



Published in final edited form as:

*S Afr Med J.* 2010 January ; 100(1): 58–64.

## Treatment of trichomoniasis in pregnancy in sub-Saharan Africa does not appear to be associated with low birth weight or preterm birth

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### Abstract

**Objectives**—To determine whether treatment of trichomoniasis increases the risk of prematurity.

**Design**—Sub-analysis of a randomised trial.

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**Setting**—We analysed data from HPTN 024, a randomised trial of antenatal and intrapartum antibiotics to reduce chorioamnionitis-related perinatal HIV transmission.

**Subjects**—Pregnant women from four sites in Africa.

**Outcome measures**—Gestational age at the time of delivery or mean birth weight.

**Results**—Of 2 428 women-infant pairs included, 428 (18%) had trichomoniasis at enrolment. There were no differences in infant age or birth weight between women with or without trichomoniasis. By randomisation group, there were no differences in gestational age at birth or birth weight. Of the 428 women diagnosed with trichomoniasis, 365 (83%) received antibiotics and 63 (15%) did not. In analysis of actual use of antibiotics, women with trichomoniasis who received no treatment were more likely to deliver a preterm infant when the symphysis-fundal height was used to estimate gestational age (36% v. 23%;  $p=0.03$ ), but not when the Ballard score was used (16% v. 21%;  $p=0.41$ ). There were no differences in mean birth weight between groups.

**Conclusions**—In pregnant women in sub-Saharan Africa, most of whom were HIV-infected, neither trichomoniasis nor its treatment appears to influence the risk of preterm birth or a low-birth-weight infant.

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Preterm birth is an important cause of neonatal morbidity and mortality worldwide.<sup>1,2</sup> Studies have suggested that bacterial infections of the placenta and fetal membranes may play a major role in preterm birth.<sup>3,4</sup> Although the most common micro-organisms associated with preterm birth are *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Gardnerella vaginalis*, *Bacteroides* species, *Mobiluncus curtisii* and a variety of anaerobic species, some studies have suggested that infection with *Trichomonas vaginalis* may increase the risk of preterm birth.<sup>5</sup> A high prevalence of trichomoniasis among adults in eastern and southern Africa, ranging from 17% to 42%, has been reported.<sup>6–8</sup> Use of antibiotics to prevent preterm labour and premature membrane rupture, or to reduce the risk of preterm birth for women in preterm labour, has been widely studied for over 30 years. About a third of the studies have suggested benefit in reducing preterm birth, while most have not.<sup>9–11</sup>

Two studies have suggested that treatment of trichomoniasis with metronidazole in pregnancy is associated with an increased risk of preterm birth and low birth weight.<sup>12,13</sup> In one of these, a multicentre trial in the USA, women with asymptomatic trichomoniasis treated with metronidazole were significantly more likely than those not treated to deliver a preterm infant.<sup>12</sup> The second, a sub-analysis of a study in rural Uganda, showed that women who were treated for trichomoniasis were 2.5 times more likely to deliver a low-birth-weight infant compared with controls.<sup>13</sup>

In a planned secondary analysis we hypothesised, on the basis of these earlier studies, that women with trichomoniasis who were randomised to the study group given metronidazole (active against *T. vaginalis*) would have a higher rate of preterm and low-birth-weight infants than women randomised to placebo.

## Materials and methods

HPTN 024 was a trial of antibiotics to reduce both mother-to-child transmission of HIV and preterm birth.<sup>14</sup> The first women were enrolled in July 2001, and the last delivery occurred in August 2003. The study was conducted in four sub-Saharan African sites: Blantyre and Lilongwe, Malawi; Dar es Salaam, Tanzania; and Lusaka, Zambia. Enrolment required knowledge of HIV infection status. In three of the four sites, 1 HIV-uninfected woman was enrolled for every 5 infected women in order to mask HIV infection status. In Dar es

Salaam, only HIV-infected women were enrolled. Women were enrolled between 20 and 24 weeks.

At enrolment, blood for syphilis testing and cervico-vaginal samples were obtained. Vaginal samples were analysed by microscopy in site laboratories for the presence of motile *Trichomonas*, candidiasis and bacterial vaginosis (through whiff test, vaginal pH, and presence of clue cells). Cotton-tipped applicators were also used to collect vaginal specimens for Gram staining, which were shipped to the University of Alabama at Birmingham for evaluation. For gonococcal culture, a cotton-tipped swab was placed in the endocervical canal and allowed to sit for at least 10 seconds. This swab was then used to inoculate a plate for gonococcal isolation. *Chlamydia* infection was detected by *Chlamydia trachomatis* antigen enzyme immunosorbent assay. Women were offered treatment for these infections at no cost, although treatment regimens differed across the sites.

Women were randomised to receive either antibiotics (metronidazole 250 mg and erythromycin 250 mg orally, both 3 times daily for 7 days) or placebo. Tests were repeated between 26 and 30 weeks' gestation for bacterial vaginosis, vaginal candidiasis and trichomoniasis. Women found to have any of these infections were treated, but not all women received treatment. With the onset of labour contractions and/or premature rupture of membranes (PROM), study participants initiated a second oral course of antibiotics consisting of metronidazole 250 mg orally and oral ampicillin 500 mg or placebo every 4 hours until delivery. These antibiotics were chosen because the organisms associated with clinical or sub-clinical chorioamnionitis (bacterial vaginosis-associated organisms such as *Ureaplasma*, *Mycoplasma*, *Bacteroides*, *Mobiluncus* and *Gardnerella*) are generally sensitive to one or more of these antibiotics.<sup>15</sup>

Because the study was conducted in four resource-limited settings and ultrasound was not generally available, it was not used to determine the estimated due date. Gestational age was determined by patient recall of the last menstrual period (LMP), corroborated with uterine size. If uterine size was not within 2 weeks of recall of the LMP, uterine size defined the obstetric gestational age. At delivery, each baby also had a modified Ballard examination to allow for a paediatric estimation of gestational age.<sup>16</sup> If the Ballard examination and obstetric gestational age determination were consistent within 2 weeks, the obstetric gestational age was used; if not, the final study gestational age was based on the Ballard examination. Nurses at all locations were trained to determine both the obstetric and the paediatric gestational ages. Preterm birth was defined as birth occurring before 37 completed weeks of gestation, low birth weight as birth weight less than 2 500 g, and very low birth weight as birth weight less than 1 500 g. Results are presented independently for each of the methods. The analysis was restricted to singleton deliveries because twins have a higher baseline risk of preterm birth.<sup>17</sup>

### Statistical analysis

We performed a secondary analysis using data from the HPTN 024 trial.<sup>11</sup> Independent two-sample *t*-tests, Wilcoxon rank sum tests and two-sample chi-square tests were performed to compare means, medians, and proportions, respectively. Kaplan-Meier estimates were calculated and log rank tests were performed in time-to-event analysis of time to delivery following randomisation.

### Results

A total of 2 661 women were enrolled into HPTN 024 trial and randomised (86% of whom were HIV infected). Of these, 2 656 (almost 100%) had a baseline trichomoniasis result, but 188 (7%) were lost to follow-up before delivery, 32 (1%) delivered twins, 7 died before

delivery, and 1 woman's delivery outcome was unknown. The study population therefore comprised 2 428 mother-infant pairs. Characteristics of the study population according to presence or absence of trichomoniasis at enrolment are set out in Table I. Compared with those without trichomoniasis, women with trichomoniasis were more likely to be HIV infected, to have bacterial vaginosis or gonorrhoea, to be younger, and to be slightly less educated (Table I).

Of the 428 women diagnosed with trichomoniasis, 231 (54%) were randomised to receive the study antibiotics and 197 (46%) were randomised to placebo (Table II and Fig. 1). There were no significant differences in baseline characteristics between the two groups. Women randomised to receive antibiotics were more likely to have resolution of trichomoniasis at their second visit than women randomised to placebo ( $p<0.0001$ ). In the analysis by randomisation group, women randomised to the antibiotic arm were not more likely to deliver a preterm infant, whether the gestational age was based on fundal height obtained at randomisation (23.8% v. 27.4%;  $p=0.39$ ) or on Ballard examination (20.6% v. 19.8%;  $p=0.84$ ) or to deliver an infant with a lower mean birth weight (2 992 g v. 2 930 g;  $p=0.27$ ) (Table II).

A second analysis was performed based on actual metronidazole use. Of the 428 women diagnosed with trichomoniasis, 365 (85%) received antibiotics active against trichomoniasis and 63 (17%) did not (Fig. 1). Women who received antibiotics active against trichomoniasis were more likely to have a *Chlamydia* infection and to have resolution of the trichomoniasis at their second visit compared with women who did not ( $p<0.001$ ). Women who were diagnosed with trichomoniasis but did not receive antibiotics active against this infection were more likely to deliver a preterm infant when that assessment was based on symphysis-fundal height gestational age assessment (40% v. 23%;  $p=0.005$ ), but not when the gestational age assessment was based on Ballard estimation (19% v. 20%;  $p=0.97$ ). There were no differences in mean birth weights at delivery between women not receiving and those receiving treatment for trichomoniasis (2 972 g and 2 911 g, respectively) (Table III).

To examine the association of receipt of antibiotics and infant outcomes further among women with treated trichomoniasis, we examined time from randomisation to delivery for women with trichomoniasis who were treated with antibiotics compared with those who were not treated, since calculation of gestational age may be inaccurate without an ultrasound scan. There was no difference in the time from randomisation to delivery between those with treated and untreated trichomoniasis (log-rank  $p$ -value = 0.12) (data not shown).

## Discussion

We found no differences in pregnancy outcomes among women diagnosed with trichomoniasis compared with women without trichomoniasis. Analysis of the treatment results of women who had trichomoniasis by both randomisation arm and actual-use analysis found no substantial differences in pregnancy outcomes. Women in the actual-use analysis who received metronidazole were more likely to have a preterm infant when gestational age was based on fundal height obtained at randomisation, but not when it was based on modified Ballard examination. In addition, there were no significant differences in infant birth weights between women with trichomoniasis according to randomisation arm or actual receipt of antibiotics. The time to delivery also did not differ according to randomisation arm or actual receipt of antibiotics.

A systematic review of well-conducted studies of pregnant women with either bacterial vaginosis or trichomoniasis receiving antibiotics in the second or third trimesters concluded that treatment of trichomoniasis in pregnancy may be harmful.<sup>18</sup> This conclusion was primarily based on two studies. One showed that women with asymptomatic trichomoniasis treated with two 2 g doses of metronidazole 48 hours apart were more likely to have a preterm infant (relative risk (RR) 1.8, 95% confidence interval (CI) 1.2 – 2.7), but were not more likely to have a low-birth-weight infant (RR 1.4, 95% CI 0.9 – 2.1).<sup>12</sup> The second study was a sub-analysis from a large community randomised trial in Uganda.<sup>13</sup> This study found that pregnant women with trichomoniasis in the treatment arm (which included 2 g metronidazole) were 2.5 times as likely to deliver a low-birth-weight infant at 1 week of follow-up compared with women in the untreated arm. A major limitation of this study was its preferential follow-up of infants in the treatment arm; 84% of infants born to women in the treatment group were followed up within the first week, as opposed to only 67% of infants in the control group. In addition, there was no statistically significant difference in gestational age at birth between the control and treatment arms. Another observational study conducted in South Africa found no difference in mean birth weight or gestational age between infants born to women who were treated for trichomoniasis and those who were not.<sup>19</sup>

Our results are consistent with the findings in other studies that women who received antibiotic treatment for trichomoniasis are more likely to have resolution of their trichomoniasis. For example, trichomoniasis in our study was reduced by 68% in the group who received antibiotics active against trichomoniasis versus 21% in the placebo group (as previously reported). Women diagnosed with trichomoniasis in our population also were more likely to have other infections such as HIV infection, bacterial vaginosis, *Chlamydia* infection, and gonorrhoea than women without trichomoniasis. One limitation of our study is that a significant number of women randomised to the placebo arm in HPTN 024 were exposed to metronidazole. Because of this we also performed an actual-use analysis, for which results were similar to those of the intention-to-treat analysis. Another limitation of this study is in the imperfect gestational age dating using fundal height estimation and the modified Ballard examination. Since the modified Ballard examination can be performed only on women who deliver at a health centre, all of the women who were lost to follow-up, had a stillbirth, or delivered at home could not have a Ballard examination performed on their infant. The sample size for analyses including a modified Ballard examination was therefore diminished.

In conclusion, data regarding whether treatment of trichomoniasis in pregnancy is associated with adverse infant outcomes is limited by variation in the types of study, study size and even treatment regimens. In addition, some studies have examined treatment of asymptomatic trichomoniasis while others, such as ours, have examined antibiotic receipt by both asymptomatic and symptomatic subjects. Our results for sub-Saharan African women, mostly HIV-infected and with a high prevalence of trichomoniasis, do not indicate an increased risk of preterm birth according to both intention-to-treat and actual-use analyses. While this study was not designed to provide conclusive evidence of safety, we believe that our results, taken with other available evidence, do not suggest that treatment of trichomoniasis is associated with a substantially increased risk of preterm birth among HIV-infected African women.

## Acknowledgments

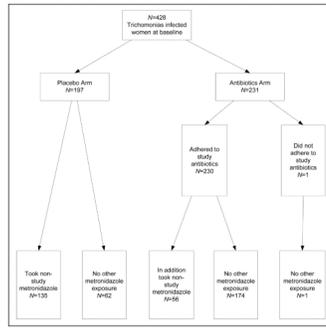
This work was supported by the HIV Prevention Trials Network (HPTN) and sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, Department of Health and Human Services, through contract N01-AI-35173 with Family Health International; contract N01-AI-45200 with Fred Hutchinson Cancer Research Center; and subcontract N01-AI-35173-117/412 with Johns Hopkins University.

In addition, this work was supported and sponsored by the National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute on Drug Abuse, National Institute of Mental Health, and Office of AIDS Research, of the National Institutes of Health, US Department of Health and Human Services, Harvard University (U01-AI-48006), Johns Hopkins University (U01-AI-48005), and the University of Alabama at Birmingham (U01-AI-47972). Nevirapine (Viramune) for the study was provided by Boehringer Ingelheim Pharmaceuticals, Inc. The conclusions and opinions expressed in this paper are those of the authors and do not necessarily reflect those of the funding agencies and participating institutions.

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**Fig. 1.**  
Profile of women with trichomoniasis at baseline.

**Table I**Characteristics of women and their infants, according to presence or absence of trichomoniasis ( $N=2\ 428$ )

Characteristic	With trichomoniasis ( $N\ 428$ )	Without trichomoniasis ( $N\ 2\ 000$ )	<i>p</i> -value
<b>Categorical variables*</b> ( $N$ (%))			
Maternal			
History of stillbirth	33/428 (7.7)	162/2 000 (8.1)	0.79
Married	387/428 (90.4)	1 856/2 000 (92.8)	0.09
HIV infected	392/428 (91.6)	1 701/2 000 (85.0)	0.004
STI			
Bacterial vaginosis	217/428 (50.7)	867/2 000 (43.3)	0.003
<b>Chlamydia</b>	10/428 (2.3)	47/2 000 (2.3)	0.94
Syphilis	36/428 (8.4)	120/2 000 (6.0)	0.07
Gonorrhoea	14/428 (3.3)	24/2 000 (1.2)	0.002
Delivery			
Duration of rupture of membranes >4 h	75/389 (19.3)	360/1 852 (19.4)	0.94
Vaginal delivery	405/427 (94.8)	1 878/1 998 (94.0)	0.50
Infant			
Preterm birth			
By fundal height	109/428 (25.5)	497/2 000 (24.9)	0.80
By Ballard examination	71/351 (20.2)	349/1 729 (20.2)	0.99
Birth weight (g)			
<1 500	10/389 (2.6)	42/1 859 (2.3)	0.98
1 501 – 2 500	63/389 (16.2)	296/1 859 (15.9)	
2 501 – 3 000	140/389 (36.0)	669/1 859 (36.0)	
≥3 001	176/389 (45.2)	852/1 859 (45.8)	
<b>Continuous variables†</b> (median (IQR))			
Age (yrs)	24.0 (21 – 27)	25.0 (21 – 28)	0.002
No. of pregnancies	3.0 (2 – 4)	3.0 (2 – 4)	0.42
No. of live births	1.0 (1 – 3)	1.0 (1 – 3)	0.79
Years of education	7.0 (3 – 8)	7.0 (5 – 9)	0.0002
Baseline CD4 count (cells/–1)	386 (238 – 566)	366 (226 – 564)	0.43
Baseline fundal height (cm)	22.0 (20 – 24)	22.0 (20 – 24)	0.70
Birth weight (g)	3 000 (2 700 – 3 300)	3 000 (2 700 – 3 300)	0.95

\* *p*-values based on the  $\chi^2$  test.† *p*-values based on the Wilcoxon rank sum test.

STI = sexually transmitted infection; IQR = intraquartile range.

**Table II**Characteristics of women with trichomoniasis, according to randomisation arm ( $N=428$ )

Characteristic	Antibiotics ( $N=231$ )	Placebo ( $N=197$ )	<i>p</i> -value
<b>Categorical variables* (<math>N</math> (%))</b>			
Maternal			
Reported history of stillbirth	17/231 (7.4)	16/197 (8.1)	0.77
Married	208/231 (90.0)	179/197 (90.9)	0.77
History of STI			
HIV infected	217/231 (93.9)	175/197 (88.8)	0.06
Bacterial vaginosis	116/227 (51.1)	101/191 (52.9)	0.60
<i>Chlamydia</i>	3/217 (1.4)	7/195 (3.6)	0.15
Syphilis	18/228 (7.9)	18/196 (9.2)	0.07
Gonorrhoea	7/223 (3.1)	7/195 (3.6)	0.80
Delivery			
>4 hours between rupture of membranes and delivery	42/206 (20.4)	33/183 (18.0)	0.56
Vaginal delivery	219/230 (95.3)	186/197 (94.4)	0.71
Infant			
Gestational age at time of delivery (wks)			
<37 (fundal height)	55/231 (23.8)	54/197 (27.4)	0.39
<37 (Ballard score)	39/189 (20.6)	32/162 (19.8)	0.84
Birth weight (g)			
<1 500	5/207 (2.4)	5/182 (2.7)	0.92
1 501 – 2 500	32/207 (15.5)	32/182 (17)	
2 501 – 3 000	73/207 (35.3)	67/182 (36.8)	
≥3 001	97/207 (46.9)	76/182 (43.4)	
Other			
Resolution of trichomoniasis by visit 2	192/224 (85.7)	126/186 (67.7)	<0.0001
<b>Continuous variables† (median (IQR))</b>			
Age	24.0 (21 – 27)	23.0 (21 – 27)	0.35
No. of pregnancies	3.0 (2 – 4)	3.0 (2 – 4)	0.15
No. of live births	2.0 (1 – 3)	1.0 (0 – 2)	0.19
Years of education	7.0 (3 – 9)	7.0 (3 – 8)	0.36
Baseline CD4 count (cells/ $\mu$ l)	378 (238 – 518)	398 (238 – 638)	0.14
Baseline fundal height (cm)	22.0 (20 – 24)	22.0 (20 – 24)	0.77
Birth weight (g)	3 000 (2 700 – 3 300)	3 000 (2 700 – 3 300)	0.41

\* *p*-values based on the  $\chi^2$  test.† *p*-values based on the Wilcoxon rank sum test.

Table III

Characteristics of women with trichomoniasis, according to actual receipt of antibiotics effective against trichomoniasis

Characteristic	Trichomoniasis treated (N=365)	Trichomoniasis untreated (N=63)	p-value
<b>Categorical variables* (N (%))</b>			
Maternal			
Reported history of stillbirth	30/365 (8.2)	3/63 (4.8)	0.34
Married	333/365 (91.2)	54/63 (85.7)	0.17
STI			
HIV infected	335/365 (91.8)	54/63 (85.7)	0.07
Bacterial vaginosis	191/365 (52.3)	26/63 (41.3)	0.09
<b>Chlamydia</b>	6/365 (1.6)	4/63 (6.3)	0.03
Syphilis	29/365 (7.9)	7/63 (11.1)	0.39
Gonorrhoea	12/365 (3.3)	2/63 (3.2)	0.93
Delivery			
Vaginal delivery	344/361 (95.3)	61/66 (96.8)	0.44
Infant			
Gestational age at time of delivery (wks)			
< 37 (fundal height)	84/365 (23.0)	25/63 (39.7)	0.005
< 37 (Ballard score)	61/302 (20.2)	10/49 (20.4)	0.97
Birth weight (g)			
<1 500 g	9/333 (2.7)	1/56 (1.8)	0.831
1 501 – 2 500	54/333 (16.2)	9/56 (16.1)	
2 501 – 3 000	117/333 (35.1)	23/56 (41.1)	
≥3 001	153/333 (45.9)	23/56 (41.1)	
Other			
Resolution of trichomoniasis by visit 2	286/346 (82.7)	32/64 (50.0)	0.001
<b>Continuous variables† (median (IQR))</b>			
Age (yrs)	24.0 (21 – 27)	23.0 (20 – 26)	0.14
No. of pregnancies	3.0 (2 – 4)	2.0 (2 – 4)	0.33
No. of live births	2.0 (1 – 3)	1.0 (0 – 2)	0.22
Years of education	7.0 (3 – 8)	7.0 (5 – 8)	0.24
Baseline CD4 counts (cells/–1)	379 (237 – 534)	457 (266 – 666)	0.11
Baseline fundal height (cm)	22.0 (20 – 24)	22.0 (20 – 23)	0.34
Days between visit 1 and visit 2	39.5 (28 – 56)	48.5 (37 – 56)	0.004
Birth weight (g)	3 000 (2 650 – 3 300)	3 000 (2 720 – 3 300)	0.74

\* p-values based on the  $\chi^2$  test.

† p-values based on the Wilcoxon rank sum test.

STI = sexually transmitted infection; IQR = intraquartile range.