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Aetiological testing compared with syndromic management for sexually transmitted infections in HIV-infected pregnant women in South Africa: a non-randomised prospective cohort study

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Objective To measure the frequencies of sexually transmitted infections (STIs) and adverse pregnancy outcomes among women receiving either aetiological testing or syndromic management for STIs.

Design Non-randomised prospective cohort study.

Setting Primary healthcare facilities in Tshwane, South Africa.

Population HIV-infected pregnant women attending antenatal care services.

Methods Participants were enrolled to receive aetiological testing using Xpert® CT/NG and Xpert® TV assays or standard syndromic management. Outcome data were collected at the postnatal care visit (≤30 days from delivery) and from maternity records. Enrolment gestational age-adjusted relative risk (aRR) was calculated.

Main outcome measures STI prevalence at postnatal visit, and frequency of adverse pregnancy outcomes (preterm birth, low birthweight).

Results We enrolled 841 women. The prevalence of any STI at baseline was 40%; *Chlamydia trachomatis* 30%, *Neisseria gonorrhoeae* 5.6%, *Trichomonas vaginalis* 20%. The prevalence of STIs at postnatal care was lower among those receiving aetiological testing compared with those receiving syndromic management (14% versus 23%; aRR 0.61; 95% CI 0.35–1.05). No difference was observed between study groups for frequency of preterm birth (23% versus 23%; aRR 1.2, 95% CI 0.81–1.8) and low birth weight (15% versus 13%; aRR 1.1, 95% CI 0.66–1.7).

Conclusions Aetiological testing provides an effective intervention to reduce the high burden of STIs in pregnant women in South Africa; however, the optimal implementation strategy remains to be determined.

Keywords Aetiological testing, HIV, low birthweight, pregnancy, preterm birth, sexually transmitted infections, syndromic management, Xpert®.

Tweetable abstract Aetiological testing effectively reduces the burden of sexually transmitted infections in pregnancy.

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Introduction

The World Health Organization (WHO) estimates that 12 million new cases of *Chlamydia trachomatis* occur annually in the African region, 11.4 million cases of *Neisseria gonorrhoeae* and 37.4 million cases of *Trichomonas vaginalis*.[1] In the African region, South Africa ranks among the countries with the highest burden of those sexually transmitted infections (STIs).[2] Compared with men, women have a higher prevalence of *Chlamydia trachomatis* (14.7%

versus 6.0%) and *Neisseria gonorrhoeae* (6.6% versus 3.5%),[3] with the highest STI burden found among pregnant women, especially those living with HIV.[4,5]

Sexually transmitted infections in pregnant women pose a significant public health concern.[6,7] Untreated STIs have been associated with adverse pregnancy outcomes including miscarriage, stillbirth, premature rupture of membranes, chorioamnionitis, preterm birth and low birthweight.[8–16] Untreated STIs may also cause neonatal morbidity, as neonates may acquire these infections around the time of delivery and develop conjunctivitis, pneumonia and sepsis.[13,17–22] Finally, untreated STIs may facilitate the acquisition of HIV infection if exposed, and may enhance in utero and intrapartum mother-to-child transmission of HIV infection in women with unsuppressed viral load.[13,23]

Syndromic management is currently the cornerstone of STI care in South Africa. Specifically, during antenatal care (ANC), pregnant women are asked about STI-associated symptoms (e.g. vaginal discharge), with empirical antimicrobial treatment provided to symptomatic individuals. Although that approach is low-cost and easy to implement, the majority of STIs are asymptomatic, and so remain untreated.[24] Using highly accurate molecular diagnostic tests (i.e. aetiological testing) and providing targeted treatment in the case of a positive result provides an alternative approach to syndromic management, with the potential to improve STI management and reduce STI-related adverse outcomes of pregnancy.[24] Aetiological STI testing has been shown to be superior to syndromic management for the detection and treatment of STIs in various populations across Africa.[25–28] However, most studies have been cross-sectional in nature. Given the high incidence of STIs in those settings, the impact of detecting and treating STIs on prevalence and health outcomes may be brief. Furthermore, it is unclear if aetiological testing for STIs during pregnancy has any impact on the STI prevalence around time of delivery and occurrence of adverse pregnancy outcomes when compared with syndromic management. We prospectively compared aetiological testing with syndromic management of STIs among pregnant women living with HIV in South Africa.

Methods

Study populations

Pregnant women living with HIV were enrolled into a non-randomised prospective cohort study between June 2016 and September 2017. Recruitment occurred at three primary healthcare facilities in the Tshwane District, Gauteng Province, South Africa. Eligibility criteria included: (1) age ≥18 years, (2) confirmed pregnant as determined by urine pregnancy test, (3) ≤34 weeks of gestation based on report of last menstrual period, (4) documented HIV infection, (5) residing in Tshwane with the intention to deliver and remain in the district following delivery. Upon provision of informed consent, a nurse-administered baseline questionnaire was used to collect demographic, behavioural and clinical characteristics.

Participants attending their first ANC visit for that pregnancy were enrolled for aetiological testing for STIs whereas those attending their second or later ANC visit were enrolled to receive standard syndromic management. The main study outcomes were: (1) prevalence of STIs at time of delivery, and (2) frequency of adverse pregnancy outcomes (preterm birth or low birthweight). Outcome data were collected during the participant's postnatal care visit (≤30 days after delivery). If the participant was lost to follow up and the delivery facility was known, outcome data were collected from the participant's maternity files and facility birth registry. Our sample size was limited to what was practical, affordable and could generate data (e.g. about prevalence of STIs and pregnancy outcomes) that could be used to power future studies; the decision to enrol women at all stages of pregnancy, and not only their first ANC, was made for the same reasons.

Study approval was provided by the Institutional Review Board of the University of Pretoria, Faculty of Health Sciences, Research Ethics Committee (reference number: 401/2015; approved 26 November 2015).

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Study procedures

Participants offered aetiological testing were asked to self-collect vulvovaginal swabs using Xpert® CT/NG Vaginal/Endocervical Specimen Collection Kits (Cepheid, Sunnyvale, CA, USA). Study nurses processed and tested specimens using the Xpert® CT/NG and Xpert® TV assays (Cepheid). Women received same-day test results and treatment if positive for an STI. Treatment included azithromycin 1 g orally for *C. trachomatis*, ceftriaxone 250 mg intramuscular injection with azithromycin 1 g orally for *N. gonorrhoeae*, and a 7-day course of metronidazole 400 mg twice daily orally for *T. vaginalis*. All women with a positive test result were requested to return after 3 weeks post-treatment for a test-of-cure visit. Women with a positive test-of-cure result were provided with subsequent clinical management as described elsewhere.[29] Comparison group participants were managed syndromically as per

South African STI management guidelines.[30] Symptomatic individuals provided empiric treatment of single doses of azithromycin (1 g oral dose), ceftriaxone (250 mg intramuscular injection) and metronidazole (2 g oral dose). At the postnatal visit, all participants, regardless of study arm, were tested using Xpert® CT/NG and Xpert® TV and provided treatment based on test results as described above.

Definitions

An STI at the time of delivery was defined as a positive Xpert® test during the participants' postnatal visit within 30 days from delivery. WHO definitions were used for adverse birth outcomes.[30,31] Preterm birth was defined as a live birth before 37 completed weeks of gestation.[31] Preterm birth was further categorised as moderate to late (32–37 weeks), very preterm (28–32 weeks) and extremely preterm (<28 weeks). Low birthweight was defined as birthweight of an infant <2500 g regardless of gestational age.[32] Gestational age was estimated based on the last menstrual period as reported by the participant.

Data management and statistical analysis

Real-time data collection was performed using REDCap (Research Electronic Data Capture, Vanderbilt University, USA) on tablet computers.[33] Checks for data quality and consistency were performed, with verifications and corrections made where appropriate. The database MASTERFILE was exported to SPSS Statistics version 24 (IBM, Armonk, NY, USA) for statistical analysis.

Descriptive statistics are provided as numbers with proportion (%) and median with interquartile range (IQR). Prevalence of infection (%) was calculated as the number of participants with a positive STI test divided by all participants that were tested for that STI. Dichotomous and categorical variables were compared between groups using the chi-square test with Fisher's exact test when appropriate, providing the relative risk (RR) with 95% confidence interval (CI). For continuous variables, the Mann–Whitney *U* test was used. Binary logistic regression analyses were performed to adjust for baseline gestational age and potential confounders when determining the relationship between study group and STIs with pregnancy outcomes. A *P*-value of <0.05 was considered significant.

Results

A total of 1055 pregnant women were approached to participate, of which 861 (82%) were eligible and 841 (98%) consented to participate. Reasons for ineligibility (n = 194) were: gestational age >34 weeks of gestation (n = 92), intention to deliver outside the study district (n = 94), poor level of comprehension (n = 17), false pregnancy (n = 3), no documented HIV status and refusal to (re)test for HIV infection (n = 2); 14 had multiple reasons. Of those consenting to participate, 427 (51%) received aetiological testing and 414 (49%) received syndromic management.

The median age of study participants was 30 years (IQR 26–34 years), 96% reported being in a steady relationship and 58% were unemployed (Table 1). Participants in the aetiological testing group were enrolled at an earlier gestational age (median 18 weeks; IQR 13–23 weeks) compared with women that received syndromic management (median 26 weeks; IQR 20–29 weeks). Furthermore, the proportion

Table 1. Baseline characteristics of the study population, by study group, of a cohort of HIV-infected pregnant women in Tshwane, South Africa (n = 841)

	Aetiological STI screening (n = 427)	Syndromic STI management (n = 414)
Age (years), median (IQR)	30 (26–34)	30 (26–34)
Relationship status		
Single	17 (4.0)	15 (3.6)
Steady partner	186 (44)	174 (42)
Living together	167 (39)	165 (40)
Married	56 (13)	58 (14)
Employment status		
Full-time or part-time employed	157 (37)	164 (40)
Self-employed	18 (4.2)	16 (3.9)
Unemployed	251 (59)	232 (56)
Gravidity		
Primigravida	56 (13)	66 (16)
Multigravida	371 (87)	347 (84)
Gestational age (weeks), median (IQR)	18 (13–24)	26 (20–29)
HIV status at enrolment		
HIV-infected; on ART	347 (81)	410 (99)
HIV-infected; not yet on ART	80 (19)	4 (0.9)
Syphilis screening (RPR)		
Positive	6 (1.7)	9 (2.5)
Negative	348 (98)	356 (98)
STI treatment before pregnancy		
Yes	41 (9.8)	40 (10)
No	378 (90)	360 (90)
STI symptoms during pregnancy; prior to or at enrolment		
Yes	77 (18)	57 (14)
No	350 (82)	355 (86)

ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; RPR, rapid plasma reagin; STI, sexually transmitted infection.

of women that had not yet initiated antiretroviral therapy at the time of study enrolment was higher in the aetiological testing group compared with those that received syndromic management (19% versus 0.9%); the number of women on antiretroviral therapy with virological suppression (HIV viral load <1000 copies/ml) was lower in the aetiological testing group (71% versus 79%). Twenty-three women (5.8%) reported STI treatment before enrolment in the syndromic arm but the number of women with STI symptoms at or before enrolment was similar between the two groups (18% respectively 14%). Forty women (4.8%) used cotrimoxazole prophylaxis for their advanced HIV infection.

Among women receiving aetiological STI testing at baseline, 172/427 (40%) had a positive STI test result: *C. trachomatis* 126 (30%), *N. gonorrhoeae* 24 (5.6%), *T. vaginalis* 86 (20%) (Table 2). Of those, 114 (27%) had a single infection, 52 (12%) had dual infections (11 *C. trachomatis* and *N. gonorrhoeae*; 38 *C. trachomatis* and *T. vaginalis*; 3 *N. gonorrhoeae* and *T. vaginalis*) and 6 (1.4%) had triple infections. STI tests were more frequently positive in women with vaginal discharge syndrome compared with those without. Specifically, *C. trachomatis* was detected in 42% of women with discharge versus 27% without discharge ($P = 0.020$); *N. gonorrhoeae* = 15% versus 4.1%, ($P = 0.002$); *T. vaginalis* = 29% versus 19% ($P = 0.07$).

Of 420 women receiving postnatal Xpert® testing, 78 (19%) tested positive for any STI; *C. trachomatis* 57 (14%); *N. gonorrhoeae* 14 (3.3%); *T. vaginalis* 25 (6.0%). Multiple STIs were detected in 5/30 (17%) women in the aetiological testing group and 11/48 (23%) in the syndromic group. STIs were detected less frequently in women who had received aetiological testing compared with syndromic management during ANC (14% versus 23%; aRR 0.61, 95% CI 0.35–1.05). That was observed for *C. trachomatis* (9.1% versus 18%; aRR 0.57, 95% CI 0.31–0.1.07) and *T. vaginalis* (3.2% versus 9.0%; aRR 0.36, 95% CI 0.14–0.95), but not for *N. gonorrhoeae* (4.6% versus 2.0%; aRR 2.7; 95% CI 0.77–9.4).

Aetiological STI testing was effective in reducing the prevalence of STIs between antenatal and postnatal care visits with 33% (95% CI 23–43%) from 47 to 14%. This difference is attributed to reductions in the prevalence of *C. trachomatis* by 25% (95% CI 16–34%), from 34 to 9.1% and the prevalence of *T. vaginalis* by 23% (95% CI 16–30%), from 26 to 3.2%. Prevalence of *N. gonorrhoeae* did not change (risk difference of 0.9% (95% CI −3.3 to 5.1%) with 5.5% prevalence at ANC and 4.6% at the postnatal visit).

Pregnancy outcomes were available for 689 (82%) women; 348/427 (81%) in the aetiological testing group and 341/414 (82%) in the syndromic management group (see Supplementary material, Table S1). Live birth was reported by 655 (95%) women, stillbirth by 13 (1.9%), miscarriage by 20 (2.9%) and ectopic pregnancy by 1 (0.1%). Among women having a live birth, no statistical difference was detected between the aetiological testing and syndromic management groups with regards to mode of delivery (normal vaginal delivery: 65% versus 71%, aRR 0.76, 95% CI 0.53–1.1), the occurrence of preterm birth (23% versus 23%, aRR 1.2, 95% CI 0.81–1.8) and frequency of infants with low birthweight (15% versus 13%, aRR 1.1, 95% CI 0.66–1.7; Table 3).

Regardless of enrolment arm, when comparing women with and without a detectable STI at their postnatal delivery visit we found no association between a detectable STI and the occurrence of preterm delivery or low birthweight newborns (see Supplementary material, Tables S2–S5).

Table 2. Prevalence of sexually transmitted infections at antenatal care and postnatal care visits in HIV-infected pregnant women in Tshwane, South Africa ($n = 841$)

	Antenatal care visit		Postnatal care visit		RR (95% CI)*	aRR (95% CI)*
	Aetiological testing ($n = 427$)	Syndromic management ($n = 414$)	Aetiological testing ($n = 219$)	Syndromic management ($n = 201$)		
Any STI	172 (40%)	ND	30 (14%)	48 (24%)	0.70 (0.52–0.94)	0.61 (0.35–1.05)
Chlamydia trachomatis	126 (30%)	ND	20 (9.1%)	37 (18%)	0.64 (0.44–0.92)	0.57 (0.31–1.07)
Neisseria gonorrhoeae	24 (5.6%)	ND	10 (4.6%)	4 (2.0%)	1.4 (0.98–2.0)	2.7 (0.77–9.4)
Trichomonas vaginalis	86 (20%)	ND	7 (3.2%)	18 (9.0%)	0.52 (0.28–0.99)	0.36 (0.14–0.95)

aRR, adjusted relative risk; ND, not done; RR, relative risk; STI, sexually transmitted infection.
*Relative risk is calculated for prevalence of infection between aetiological testing and syndromic management at the postnatal visit. Adjustment was done for gestational age at enrolment.

Table 3. Pregnancy outcomes in HIV-infected women non-randomly enrolled to receive aetiological testing or syndromic management for sexually transmitted infections in South Africa

(A) Gestational age at delivery

	Aetiological testing (n = 314)	Syndromic management (n = 327)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Preterm delivery*	73 (23)	74 (23)	1.03 (0.77–1.4)	1.2 (0.81–1.8)
Full term delivery**	241 (77)	253 (77)		

(B) Birthweight

	Aetiological testing (n = 317)	Syndromic management (n = 334)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Low birth weight***	48 (15)	43 (13)	1.2 (0.80–1.7)	1.1 (0.66–1.7)
Birth weight ≥2500 g	269 (85)	291 (87)		

CI, confidence interval; RR, relative risk.
Adjusted relative risk was calculated adjusting for gestational age at enrolment.
*Preterm is defined as delivery at gestational age <37 weeks.
**Full term is defined as delivery at gestational age ≥37 weeks.
***Low birthweight is defined as <2500 g.

However, when comparing women with a positive Xpert® test at either their antenatal or postnatal care visit with women without a detectable STI during their pregnancy in the aetiological group alone, we found *N. gonorrhoeae* infection to be associated with low birthweight: 5/19 (26%) newborns of mothers with *N. gonorrhoeae* infection had low birthweight compared with 20/192 (10%) among mothers without *N. gonorrhoeae* infection (RR 2.5; 95% CI 1.07–6.0, P = 0.056). No other associations between STIs during pregnancy and gestational age or birthweight were observed.

Discussion

Main findings

This prospective study shows a high prevalence of STIs among pregnant women living with HIV infection and attending ANC in South Africa. Though aetiological STI testing during pregnancy is an effective intervention to reduce the burden of STIs around time of delivery, we did not demonstrate any effect on the occurrence of adverse pregnancy outcomes when compared with syndromic management.

Strengths and limitations

Although it was the first of its kind from sub-Saharan Africa, this study had several limitations. First, for reasons of convenience, we used a non-random study design and our results may therefore be affected by unknown bias or unmeasured confounding. Second, lead time bias occurred due to enrolling women attending their first ANC to aetiological testing, whereas women attending for subsequent ANC visits were enrolled to receive syndromic management. This is reflected in the substantial difference in median gestational age at enrolment between the two study groups and the relatively higher frequency of stillbirth and miscarriage in the aetiological testing group. All analyses of birth outcomes were adjusted for gestational age at enrolment to reduce the effects of lead time bias. However, given that the optimal timing of STI management to improve pregnancy outcomes is unknown, it is difficult to predict in which direction this bias may have influenced our findings. Third, we used a 30-day window to test for STIs at the postnatal visit as proxy for STI status at time of delivery. Post-delivery incident infection cannot be ruled out; however, less than 3% of participants reported having resumed sexual intercourse between time of delivery and the postnatal clinic visit when testing was performed. Also, post-delivery selection bias may have occurred whereby women with adverse pregnancy outcomes did not return for follow up, e.g. because the baby died or was admitted to hospital. While we tried to mitigate this by collecting pregnancy outcome data directly from delivery sites, delivery medical records and notes could not be identified for a substantial number of participants. That could have resulted in an underestimation of the occurrence of adverse

pregnancy outcomes. Last, there were poor clinical notes regarding STI treatment provided by clinic nurses during routine ANC visits between study enrolment and postnatal study visits. Also, we did not collect data on the use of cotrimoxazole prophylaxis during pregnancy after the enrolment visit. Consequently, we do not know how many women received additional STI treatment during pregnancy.

Interpretation (in light of other evidence)

The observed prevalence (40%) of STIs in our cohort of pregnant women living with HIV infection was high. A similarly high prevalence of STIs among pregnant women living with HIV was also reported in studies from Cape Town (39% prevalence) and Durban (39% prevalence).[4,34] Various sociodemographic and behavioural factors drive the high and complex burden of STIs in pregnant women in our setting, including economic dependency, multiple and concurrent sexual partnerships, limited efficacy of partner notification and low rates of condom use.[4,29,35]

We implemented the Xpert® CT/NG and Xpert® TV tests within ANC clinics for same-day detection and targeted antimicrobial treatment of STIs. That intervention has demonstrated high acceptability, feasibility and reliability within primary care settings globally.[36,37] Implementation of aetiological testing during ANC resulted in a significantly lower prevalence of STIs around the time of delivery compared with syndromic management. Our finding was attributed to a two-fold lower prevalence of *C. trachomatis* and three-fold lower prevalence of *T. vaginalis* in women receiving aetiological testing compared with syndromic management. Nevertheless, despite the benefits of aetiological STI testing, the prevalence of STIs was still unacceptably high (~14%) at the time of delivery. Additional interventions, including repeat aetiological STI testing during the third trimester, strengthening of partner notification and treatment, and primary prevention efforts are required to further reduce the burden of STIs in pregnant women.[29]

The pregnancy outcomes observed in our study are reflective of the wider South African public healthcare context where the prevalence of stillbirth is 1–3%, and preterm delivery and low birthweight infants occur in 10–25% of pregnancies.[38–42] Our observed association of *N. gonorrhoeae* infection during pregnancy with low birthweight confirms previous reports.[43,44] However, we did not observe any difference in the occurrence of adverse birth outcomes between (1) women with and without STIs and (2) etiological testing and syndromic management groups. This probably reflects the complex relationship between STIs and pregnancy outcomes.

Among those studies reporting on the effect of STIs during pregnancy on preterm delivery and/or low birthweight, there is large heterogeneity with regards to study population, sample size, definition of outcome, and presence and strength of associations.[8–16] Pathogenic inflammatory mechanisms have been suggested to influence adverse pregnancy outcomes.[7] However, the optimal timing for testing and treatment of STIs during pregnancy remain to be determined. A study by Folger suggested that the detection and treatment of *C. trachomatis* before 20 weeks of gestation was more effective than at a later stage of pregnancy.[12] However, a sub-analysis of our data did not show any difference in pregnancy outcomes related to the detection and treatment of STIs in women before or after 20 weeks gestation [data not shown]. Furthermore, the complex interplay between HIV infection, STIs and the vaginal microbiome may also have a impact on pregnancy outcomes.[45–48] Unfortunately, our study cohort characteristics and data collected limit our ability to address these issues.

Conclusion

The burdens of STIs and adverse pregnancy outcomes are high in women living with HIV in sub-Saharan Africa. This warrants a strong public health response and increased resource allocation. Implementation of aetiological STI testing during ANC can substantially reduce prevalent STIs among pregnant women. It is possible that by decreasing the burden of STIs during pregnancy the occurrence of adverse outcomes may be reduced. However, further research is required to identify the critical period during which STIs impact birth outcomes, the most effective gestational age range in which to conduct STI screening and treatment, and the optimal implementation strategies for aetiological testing during pregnancy.

Disclosure of interests

Dr Klausner reports personal fees from Cepheid, during the conduct of the study, and personal fees from Danaher, outside the submitted work. None of the other authors declares a conflict of interest. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

JDK and AM-M were the principal investigators of this study and wrote the study protocol with technical expertise from RPHP and UDF. LdV managed the data collection and quality assurance processes. Study implementation was supervised by RPHP, JDK, UDF and AM-M. RPHP performed the data analysis and wrote the draft version of the manuscript; all authors contributed to the final version.

Details of ethics approval

Study approval was provided by the Institutional Review Board of the University of Pretoria, Faculty of Health

Sciences, Research Ethics Committee (reference number: 401/2015; approved 26 November 2015).

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Birth outcomes in a cohort of HIV-infected pregnant women, by study arm, in Tshwane, South Africa (n = 689).

Table S2. Gestational age (a) and birthweight (b) in HIV-infected women with and without sexually transmitted infection detected at their postnatal visit in Tshwane, South Africa.

Table S3. Gestational age (a) and birthweight (b) in HIV-infected women with and without *Chlamydia trachomatis* infection detected at their postnatal visit in Tshwane, South Africa.

Table S4. Gestational age (a) and birthweight (b) in HIV-infected women with and without *Neisseria gonorrhoeae* infection detected at their postnatal visit in Tshwane, South Africa.

Table S5. Gestational age (a) and birthweight (b) in HIV-infected women with and without *Trichomonas vaginalis* infection detected at their postnatal visit in Tshwane, South Africa. ■

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