CAP016 PrEP in pregnancy - a phase 2b open-label randomised control safety study of daily oral TDF/FTC when used as pre-exposure prophylaxis for HIV prevention in pregnant and lactating women

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Background

- Daily oral TDF/FTC has been widely studied and recommended as a safe option for prevention of HIV in men and women at substantial risk.
- With limited safety data, TDF/FTC has also been recommended for pregnant women on the assumption that the benefit of TDF/FTC in prevention of HIV outweighs the risk of adverse pregnancy outcomes.
- PrEP policy change for pregnant women in SA was effective in December 2019.

Aim

- To explore the safety of Truvada (TDF/FTC) when used as PrEP during pregnancy and lactation.

Methods

Study Design: We conducted an open-label randomized trial of oral TDF/FTC used as PrEP among HIV-1 seronegative pregnant women in South Africa (NCT03227731). Pregnant women were randomised to either initiating oral TDF/FTC in pregnancy (Treatment Arm) or deferred until cessation of breastfeeding (Control Arm) between September 2017 and December 2019. Women were followed monthly until delivery.

Eligibility: At least 18 years old. Confirmed HIV-1 uninfected.Willing to provide screening informed consent Currently pregnant Considered high risk for HIV infection, Unprotected sex during pregnancy, HIV status of current sexual partner is positive or unknown, Plans to deliver in the study affiliated hospital.

Study Visits: Enrolment <14 weeks gestation, 4 weekly antenatal visits until delivery, 2 weeks, 6 weeks and 4 weekly postnatal visits until 18 months.

Study Investigations: Clinical assessments, vitals and HIV tests at every scheduled visit. Laboratory investigations included CrCl, Chemistry and Haematology at alternate study visits. Plasma and DBS storage at every study visit. DBS was used to measure TFV levels.

Study Measures: Pregnancy and neonatal outcomes, Grade 2 or higher clinical and laboratory events for mother-infant pairs until 6 weeks postdelivery. HIV Incidence and TDF/FTC adherence.

Primary Endpoints: Pregnancy and Neonatal Outcomes

Preterm Birth- A preterm birth was defined as a livebirth <37 weeks gestation and a severe preterm birth as a livebirth <34 weeks gestation. **Gestational age by early ultrasound.** *Stillbirth-* Baby born with no signs of life at or after 22 weeks' gestation or dead fetus of 1000 g or more at birth. *Spontaneous abortion or miscarriage-* We used the WHO definition which defines a spontaneous abortion or miscarriage as a pregnancy loss before 22 weeks of gestation or expulsion or extraction of a fetus weighing 500 g or less. *Low birth weight-* Birth weight of an infant of 2,499 g or less, regardless of gestational age. Low birth weight was further categorised into very low birth weight (less than 1500 g) and extremely low birth weight (less than 1 000 g) *Small for gestational age-* <10th percentile using WHO norms for weight-for-age and ultrasound derived gestational age at delivery *Maternal Adverse Events:* Maternal Grade 3 or higher adverse events including clinical signs, symptoms, laboratory findings and diagnoses. Maternal Grade 2 or higher chemistry abnormalities – creatinine clearance rate, and abnormal liver function (ALT, AST) *Neonatal Adverse Events:* Neonatal death within 14 days of birth, Grade 3 or higher adverse events that include clinical signs and symptoms, laboratory abnormalities and final diagnoses within 14 days of birth; and Serum creatinine at birth

Results

We report pregnancy and neonatal outcomes for 252 and 248 women in the PrEP and Control arms respectively. The mean(SD) gestational age at randomization were 17.1(5.1) and 17.6(5.3) weeks respectively.

Baseline Characteristics	Immediate PrEP (n=271) N (%)	Deferred PrEP (n=269) N (%)
Age (Years) Median (IQR)	23 (20; 26)	23 (20; 26)
Education N (%)		
Primary-Secondary	60 (22.1%)	63 (23.4%)
Matriculation	176 (49.6%)	179 (50.4%)
Tertiary	35 (12.9%)	27 (10.0%)
Gravidity Mean (SD)	1.8 (0.9)	1.8 (0.9)
Previous Pregnancies	144	134
Complications	7 (4.86)	9 (6.71)
Term Births (≥37 weeks)	128 (88.89)	129 (96.27)
Preterm Births (<37 weeks)	7 (4.86)	5 (3.47)
Stillbirths	5 (3.47)	6 (4.48)
Spontaneous Abortions	20 (13.89)	18 (12.50)
Neonatal Deaths	4 (2.78)	2 (1.39)
Gestational Age at Enrolment (wk) Mean (SD)	16.7 (5.2)	17.3 (5.3)

Results cont.

Preterm Births

	Immediate PrEP (n=250) N (%)	Deferred PrEP (n=247) N (%)	Total (n=497) N (%)
Preterm (< 37 weeks) by US (All Births n=497)	23 (9.20)	22 (8.91)	45 (9.05)
Using US to measure gestational age the 2-sided risk difference is -0.3% (90% CI -4.5% to 3.9%). The 40% relative equivalence is -3.6% to 3.6%. Since the observed confidence intervals overlaps the prior established margins we cannot conclude equivalence. The study is most likely underpowered for the test for equivalence.			
Preterm (< 37 weeks) by US (Live Births n=478)	15 (6.25)	16 (6.72)	31 (6.49)
Preterm (<37 weeks) By LMP (Live Births)	29 (13.18)	40 (18.69)	69 (15.90)
Using LMP to measure gestational age the 2-sided risk difference is 3.99% (90%CI -6.2% to 8.6%). The margin specified in the protocol is 7.5% and the upper margin of the 90% CI exceeds this boundary. Thus we have concluded that the two arms are not equivalent.			
Very Preterm (<34 weeks) by US (All Births)	10 (4.00)	11 (4.45)	21 (4.23)
Using US to measure gestational age the 2-sided risk difference is 0.5% (90%CI -1.4% to 2.5%). The 50% relative equivalence margins is -2.15% to 2.15%. Since the observed CI overlaps the prior established margins we cannot conclude equivalence. The study is most likely underpowered for the test for equivalence.			

Still Births

	Immediate PrEP (n=252) N (%)	Deferred PrEP (n=248) N (%)	Total (n=500) N (%)
Stillbirths	10 (3.97)	7 (2.82)	17 (3.40)
Prevalence of stillbirths is slightly higher (3.4%) than expected in the SAP (2.2%). From the model the 2-sided risk difference is -1.1% (90%CI -3.8% to 1.5%). The 45% relative equivalence margin is -1.53% to 1.53%. Due to small numbers, the observed confidence intervals overlaps the prior established margins and we cannot conclude equivalence.			

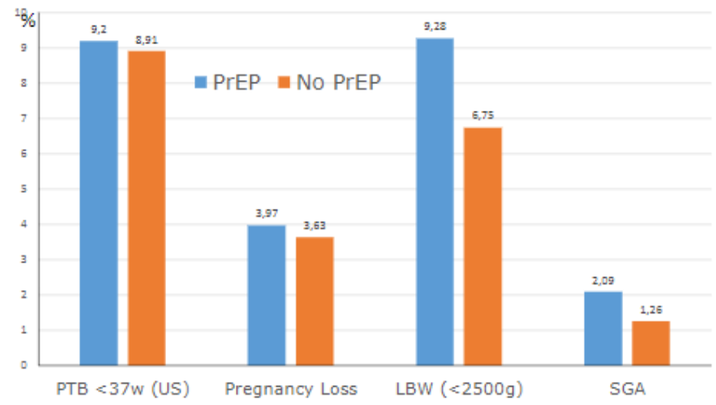
Signs and Symptoms

	Immediate PrEP (n=271) N (%)	Deferred PrEP (n=269) N (%)
Any Sign or Symptom (Participants)	77 (28.41)	95 (35.32)
Specific Sign/Symptom (Events) at any antenatal visit		
Total	304 (54.7)	252 (45.3)
Abnormal Vaginal Discharge	30 (9.9)	41 (16.3)
Lower Abdominal Pain	30 (9.9)	25 (9.9)
Non-Allergic Rash	8 (2.6)	6 (2.4)
Vaginal Bleeding	5 (1.6)	4 (1.6)
Epigastric Burning	5 (1.6)	5 (1.9)
Vaginal Warts	4 (1.3)	4 (1.6)
Vaginal Pruritis	14 (4.6)	17 (6.7)
Abnormal Urine Dipstick	103 (33.9)	95 (37.7)
Headache	15 (4.9)	4 (1.6)
Loss of Appetite	7 (2.3)	4 (1.6)
Cough	2 (0.6)	6 (2.4)
Nausea	9 (2.9)	2 (0.8)
Vomiting	35 (11.5)	6 (2.4)
Diarrhoea	6 (1.9)	6 (2.4)
Dysuria	6 (1.9)	8 (3.2)
Elevated Blood Pressure	5 (1.6)	4 ((1.6)
Other	20 (6.6)	15 (5.9)
Incidence Rate of Sign/Symptom	1.122	0.937
Incident rate ratio 1.19 (95% CI 1.00 to 1.42). PrEP arm had significantly higher incidence of signs and symptoms (p=0.0342). Headache OR 3.2 (1.1-9.8) p = 0.0349 . Nausea/Vomiting OR 5.2 (2.4-11.2) p < 0.0001. Both side effects were significantly more common in PrEP arm and occurred within 1 week of PrEP initiation.		

Infant Outcomes

	Immediate PrEP (n=252) N (%)	Deferred PrEP (n=248) N (%)
Live Births	242 (96.0)	239 (96.4)
StillBirths	10 (3.97)	7 (2.8)
Spontaneous Abortions	0	2 (0.8)
Birth Weight (kg) Mean (95%CI)	3.14 (3.1-3.2)	3.08 (3.02-3.14)
No difference in birthweight (p=0.267) 19 infants with no birth weight recorded		
Low Birth Weight		
<1.5 kg	2 (0.84)	2 (0.84)
1.5-2.499 kg	20 (8.44)	14 (5.91)
>2.499 kg	215 (0.72)	221 (3.25)
No difference in birth weight.		
Very Low Birth Weight (<1500g)	2 (0.84)	2 (0.84)
Risk difference is 0. The inferiority margins for this outcome is -1.2 to 1.2%. Since the 90% CI is -1.4% to 1.4% overlaps the margins we cannot conclude non-inferiority. This is most likely the esult of a small sample size and thus lack of power. The observed difference is 0%.		
Gestational Age		
LGA (>90%)	11 (4.6%)	2 (0.84)
AGA	213 (89.1)	225 (94.14)
SGA (<10%)	5 (2.09)	3 (1.26)
IUGR (<3%)	1 (0.42)	0
Neonatal Deaths	0	3
Sudden Infant Death (n=1) and Extremely Low Birth Weight (n=2)		

Results contd.



HIV Incidence

	Immediate PrEP (n=271) N (%)	Deferred PrEP (n=269) N (%)
HIV Infections (%)	3 (1.1)	1 (0.4)
HIV Incidence per 100 person years	3.3	1.1
The specified non-equivalence criteria were incidence of 3/100 py in the PrEP arm or a 50% increase in PrEP arm over the control. Both these criteria have been met observationally. The incidence rate ratio is 2.9 (90%CI 0.3 to 75.1). This interval contains 1 and the wide intervals reflect the lack of precision due to the sample size.		

Maternal Lab Toxicity

	Immediate PrEP (n=267)	Deferred PrEP (n=265)
AST (Severity Grade 2 or higher) n(%)	0	2 (0.8%)
No Grade 3 or higher AST abnormalities at any time point during pregnancy in either arm.		
ALT (Severity Grade 2 or higher) n(%)	1 (0.4%)	1 (0.4%)
No Grade 3 or higher ALT abnormalities at any time point during pregnancy in either arm.		
Serum Creatinine (umol/L) Baseline Mean (SD)	42.4 (6.8)	42.5 (7.3)
Creatinine Clearance (mls/min) Baseline Mean (SD)	204.5 (45.0)	200.1 (47.7)
Serum Creatinine (Severity 2)	1 (0.4%)	4 (1.5%)
No Grade 3 or higher Serum Creatinine Abnormalities at any time point during pregnancy in both arms.		

TDF Detection in the PrEP Arm (Adherence)

Antepartum Study Visit	TNF Detected n(%)	TNF Undetected n(%)
2 weeks	0	1 (100)
4 weeks	8 (100)	0
8 weeks	31 (79.5)	8 (20.5)
12 weeks	44 (68.8)	20 (31.4)
16 weeks	41 (63.1)	24 (36.9)
20 weeks	40 (63.5)	23 (36.5)
24 weeks	11 (55)	9 (45)
Total	175 (67.3)	85 (32.7)
In a cross-sectional sample 32.7% of participants had undetectable level of TNF at the time of sampling. The proportion of participants with detectable levels of TNF decreased with timing of sampling.		

TDF Levels Translated to Adherence in the PrEP Arm

Doses per week	TFV-DP (fmol/punch)	Number (%; 95%CI)
7 doses/wk	>650	41 (23.6; 17.5-30.6)
2-6 doses/wk	200-649	84 (48.3: 40.7-71.8)
2 doses/wk	<200	49 (28.2; 21.6-35.5)

Conclusion

The observed risk of adverse pregnancy and neonatal outcomes was similar between the Immediate PrEP and Deferred PrEP Arms. Early stopping of accrual due to change in the national PrEP policy led to a smaller sample size with resulting loss of power to conclude equivalence between PreP and Standard of care arms formally.

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Study Participants
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