal plasma VL >5.00 $\log_{10}$ copies/ml, pre-eclampsia, IRIS, concurrent ART and tuberculosis treatment, and CD4 count <100 cells/µl were not significantly predictive of maternal death on multivariate analysis.

Conclusion. Despite the availability of ART in the public sector, maternal mortality remains a concern. Reasons include late entry of pregnant women into care, as well as suboptimal management of women initiated on ART who develop opportunistic infections. There is an urgent need to develop national ART guidelines specifically for pregnant women.

Antiretroviral therapy (ART) has been available in the public sector since 2004, but limited data exist on maternal outcomes following its introduction. This may be because ART services for pregnant women and antenatal care services function separately and independently of each other, making longitudinal studies on pregnant women on ART difficult to perform at a practical level. Decisions guiding management of pregnant women requiring lifelong ART are drawn from the national adult ART guidelines[1] or the prevention of mother-to-child transmission (PMTCT) guidelines.[2] No ART guidelines specifically for pregnant women have been developed nationally.

HIV-related mortality and morbidity have declined internationally as a result of the wider availability and use of ART.[3] In South Africa, however, an estimated 346 000 people still die from the disease every year before entering ART services. A Medical Research Council of South Africa/Actuarial Society of South Africa (MRC/ASSA) report stated that only 30% of the 711 000 South Africans needing ART were receiving treatment in 2006.[4]

Non-pregnancy-related infections (NPRIs) were the leading cause of maternal deaths in South Africa between 2002 and 2004, accounting for 37.8% of all maternal deaths according to the third Saving Mothers

Report.[5] The women in this report died predominantly from AIDS (20%), pneumonia (9.6%), tuberculosis (TB) (3.2%) and meningitis (2.4%). TB, however, is reportedly the commonest cause of death in South Africa, and has been since 1997.[6] The small proportion of deaths from TB in this report warrants scrutiny. Analysis of the data identifies a significant number of deaths (59%) due to NPRIs in women of unknown HIV status. In addition, many women with an HIV diagnosis at death had concomitant TB infection (45.1%). From the authors' own analysis, the HIV infection rate among maternal deaths has consistently been above 70% since 2000. Taking HIV prevalence estimates into consideration, maternal deaths due to HIV-related infections possibly accounted for 30% or more of all maternal deaths in this report. The proportion of TB-related deaths with HIV co-infection may have been underestimated by the assessors. HIV-associated TB emerged as the leading cause of maternal death just over a decade ago.[7]

A recent study examined the effects of integrating ART access within an antenatal care setting, with considerable success in time-to-treatment initiation and reduced infant HIV-1 transmission.[8] Our centre has similarly combined ART provision and antenatal care, to enable accelerated ART access for pregnant women who need it. Against this background we sought to determine maternal outcomes in HIV-1-infected pregnant women who had started lifelong ART.

Setting

Frere Maternity Hospital is a poorly staffed tertiary hospital that accepts referrals from a large geographical area in the Eastern Cape. HIV prevalence in this province is estimated at 29% among pregnant women.[9] The uptake of HIV testing by pregnant women at this hospital is currently 81%.

Just over 7 000 babies are born annually at this institution. The maternal mortality ratio (MMR) for the period 2004 - 2007 was 286/100 000 deliveries, nearly twice the national MMR of 150/100 000.[5] HIV-related infections, primarily TB, were responsible for 43% of all maternal deaths during this period (unpublished data).

Methods

ART centres and antenatal clinics in the local area referred pregnant women with indications for lifelong ART to our centre. The women were commenced on ART after a preparation period of 2 weeks. The preparation process was patient-centred and managed by mentor mothers from the Mothers-to-Mothers (M2M) programme. The success of this initiative has been reported previously.[10] Women initiated on ART were followed up antenatally, through delivery, until 6 weeks postpartum. They were then referred down to ART centres for continued care.

Requirements for lifelong ART at our centre included a CD4 count below 250 cells/µl or World Health Organization (WHO) stage 4 disease regardless of gestational age. In a small number of very selected cases where a woman's CD4 count was between 250 and 350 cells/µl, she was commenced on ART if she expressed a willingness to take ART lifelong *and* one or more of the following applied: WHO stage 3 disease, plasma HIV-1 RNA viral load (VL) more than 100 000 copies/ml, or she planned to exclusively breastfeed her infant. This was at a time when single-dose nevirapine (sd-NVP) was the only intervention available as prophylaxis against mother-to-child transmission (MTCT) at our institution. Authority for zidovudine (AZT) use as prophylaxis against MTCT was obtained from our HIV directorate in January 2007. Since then only women with CD4 counts below 250 cells/µl or WHO stage 4 disease have been eligible for access to ART. Women without indications for lifelong ART were offered AZT monotherapy from 28 weeks' gestation until delivery, with sd-NVP at the onset of labour.

The drugs most commonly prescribed were stavudine (d4T), lamivudine (3TC) and efavirenz (EFV). We were unable to use the recommended second-line agents, namely AZT and lopinavir/ritonavir (LPV/r), as primary treatment for pregnant women requiring lifelong ART. AZT use was authorised only when toxicity to d4T occurred, and LPV/r use was restricted to the first trimester, as a substitute for EFV in women with CD4 counts >250 cells/µl. Since January 2007 all pregnant women initiating ART were provided with 30 mg d4T, regardless of weight.[11] Women who were on 40 mg d4T were switched to 30 mg d4T after delivery.

EFV-based ART was provided only once the following requirements were met – the pregnancy had progressed beyond 14 weeks' gestation; a detailed ultrasound scan of the fetal anatomy was performed before initiating treatment, usually at 18 - 23 weeks' gestation but earlier where necessary; the woman gave written undertaking to use contraception postpartum; and major psychiatric illness in the woman was excluded. Women in whom EFV-based ART was commenced between 14 and 18 weeks had a repeat ultrasound scan done at 20 weeks.

The women were entered into a local Efavirenz in Pregnancy Registry to enable evaluation of infant outcomes in this cohort. Women with CD4 counts <200 cells/µl were provided with co-trimoxazole (CTX) prophylaxis.

Baseline demographic details were collected, including age, parity, gestation at commencement of ART, CD4 count, plasma VL, WHO stage, and concurrent medical/obstetric disorders. Once enrolled, the women were followed up initially every 2 weeks for a month, then 4-weekly until 36 weeks, followed by 2-weekly visits until delivery.

Adherence support was provided at each visit. Adherence was assessed by the woman honouring return dates given to her, direct enquiry regarding missed doses, recording pill counts at each visit, and retrospective review of her prescription chart at 6 weeks postpartum. Calculated adherence was stratified into optimal adherence (>95% of all medication taken); suboptimal adherence (80 - 94% of all medication taken); and poor adherence (<80% of all medication taken).

Details of gestation and mode of delivery were obtained. Preterm birth in this cohort was defined as birth before 34 weeks. At delivery, maternal plasma VL assays were done as an adjunct to evaluate response to treatment as well as to determine any association between VL and subsequent infant HIV-1 transmission. Caesarean section was reserved for obstetric indications. Universal intrapartum precautions were followed to limit perinatal HIV-1 transmission.

The mothers and infants were examined before discharge from hospital, and seen again at 2 weeks and 6 weeks after delivery. Infants were tested for HIV-1 at the 6-week visit using the DNA polymerase chain reaction (PCR). The mothers were referred to local ART centres for continued care.

The primary outcome measured was maternal death; secondary outcome measures were any of the following: pre-eclampsia, preterm birth, opportunistic and non-opportunistic infections, maternal morbidity following delivery, discontinuation of ART, immune reconstitution inflammatory syndrome (IRIS), and symptomatic hyperlactataemia.

Data were analysed using Epi-info software version 3.2.2 (Centers for Disease Control, Atlanta, Georgia, 2005). Continuous data are presented as medians with interquartile ranges (IQRs). Dichotomous data are presented as proportions with 95% confidence intervals (CIs). The probability of maternal survival censored at 6 weeks postpartum was determined using Kaplan-Meier curves, adjusted for variables found to be statistically significant at multivariate analysis. Multivariate logistic regression was employed for analysis of variables found to be statistically significant by univariate analysis. The risk factors tested as predictors for maternal death included CD4 count, pre-ART plasma VL, WHO stage, IRIS, TB and pre-eclampsia.

Approval for the study was obtained from the local research and ethics committee.

Results

Between January 2006 and January 2008, 401 women were commenced on lifelong ART. Sixteen women (4.0%) were lost to follow-up. Data on 385 women are presented.

Baseline demographic characteristics of the women are shown in Table I. All were ART-naïve. Their median age was 28 years, and median gestation when ART commenced was 30 weeks. One hundred and forty-two women (36.9%) were primigravidas. The median CD4 count and plasma VL were 173 cells/µl and 4.56 $\log_{10}$ copies/ml, respectively. Seventy-eight women (20.3%) had CD4 counts <100 cells/µl, and 109 of the 360 women for whom data on VL were available (30%) had plasma VLs above 100 000 copies/ml. Fifty-five women (14.2%) had WHO stage 3 disease and 19 (4.9%) had stage 4 disease. Twenty-five women (6.5%) were on treatment for TB at the time of commencing ART. Fourteen women (3.6%) were on treatment for serious opportunistic infections, which included cryptococcal meningitis, *Pneumocystis jirovecii* pneumonia (PCP) and hepatitis. Another 4.7% of women had pre-existing medical disorders, ranging from asthma to epilepsy.

EFV-based ART was commenced in 96.4% of the women, and 4.2% received NVP-based ART. In 2 cases NVP was switched to EFV following the initiation of TB treatment, and d4T was substituted for AZT in 1 case following diagnosis of hepatitis. Only 10 women (2.6%) were commenced on AZT-based ART *de novo*.

IRIS occurred in 27 out of 385 women (7.0%). The diagnosis of IRIS was made on the basis of the definition by Shelburne *et al*.[12] In brief, an IRIS event was identified as either a first presentation of a new condition compatible with an inflammatory response following the initiation of ART, or a paradoxical worsening of a known opportunistic infection in a woman following her introduction to ART. The condition had to be accompanied by a rising CD4 count and/or a decline in VL. Agreement by two investigators was a prerequisite for IRIS diagnosis.

The most frequent IRIS observed was TB IRIS (44.4%), followed by varicella zoster IRIS (14.8%) and herpes simplex IRIS (11.1%). The prevalence of IRIS was 17.9% in women with CD4 counts <100 cells/µl and 30% in women who commenced ART 2 weeks after initiation of TB treatment, compared with 3.7% in the remaining cases. IRIS developed a mean of 6 weeks after ART initiation, the period ranging from 1 week to 10 weeks. Although most cases were mild, one of the maternal deaths was attributed to PCP IRIS. After an initial recovery from PCP during pregnancy, the woman's condition deteriorated during the postpartum period. The diagnosis was not considered, and ART was discontinued. In all other cases of IRIS diagnosis, ART was not interrupted and resolution was the outcome.

Pre-eclampsia developed in 29 out of 385 women (7.5%, 95% CI 5.2 - 10.8), complicated by eclampsia and HELLP syndrome in 10.3% and 3.4% of cases, respectively. During the course of pregnancy 4.4% of women developed symptomatic urinary tract infections, and another 1.8% developed bacterial pneumonia unrelated to PCP or TB. Twenty-three women (6.0%) gave birth preterm.

Median gestation at delivery was 39 weeks. Maternal plasma VL results were available for 244 out of 385 women (63.3%) at the time of delivery. Of this group, 66% of women had undetectable plasma VL (<25 copies/ml).

Four women (1.0%) had miscarriages shortly after ART initiation. Of the remaining 381 women, 30 (7.8%) had elective caesarean sections and 275 (72.2%) normal vaginal deliveries. Fetal distress and poor progress in labour accounted for 80% of emergency caesarean sections, done on 69 women (18.1%). Six women (1.6%) had assisted vaginal deliveries, and 1 had a laparotomy for advanced extra-uterine pregnancy.

Seven maternal deaths (1.8%, 95% CI 0.8 - 3.9) occurred in

Table I. Baseline characteristics of women commencing ART (*N*=385)

Median age (yrs) (IQR)	28 (25 - 32)
Primigravidas (*N* (%))	142/384 (36.9)
Median gestation at ART initiation (wks) (IQR)	30 (25 - 33)
ART commenced at >34 wks gestation (*N* (%))	65/385 (16.9)
Median CD4 count (cells/µl) (IQR)	173 (114 - 223)
CD4 <100 cells/µl (*N* (%))	78/385 (20.3)
CD4 101 - 250 cells/µl (*N* (%))	256/385 (66.5)
CD4 251 - 350 cells/µl (*N* (%))	51/385 (13.2)
Median HIV-1 RNA viral load (log_{10} copies/ml) (IQR)	4.56 (4.00 - 5.10)
HIV-1 RNA viral load >100 000 copies/ml (*N* (%))	109/360 (30.3)
WHO stage 3 disease (*N* (%))	55/385 (14.3)
WHO stage 4 disease (*N* (%))	19/385 (4.9)
Concurrent TB treatment and ART (*N* (%))	25/385 (6.5)
AZT ART (*N* (%))	11/385 (2.9)
d4T ART (*N* (%))	375/385 (97.4)
EFV ART (*N* (%))	371/385 (96.4)
NVP ART (*N* (%))	16/385 (4.2)
Median gestation at delivery (wks) (IQR)	39 (37 - 40)
Elective caesarean section (*N* (%))	30/381 (7.9)
Emergency caesarean section (*N* (%))	69/381 (18.1)
Normal vaginal delivery (*N* (%))	275/381 (72.2)
Assisted vaginal delivery (*N* (%))	6/381 (1.6)
Median duration of ART (wks) (IQR)	15 (11 - 19)

IQR = interquartile range; WHO = World Health Organization; TB = tuberculosis; AZT = zidovudine; d4T = stavudine; EFV = efavirenz; NVP = nevirapine.

this cohort (Table II). All 7 women died in the postpartum period. Five women died within 5 weeks of commencing ART, of whom 2, who were severely ill, died within 10 days of initiating ART.

Two women died of PCP, and 2 of liver failure – 1 maternal death was presumed to be a result of complications from lactic acidosis following d4T toxicity. This patient had had normal renal and liver function before ART initiation, and presented with lactic acidosis 14 weeks into treatment with EFV-based ART. Her serum lactate level was 9.1 mmol/l, pH 7.246, and standard bicarbonate 11.0 mmol/l. Blood and urine cultures were negative. Despite ART discontinuation, early intensive care unit (ICU) admission and respiratory support, she died of liver failure 3 days after delivery.

The 3 remaining deaths were due to PCP IRIS, meningitis and TB, respectively. ART was discontinued by the attending clinicians in 2 women who died from liver failure, and another 2 women who died following PCP IRIS and meningitis, respectively. The woman with pneumococcal meningitis initially improved on antibiotic treatment antenatally, but deteriorated after delivery and died 6 weeks after initiation of ART. She was one of 2 patients excluded as an IRIS event owing to discordance in the investigators' analysis. The woman who died of TB had been without TB treatment for 4 weeks following her discharge from hospital.

Although postmortem examinations were not done on any of the women who died, sufficient reasonable quality information was obtained from radiographs, blood results and cerebrospinal fluid findings to suggest the most likely cause of death in each case, except for one woman who died at home. She was treated for PCP a week before her death, and PCP was suggested as the cause.

Kaplan-Meier survival probability curves are shown in Fig. 1, adjusted for WHO stage 4 disease.

Pre-eclampsia and IRIS were not associated with an increased risk of maternal death. The strongest predictor of maternal death in this cohort was WHO stage 4 disease. Concurrent ART and TB treatment, CD4 count <100 cells/µl, and plasma VL >5.00 log_{10} copies/ml were not significantly predictive of maternal death on multivariate analysis (Table III).

Maternal morbidity following delivery occurred in 46 out of 385 women (11.9%). The most frequent complication observed was postpartum haemorrhage (43.5%), followed by obstetric sepsis (17.4%). Maternal morbidity was no

Table II. Maternal deaths after ART commencement

Patient	Age (yrs)	CD4	VL	WHO stage	Reason for presentation	Duration of ART	Cause of death
1	32	304	4.86	1	Tachypnoea, liver failure	14 wks	Lactic acidosis Liver failure ART discontinued
2	27	16	5.08	3	On TB Rx. Tachypnoea and hypoxia	10 d	PCP Respiratory failure
3	29	98	5.26	4	Septicaemia, bleeding oesophageal candidiasis	7 d	Liver failure Septic shock ART discontinued
4	35	96	6.40	4	PCP Rx before. Tachypnoea and hypoxia	31 d	Respiratory failure PCP IRIS ART discontinued
5	35	46	4.99	3	Smear +ve TB, no Rx for 4 wks	32 d	TB
6	19	134	5.59	3	*S. pneumoniae* meningitis Rx. Fever, confusion	45 d	Meningitis ART discontinued
7	33	147	6.48	2	PCP treatment postpartum	3 wks	Death at home PCP

CD4 = CD4 count (cells/µl); VL = viral load (log_{10} copies/ml); PCP = pneumocystis pneumonia; TB = tuberculosis; Rx = treatment; *S. pneumoniae* = *Streptococcus pneumoniae*.

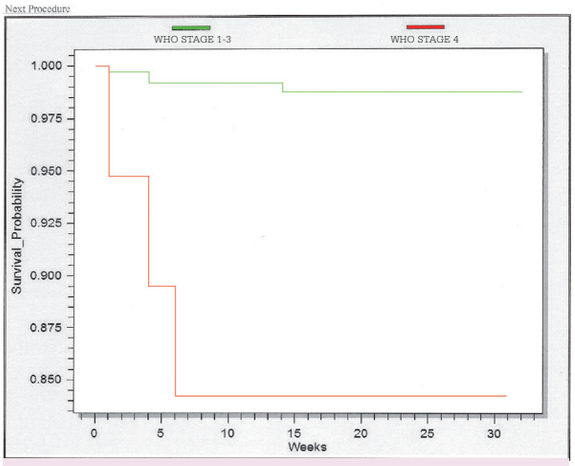

Fig. 1. Kaplan-Meier survival probability curves, WHO stage 1 - 3 disease v. WHO stage 4 disease (p<0.0001).

more frequent in women who had elective caesarean sections (6.7%, 95% CI 0.8 - 22.1) than in those in whom vaginal deliveries were planned (12.3%, 95% CI 9.1 - 16.3). However, in the latter group the rate of maternal morbidity was 20.3% in women who had emergency caesarean sections compared with 9.8% in women who delivered vaginally.

Three women were admitted to ICU, of whom one was the woman who developed lactic acidosis.

The median duration of ART was 15 weeks, which included the period up to 6 weeks postpartum. Optimal adherence to ART was achieved by 95.7% of women, poor adherence being observed in 1.9%. Adherence was not calculated in 13 women (3.4%). ART was discontinued by the attending clinicians in 6 women (1.6%).

Table III. Predictors of maternal death following logistic regression analyses*

Variable	Univariate *p*-value	Multivariate *p*-value
CD4 <100 cells/µl	0.0269	0.1649
ART + TB treatment	0.0170	0.8605
VL >100 000 copies/ml	0.0346	0.3140
WHO stage 4	<0.0001	0.0006

*Results of univariate and multivariate logistic regression analyses of risk factors for maternal deaths. After adjustment WHO stage 4 disease remained the only significant predictor.

Discussion

Unlike previous studies of combination ART in immunocompetent women to reduce MTCT of HIV-1, this study examined outcomes in pregnant women, in the overwhelming majority of whom lifelong ART was indicated. The women in this cohort had clinical and immunological evidence of advanced disease. The probability of maternal survival censored at 6 weeks postpartum was 93.9% (95% CI 90.9 - 96.0). This survival probability is adjusted for women who were lost to follow-up, included as statistical deaths in this analysis. This survival estimate is consistent with 3-month survival estimates from studies done in adults with 2-year duration of follow-up.[13] Despite reasonable survival data and good patient retention, avoidable factors were identified in some of the maternal deaths. The excess number of deaths within the first few weeks of ART suggests late entry into care, and is of concern.

The requirements for ART access by HIV-1-infected adults in South Africa include CD4 count <200 cells/µl and WHO stage 4 disease – a more advanced disease progression entry point than in international recommendations.[14] Longitudinal studies in individuals with CD4 counts of between 200 and 350 cells/µl have shown higher rates of AIDS progression or death in South Africa compared with cohorts followed up in Europe.[15] These findings suggest a need to review criteria for commencing ART in South Africa.

Furthermore, the adult ART guidelines previously made provision for the postponement of ART in pregnant women beyond 34 weeks' gestation.[1] Reasons for this remain unclear. In this cohort 16.9% of women commenced ART beyond 34 weeks' gestation, with no difference in adherence indices or maternal outcomes related to gestation at ART initiation. Adherence to ART was found to be optimal in 95.7% of women who initiated ART beyond 34 weeks' gestation, identical to adherence in women who commenced ART before 34 weeks. The current PMTCT guidelines allow for ART access by pregnant women irrespective of duration of pregnancy.[2] It is anticipated that the revised adult ART guidelines will reflect this provision.

Another possible reason for late entry into care may be related to the interval between TB treatment and commencement of ART. From anecdotal experience in this region, women on TB treatment are advised to wait 2 months before accessing ART services. The national ART guidelines recommend a 2 - 8-week period between TB treatment and ART initiation for individuals in need of ART, citing concerns related to shared drug toxicity and IRIS.[1] The interval between TB treatment and ART initiation strongly correlates with the development of IRIS, but is by no means the only factor.[16] An extended interval may unduly impede access to ART, and needs to be balanced by efforts to reduce MTCT in these women. In this cohort IRIS occurred in 7.0% of women, a somewhat lower prevalence than the 10.4% reported elsewhere in South Africa.[17] The lower prevalence may reflect a shorter duration of follow-up, although some cases may have been undiagnosed. The risk of developing IRIS in this cohort was associated with CD4 count <100 cells/µl (OR 4.69, 95% CI 2.08 - 10.55) and a 2-week interval between ART and TB treatment (OR 5.00, 95% CI 1.11 - 22.45). The maternal death due to IRIS probably occurred as a consequence of ART discontinuation rather than IRIS itself. In all other cases where ART was continued, the outcomes were resolution of symptoms. This underscores the importance of careful clinical consideration by health care workers before interruption of ART in a patient with IRIS. Corticosteroids were not used as treatment for IRIS in any of the women, since the diagnosis was occasionally made retrospectively, after symptoms had improved.

The optimal treatment for IRIS is still not known. Corticosteroids and more recently montelukast have been used in attempts to attenuate the exaggerated host immunological response that characterises this syndrome.[18] However, the studies were uncontrolled. Randomised studies currently in progress on corticosteroids may inform future decisions on its management. The prognosis for IRIS seems generally good, provided ART is continued in all but life-threatening presentations, accompanied by treatment of the antigen responsible for the production of pro-inflammatory cytokines. A recent case-control study showed higher event-free survival rates in patients with IRIS compared with non-IRIS opportunistic infections.[19]

PCP was the leading cause of maternal deaths in this cohort, perhaps reflecting a changing pattern of infectious causes of mortality in women taking ART. However, this could be attributed to greater awareness of TB mortality in HIV-1-infected pregnant women, better adherence to national TB guidelines by health care workers, or earlier TB treatment as a result of routine symptom screening of women. The feasibility of symptomatic screening for TB as part of antenatal care in HIV-1-infected women has been investigated previously.[20]

The mean duration of ART in this cohort was 15 weeks, ranging from 1 week to 32 weeks. This period may not be long enough to unmask some long-term adverse effects of d4T, which may explain the low incidence of ART discontinuation in the women followed up. However, lactic acidosis attributed to d4T was strongly suspected as the cause of one of the maternal deaths in this cohort.

AZT is currently preferred to d4T internationally owing to extensive experience with its use in pregnant women, as well as its lower risk of mitochondrial toxicity.[21]

Pregnant women who require lifelong ART are expected to be managed in accordance with current recommendations for adults. The new 'draft' recommendations make provision for d4T to be substituted with AZT or tenofovir (TDF) in the event of toxicity to d4T.[22] Given the additional need to reduce MTCT at delivery, even for women on ART,[21] it is not clear whether 3-hourly d4T should be continued intrapartum, or whether d4T should be substituted

by AZT. While pharmacokinetic data on 3-hourly d4T are available, limited data exist on its effectiveness in reducing infant HIV-1 transmission following intrapartum use.[23] On a practical level, switching from d4T to AZT when labour starts may be difficult to manage. Also, the effectiveness of such a strategy is unknown since AZT and d4T antagonise each other *in vivo*.[24] The continued recommendation of d4T-based ART as primary treatment for pregnant women remains a major concern.

At our centre EFV was preferred ahead of NVP, because during our initial experience a significant number of women were on treatment for TB at the time of commencing ART. We were concerned about drug interactions between NVP-based ART and concomitant TB treatment.[25] In addition many women presented with very low CD4 counts, where EFV was shown to be marginally more effective than NVP.[26] Finally, in women with CD4 counts above 250 cells/µl and WHO stage 3 or stage 4 disease, we were reluctant to commence NVP-based ART owing to the higher risk of hepatitis associated with its use in this group of ART-naïve women.[27]

Compared with NVP or LPV/r, EFV-based ART has a lower pill burden, does not require extensive laboratory monitoring, can be given with rifampicin or fluconazole, and does not modify the woman's risk of developing gestational diabetes. The association between LPV/r use and gestational diabetes has however been challenged recently.[28]

On a practical level EFV-based ART may also limit the need to discontinue ART in women with pregnancy complications such as HELLP syndrome, intrahepatic cholestasis (ICP) and acute fatty liver of pregnancy (AFLP), since these conditions often resemble drug-induced hepatitis. Concerns about EFV use in pregnancy will remain given its FDA category D classification, despite limited evidence of teratogenicity.[29] Infant outcomes in this cohort are awaiting publication elsewhere.

Pre-eclampsia occurs no more frequently in untreated HIV-infected pregnant women than in HIV-negative pregnant women.[30] Whether there is an association between pregnant women taking ART and pre-eclampsia is unclear. Studies on this association have yielded conflicting results. Some investigators have found a sharp increase in the risk of pre-eclampsia in HIV-infected women, particularly women who commenced ART before becoming pregnant. They found higher levels of circulating insulin and selectins in these cases, and suggested insulin resistance and endothelial dysfunction as possible explanations for the increased rates.[31] Several other studies failed to demonstrate any association between ART use and the risk of developing pre-eclampsia, alluding to improved obstetric outcomes for women on ART.[32,33] The inconsistent findings may reflect differences in sample size, methodology and adjustments for confounding variables that may impact on the association between pre-eclampsia and ART use. In this prospective study pre-eclampsia occurred in 7.5% of women, a rate consistent with overall rates reported elsewhere in South Africa and internationally.[30,34] Additional research is warranted to clarify this association and the implications thereof.

Despite the brief preparation period before ART initiation, optimal adherence to treatment in this cohort was high, with few women lost to follow-up. Notwithstanding the limitations of adherence monitoring, this result is consistent with published data showing better adherence in pregnant women compared with non-pregnant women.[35] A robust analysis performed in South Africa recently demonstrated a striking dose-response relationship between adherence and survival. Adherence in the study was measured by a relatively simple tool – pharmacy claims.[36] Maternal mortality in our cohort could not be measured against adherence indices, considering the proportion of deaths that occurred shortly after ART commencement.

The provision of lifelong ART to pregnant women for their own health is primarily intended to reduce the risk of AIDS progression and maternal death and to improve their quality of life, with an additional benefit of reducing MTCT. The paediatric ART guidelines, which were developed separately from the PMTCT guidelines, contain revised entry criteria enabling more infants to have access to ART – a move to be applauded, since it is consistent with WHO recommendations for children needing ART.[37] The 'draft' adult ART guidelines appear to have remained stagnant with respect to entry criteria. The revised PMTCT guidelines contain major improvements with respect to efforts to combat infant HIV-1 transmission; it has however remained equally stagnant on ART options and access by pregnant women in need of lifelong treatment. It is hoped that policy makers will recognise the need for pregnant women to be managed along ART guidelines specifically for them.

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