



## HPTN083 interim results: Pre-exposure prophylaxis (PrEP) containing long-acting injectable cabotegravir (CAB-LA) is safe and highly effective for cisgender men and transgender women who have sex with men (MSM, TGW)

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**Background:** HPTN 083 is a Phase 2b/3 randomized multicenter double-blind, double-dummy, clinical trial evaluating safety and efficacy of long-acting injectable cabotegravir (CAB) compared to daily oral TDF/FTC for HIV PrEP. The blinded trial was stopped at a pre-planned interim DSMB review in May 2020.

**Methods:** HIV-uninfected MSM and TGW at increased HIV risk were randomized 1:1 to either active CAB +TDF/FTC placebo (oral cabotegravir(CAB) for 5 weeks, then IM injections every 8 weeks for 148 weeks) or active TDF/FTC+CAB placebo (oral placebo for 5 weeks, then placebo injections on the same schedule). All participants were offered daily oral TDF/FTC for 48 weeks after last injection. The primary endpoints were incident HIV infection and grade 2 or higher clinical and laboratory events.

**Results:** Participants were enrolled at 43 sites in Africa, Asia, Latin America, and the US (N=4566); median age: 26y (IQR 22-32); 12%TGW (n=567); 50% of US participants were Black (n=844). Participant retention at 6, 12, and 24 months was 91%, 87%, and 74%, respectively. Fifty-two incident HIV infections were observed over 6385 person-years, with overall HIV incidence 0.81% (95%CI 0.61-1.07); 39 infections were in the TDF/FTC arm (incidence 1.22%, 95%CI 0.87-1.67); 13 infections were in the CAB arm (incidence 0.41%, 95%CI 0.22-0.69%); HR: 0.34 (95%CI 0.18-0.62). Blinded study product injections covered 92% of person-years. Adherence to oral TDF/FTC was high; in a random subset of 372 TDF/FTC participants 87% had plasma samples with detectable concentrations, and 75% had concentrations consistent with daily dosing. CAB and TDF/FTC were both well tolerated; most adverse events were mild/moderate and balanced between arms. Injection site reactions, pyrexia, and hypertension were significantly more common in CAB participants, nausea was significantly more common in TDF/FTC participants. Injection intolerance led to discontinuation in 46 (2.2%) active CAB-LA recipients and was associated with the severity of the intolerance/reaction.

**Conclusions:** CAB and TDF/FTC were both safe and highly effective for PrEP in HPTN083, with estimated HIV incidence in the CAB arm 66% lower than in the TDF/FTC arm. CAB is the first injectable agent proven effective for HIV PrEP; a companion trial in cisgender women is ongoing.





## Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana

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**Background:** The Tsepamo study last reported neural tube defect (NTD) data collected through March 2019 (Zash et al, *NEJM* 2019), with 0.3% prevalence following exposure to dolutegravir at conception compared with 0.1% following exposure to non-DTG antiretrovirals at conception. The study is ongoing and data collected through April 2020 are now reported.

**Methods:** The Tsepamo Study conducts birth outcomes surveillance study at government hospitals throughout Botswana, currently covering ~70% of all births. Midwives perform surface examinations of all live births and stillbirths and describe abnormalities. Research assistants photograph major abnormalities after maternal consent, which are reviewed by a birth defects expert blinded to exposures. Prevalence of NTDs was determined by maternal HIV and antiretroviral exposure status (95%CI by Wilson method) and the primary analysis evaluated prevalence differences by exposure status (95%CI by Newcombe method).

**Results:** Since March 2019, 39,200 additional births were recorded, including 1908 additional DTG conception exposures. Since August 2014, there have been a total of 158,244 deliveries; 153,899 (97.2%) had an evaluable infant surface exam, with 126 (0.08%, 95%CI 0.07%, 0.09%) NTDs identified (83 with photo, 43 by description only). Among women on dolutegravir at conception, 7/3591 NTDs occurred (0.19%; 95%CI 0.09%, 0.40%): 3 myelomeningoceles, 1 anencephaly, 2 encephalocetes, and 1 iniencephaly. In comparison, NTDs occurred in 21/19,361 (0.11%; 95%CI 0.07%, 0.17%) women delivering on any non-dolutegravir antiretrovirals from conception, 8/10,958 (0.07%; 95%CI 0.03%, 0.17%) on efavirenz from conception, 2/4,581 (0.04%; 95%CI 0.1%, 0.16%) on dolutegravir started in pregnancy, and 87/119,630 (0.07%; 95%CI 0.06, 0.09%) HIV-uninfected women. NTD prevalence differed non-significantly between dolutegravir and any non-dolutegravir antiretrovirals from conception (0.09% difference; 95%CI -0.03%, 0.30%).

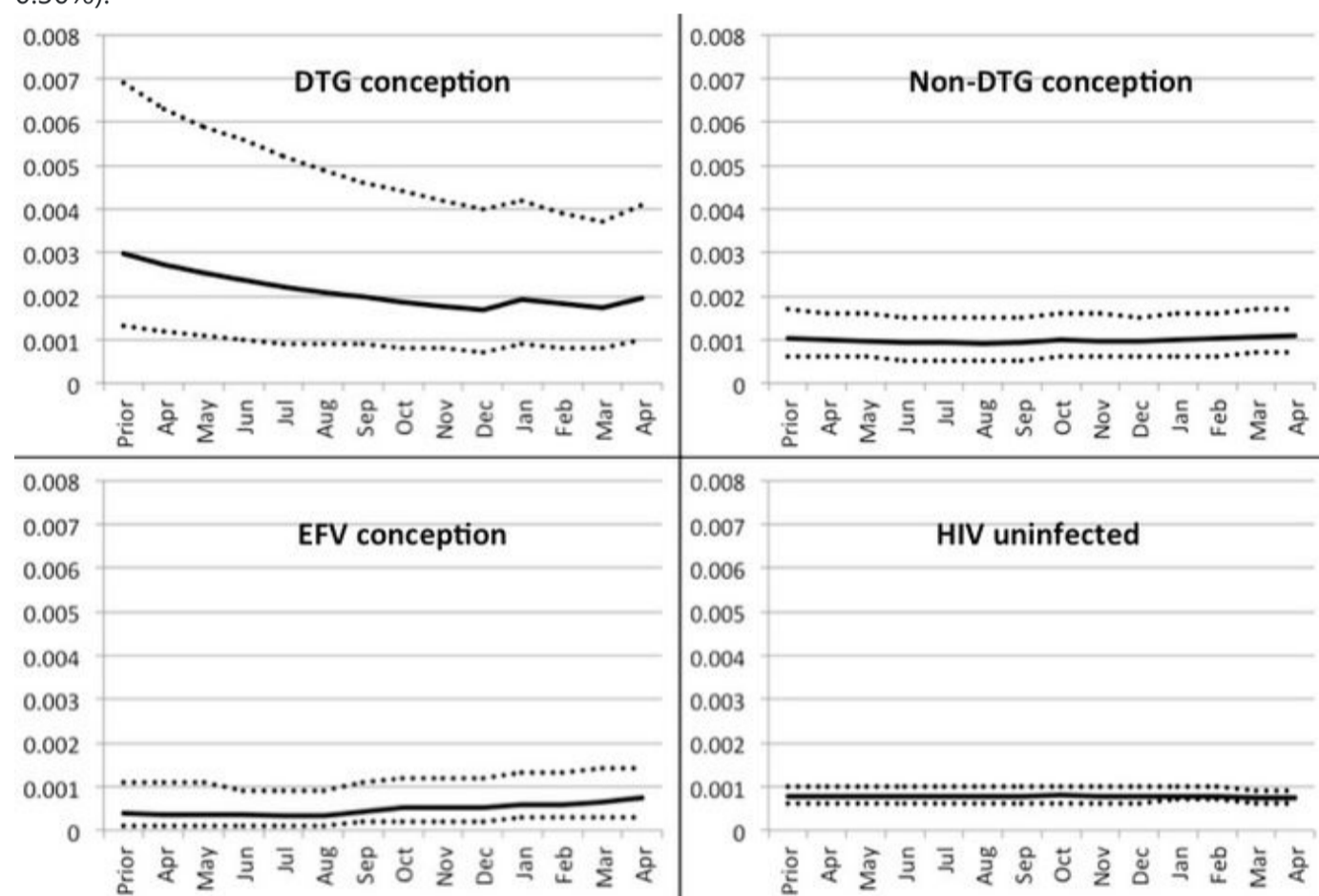


Figure. Prevalence of Neural Tube Defects (and 95% CI) from March 2019-April 2020 in Tsepamo

**Conclusions:** After a period of decline since the original safety signal, prevalence of NTDs among infants born to women on dolutegravir at conception may be stabilizing at approximately 2 per 1000.



## The ADVANCE trial: Phase 3, randomised comparison of TAF/FTC+DTG, TDF/FTC+DTG or TDF/FTC/EFV for first-line treatment of HIV-1 infection

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**Background:** In low- and middle-income countries, most treatment-naïve people living with HIV (PLWH) take tenofovir disoproxil fumarate (TDF) with emtricitabine FTC (or lamivudine (3TC)) and efavirenz (EFV). Dolutegravir (DTG) and tenofovir alafenamide (TAF) are recommended in international guidelines, but clinical experience with these ARVs in sub-Saharan Africa is limited. In South Africa, over 10% of patients have transmitted NNRTI drug resistance.

**Methods:** We conducted a 96-week, open-label randomised trial in South Africa, comparing TAF/FTC+DTG, TDF/FTC+DTG and TDF/FTC/EFV. Inclusion criteria included age  $\geq 12$  years, no prior ART  $> 30$  days, creatinine clearance  $> 60$  mL/min ( $> 80$  mL/min if  $< 19$  years), and HIV-1 RNA  $> 500$  copies/mL. Pregnancy and tuberculosis (TB) were exclusion criteria. There was no screening for baseline drug resistance, consistent with South African treatment guidelines. The primary treatment failure endpoint was 96-week HIV-1 RNA  $> 50$  copies/mL, discontinuation or missing data (Intent-to-treat population, non-inferiority margin -10%, significance level  $p=0.017$ , adjusted for multiple comparisons). We report 96-week efficacy and safety data.

**Results:** We randomised 1053 PLWH between February 2017 and May 2018: 99% black, 59% female, mean age 32 years, with mean CD4 336 cells/uL. At week 96, the percentage of participants with HIV RNA  $< 50$  copies/mL was 78.6% for TAF/FTC+DTG, 78.3% for TDF/FTC+DTG and 73.5% for TDF/FTC/EFV. In the on-treatment analysis, 96% of participants on TAF/FTC+DTG, 95.7% on TDF/FTC+DTG and 95.5% on TDF/FTC/EFV had HIV RNA  $< 50$  copies/mL at Week 96. Both DTG arms demonstrated non-inferior efficacy versus the EFV arm. Overall, 206/244 (84%) of treatment failures were from discontinuation. Clinical adverse events and laboratory abnormalities were similar between treatment arms.

**Table 1, ADVANCE trial results at Week 96**

Treatment arm	TAF/FTC+DTG	TDF/FTC+DTG	TDF/FTC/EFV
n	n=351	n=351	n=351
Week 96 Efficacy			
HIV RNA $< 50$ copies/mL	276 (78.6%)	275 (78.3%)	258 (73.5%)
HIV RNA $\geq 50$ copies/mL	11 (3.1%)	14 (4.0%)	15 (4.3%)
Discontinuation for adverse events	2 (0.6%)	1 (0.3%)	10 (2.8%)
Discontinuation for other reasons	64 (18.2%)	62 (17.7%)	80 (22.8%)
Treatment-emergent drug resistance	0 (0.0%)	2 (0.6%)	14 (4.0%)
Female mean weight change	+8.1kg	+4.8kg	+3.2kg
Male mean weight change	+5.4kg	+3.6kg	+1.1kg
Treatment emergent obesity	47 (18%)	28 (11%)	18 (8%)
Treatment emergent metabolic syndrome	23 (8%)	16 (6%)	10 (4%)

**Conclusions:** In the ADVANCE study, TAF/FTC+DTG and TDF/FTC+DTG demonstrated non-inferior efficacy versus TDF/FTC/EFV, with low rates of virologic failure in all three arms despite country-level background NRTI/NNRTI resistance.



## The first long-term remission of chronic HIV-1 infection without myeloablation?

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**Background:** A 34 yo Brazilian male received HIV diagnosis on October 11th, 2012. Baseline CD4+ T cell count was 372 cells/microliter and viral load (VL) was 20,221 cp/mL, suggesting chronic HIV infection. On December 12st, 2012 he started antiretroviral treatment with TDF/3TC/EFV maintaining VL below detection limits (BDL) since then. In 2016, he was enrolled in clinical trial NCT02961829 as one of five individuals under highly intensified ART (baseline ART+dolutegravir+maraviroc) and nicotinamide (500 mg twice daily) for 48 weeks. Nicotinamide (NAM) was chosen because of inhibition of immune exhaustion-related lymphocyte apoptosis related to its inhibitory effects on PARPs, and potential multiple mechanisms of antilateness such as Class III HDACs inhibition (NAM) and SUV39 Deacetylation (NAD). Maraviroc was also chosen due to potential HIV antilateness property.

**Methods:** Viral DNA was measured as an estimate of the viral reservoir by published qPCR techniques. Antibody quantitation was performed using the Abbott ARCHITECT HIV Ag/Ab Combo assay (Abbott, IL, USA). Mathematical modelling performed according Conway et al., 2015.

**Results:** Among 30 participating patients from NCT02961829, this study subject was the only experiencing viral load blips during experimental treatment, at weeks 16 (VL BDL with target detected) and 24 (56 cp/mL). Viral DNA showed low-level positivity in PBMCs and rectal biopsy at baseline and week 48. Antibody quantitation over time (RLU [S/CO] in duplicates) was 91.8 (baseline), 75.6 (week 12), 60.8 (w24), 56.8 (w36) and 58.0 (w48). In March 28th 2019, he underwent analytical treatment interruption (ATI). HIV Plasma VL performed every 3 weeks after ATI was BDL up to 57 weeks, and total HIV DNA on PBMCs was undetectable pre-ATI and 57 weeks post-ATI. EIA rapid test kit (TR DPP HIV 1/2 Bio-Manguinhos) on February 3rd 2020 was negative. Mathematical modelling (Conway et al., 2015) showed that the antiapoptotic and antiproliferative effects might improve clearance of productively infected cells, but only the additional contribution of the antilateness effect might induce long-term remission.

**Conclusions:** Although still an isolated case, this might represent the first long-term HIV remission without myeloablation/stem cell transplantation. Further analyses such as viral cultivation and sequential HIV antibody profile/detection are ongoing.