

Neural Tube Defects and Major External Structural Abnormalities by Antiretroviral Treatment Regimen in Botswana: 2014-2022

R. Zash,^{1,2,3} M. Diseko,² L.B. Holmes,⁴ D. L. Jacobson,⁵ E. Caniglia,⁶ S. Brummel,³ G. Mayondi², J. Mabuta², C. Fennell,³ T. Makoni,¹ T. Gaolathe,^{2,7} S. Lockman^{2,3,8}, J. Makhema², R. Shapiro^{1,2,3},

1. Beth Israel Deaconess Medical Center, Infectious Diseases, Boston, United States, 2. Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, 3. Harvard T.H. Chan School of Public Health, Boston, United States, 4. MassGeneral Hospital for Children, Boston, United States, 5. Harvard T.H. Chan School of Public Health, Center for Biostatistics in AIDS Research, Boston, United States, 6. University of Pennsylvania, Philadelphia, United States, 7. University of Botswana, Gaborone, Botswana, 8. Brigham and Women's Hospital, Infectious Diseases, Boston, United States

BACKGROUND

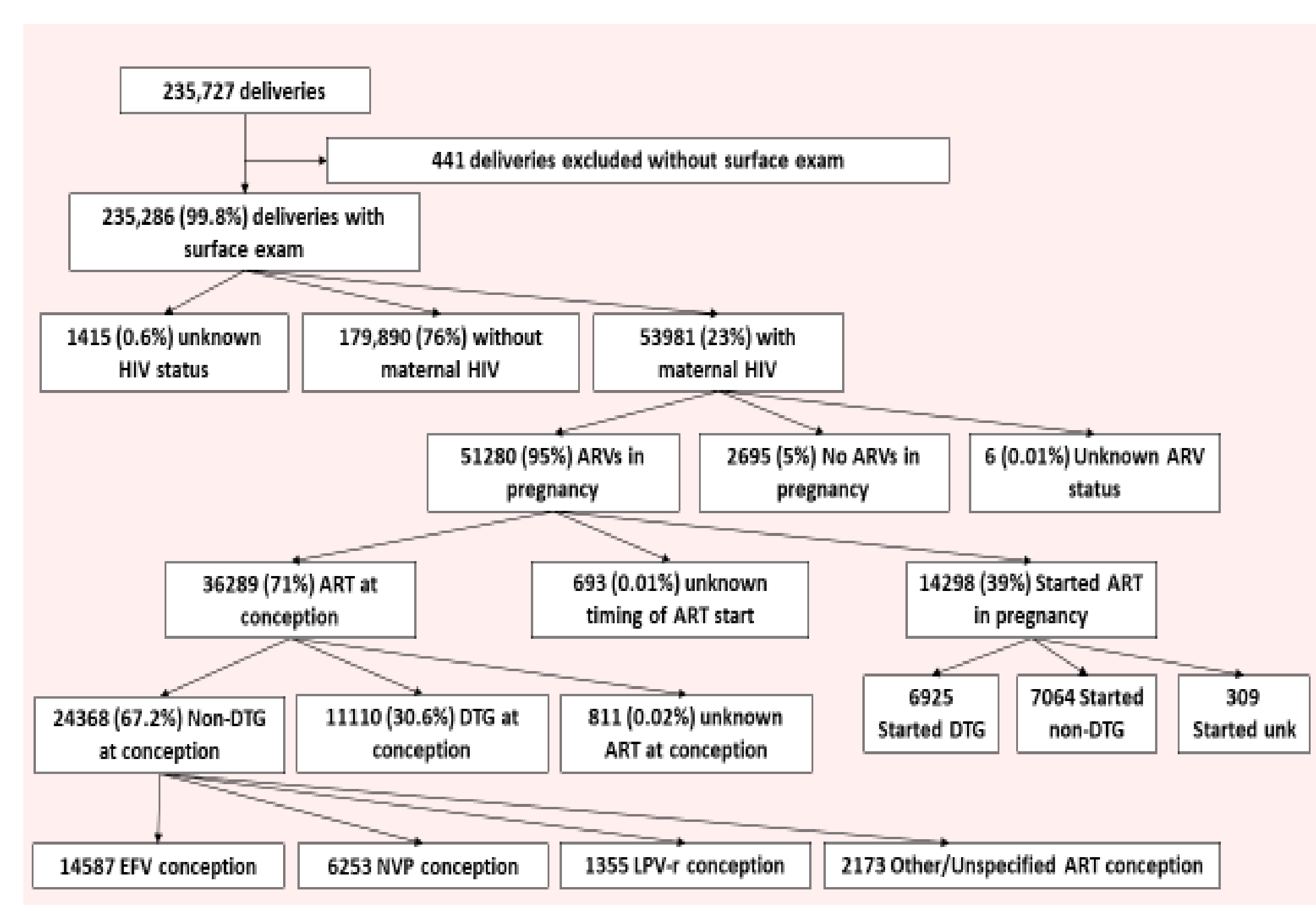
- Since August 2014, the Tsepamo Study has abstracted data from maternity records at government maternity wards across Botswana
 - Covers more than 67% of all deliveries in the country
- In 2018, Tsepamo reported a preliminary safety signal associating neural tube defects (NTDs) with dolutegravir (DTG) exposure from conception
 - There has been attenuation of the original signal over time
- We now report on complete data collected through August 2022 in Tsepamo

METHODS

- Abnormalities noted during neonatal surface exam of live births and stillbirths are described and photographed with maternal consent
- Abnormalities are considered 'major' if they have medical, surgical or cosmetic significance
 - NTDs include meningocele, myelomeningocele, anencephaly, encephalocele and iniencephaly
- Primary analyses evaluated age-adjusted prevalence differences (aPD) with 95% confidence intervals using a binomial model with identity link

RESULTS

Figure 1. Tsepamo Study Population, Aug 2014-Aug 2022



Major Structural Abnormalities were identified in 1455 deliveries (0.62%, 95% CI 0.59%,0.65%) and did not differ by exposure category (Table 1).

Table 1. Major external structural defects by exposure category

	# of major abnormalities	Prevalence (95% CI) of major abnormalities	Age adjusted prevalence difference (95% CI)
DTG conception (N=11,110)	83	0.75% (0.60%, 0.95%)	ref
Non-DTG Conception (N=24,365)	185	0.76% (0.66%, 0.88%)	-0.01% (-0.26%, 0.11%)
EFV conception (N=14,584)	118	0.81% (0.68%, 0.97%)	0.01% (-0.20%, 0.22%)
NVP conception (N=6253)	46	0.75% (0.55%, 0.98%)	-0.14% (-0.38%, 0.11%)
LPV-r concept (N=1355)	16	1.18% (0.73%, 1.91%)	0.36% (-0.21%, 0.93%)
DTG started during pregnancy (N=6924)	42	0.59% (0.45%, 0.82%)	-0.11% (-0.35%, 0.14%)
Non-DTG started during pregnancy (N=7062)	47	0.67% (0.50%, 0.88%)	-0.04% (-0.29%, 0.21%)
Without HIV (N=179,871)	1066	0.59% (0.56%, 0.63%)	-0.11% (-0.28%, 0.05%)

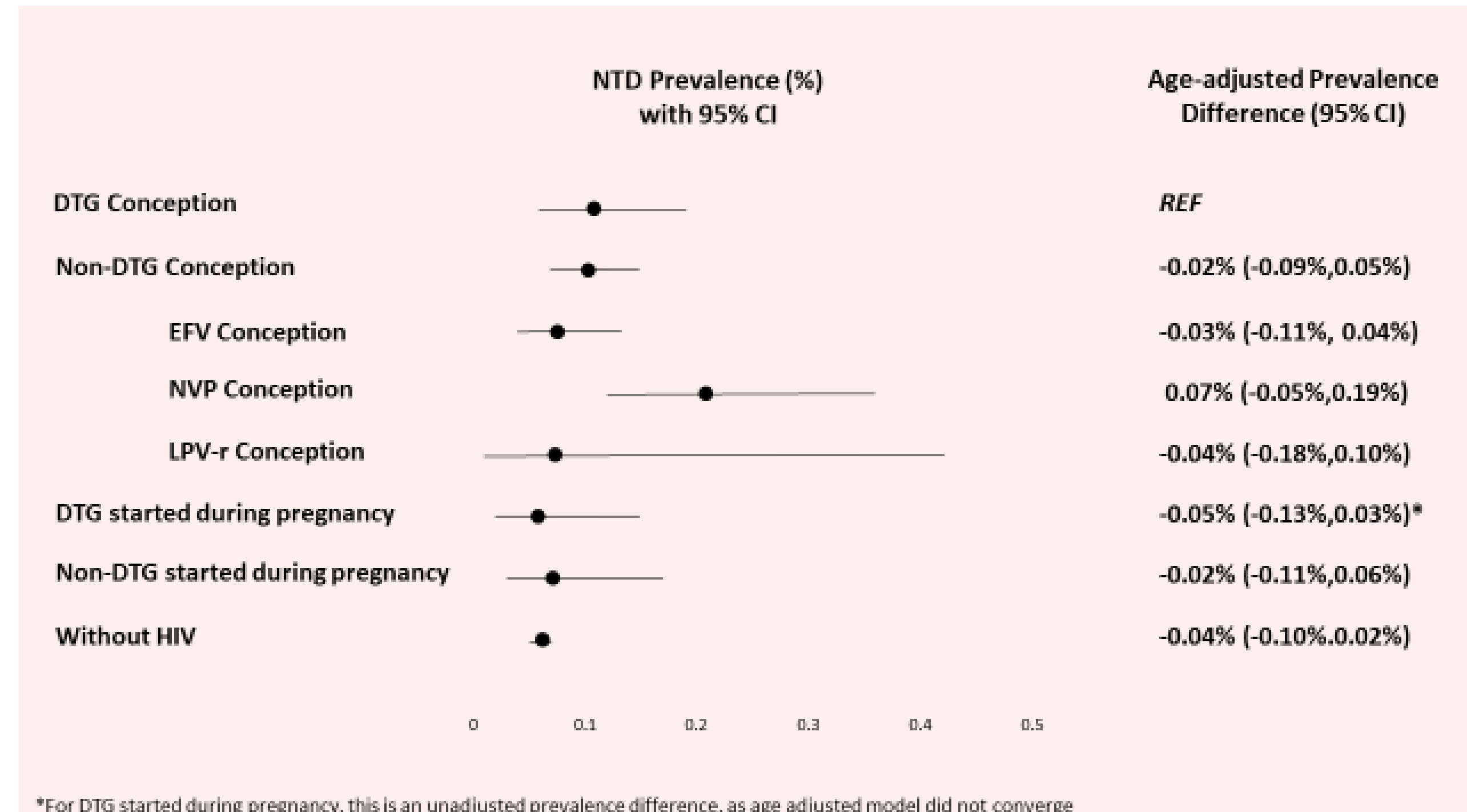
The most common major abnormalities were:

- club foot (0.18%),
- hydrocephalus (0.09%),
- NTDs (0.07%),
- postaxial polydactyly type A (0.04%),
- abdominal wall defects (0.04%) and
- cleft lip (0.04%)

Overall, there were 162 deliveries with NTDs (0.07%, 95% CI 0.06% - 0.08%), without differences by exposure category (Figure 2)

- NTD prevalence was higher when conception occurred in the early/dry period (May-July) than the late/dry period (Aug-Oct).
- NTD prevalence differed significantly by calendar year, with highest prevalence in 2014, 2015, and 2017
 - No national program for folate fortification of grains during study period, and no changes in Botswana guidelines for pre-conception folic acid supplementation

Figure 2. NTD prevalence and age-adjusted prevalence difference by exposure category

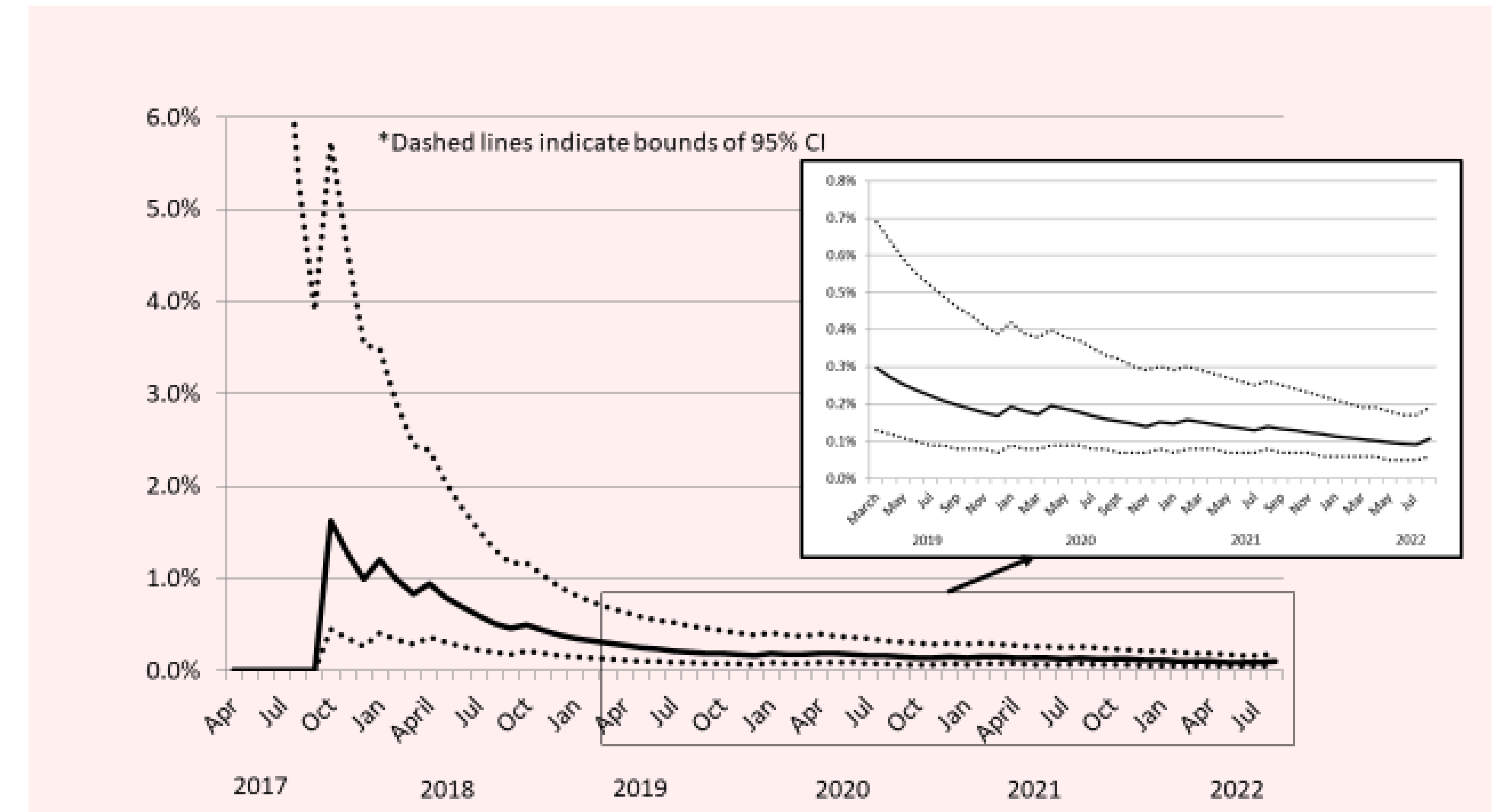


*For DTG started during pregnancy, this is an unadjusted prevalence difference, as age adjusted model did not converge

For DTG-conception exposures, NTD prevalence among pregnancies conceived in 2017 (the first year after the DTG rollout) was 0.53%, which was significantly higher than all subsequent years (0.09%, range 0.06%-0.10%)

- The prevalence of factors associated with NTDs (maternal age, diabetes, weight >90kg, antiepileptic medication, folic acid supplementation at conception) was similar in 2017 and other years
- No association with temperature or rainfall and year of conception (2017)

Figure 3. Prevalence (and 95% CI) of NTDs with DTG from conception over time



CONCLUSIONS

- There was no detectable increase in NTDs or major external structural abnormalities among more than 11,000 exposures to DTG at conception captured in the Tsepamo Study from 2014-2022
- For unclear reasons, the prevalence of NTDs with DTG conception exposure was unusually high in 2017 and then remained within the expected range (~1 per 1000 births) in all subsequent years
 - Possible explanations for this finding include: 1) statistical chance, 2) an interaction between DTG and an environmental exposure that may have occurred in 2017, such as low population folate, or, 3) increased NTD risk related to an unmeasured demographic difference in the first group of women started on DTG in Botswana

Acknowledgements

This study was funded by NIH/NICHD (R01HD080471 and R01HD095766) (PI R Shapiro). We would like to acknowledge the maternity staff, the Botswana Ministry of Health and Wellness, the Tsepamo Team (Daphne Lekorwe, Tsaone Gaonakala, Cynthia Dube, Edith Moseki, Gosego Legase, Keemeno Mosala, Mmapula Ofhentse, Naledi Kamanga, Onkabetse Mokgosi, Rosemary Moremi, Shally Morgan, Tshengang Motlotlegi, Patricia Mophutegi, Kebabonye Rabasiako, Nametsegang Tshosa, Malpelo Kegakilwe, Masego Kgafela, Tshogofato Sebetso, Tsholofelo Maswabi, Kealeboga Mmokele, Obakeng Makalane, Thuto Rabana, Seele Mafokate, Annah Kgannyeng, Thabologo Baitsemi, Priscilla Mashona and Bathoba Mabiletsa, Onalenna Mokoto, Gaogakala Legotho, Jaqueline Petros), and administrators and research assistants at BHP (Bernadette Kgage, Ria Madison, Tumulano Sekoto) and HSPH (Lendsey Melton, Molly Pretorius Holme, Lars Colson)