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Protektem pikinini blong yu trial: protocol for a single arm field trial to assess the effectiveness of treating-all pregnant women with hepatitis B infection with tenofovir prophylaxis to prevent mother-to-child transmission in Vanuatu, 2024–2025

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Abstract

Background Hepatitis B infection is a major public health concern in Vanuatu, with approximately 9% of the general population estimated to be living with chronic hepatitis B. Most new infections are due to mother-to-child transmission (MTCT). Hepatitis B vaccination is available in Vanuatu, but coverage rates for first dose within 24 h of birth and third dose are suboptimal. While treatment of chronic hepatitis B infection with tenofovir disoproxil fumarate (TDF) is available in country, there is no capacity to test hepatitis B e antigen and limited capacity to test hepatitis B virus (HBV) DNA viral load, which is a current eligibility requirement for women in pregnancy to access hepatitis B prophylaxis for MTCT per National guidelines. Recently, the World Health Organization guidelines have been updated to recommend universal peripartum antiviral prophylaxis (PAP) of pregnant women living with hepatitis B to prevent MTCT of HBV, without assessment of viral load in places without access to testing. However, these recommendations are conditional based on low-certainty evidence. The aim of this trial is to evaluate the effectiveness and safety of universal PAP and provide evidence for the global guidelines.

Methods A single arm field trial compared to real world control sites will be conducted in Vanuatu involving pregnant women attending antenatal care services with positive HBsAg rapid tests. Participants at the control sites will undergo routine care. Participants at the intervention sites will all receive oral TDF prophylaxis from second trimester to completion of infant primary hepatitis B vaccination schedule. Primary data analysis will be by intention-to-treat.

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Initial analyses will be unadjusted comparisons of the intervention sites and control sites. Adjusted analyses will be performed, as needed, and presented in addition to unadjusted comparisons.

Discussion This study will provide evidence of acceptability, effectiveness and cost-effectiveness of prophylaxis for all women with hepatitis B during pregnancy, as per the updated WHO guidelines, compared with current practice. The outcome of this trial will provide critical information to inform national and global guidelines around universal peripartum antiviral prophylaxis for hepatitis B during pregnancy.

Trial registration Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN: ACTRN12623001202651p. Registered 21 November 2023.

Keywords Hepatitis B, Pregnancy, Mother-to-child transmission, Universal peripartum antiviral prophylaxis, Tenofovir disoproxil fumarate, Vanuatu, Pacific, Western Pacific Region

Background

The burden of hepatitis B globally is large, with an estimated 254 million people living with chronic hepatitis B and 1.1 million deaths attributed to hepatitis B in 2022, mostly from cirrhosis and hepatocellular carcinoma [1, 2]. Ambitious global goals are in place to reduce new hepatitis infections by 90% and deaths by 65% between 2016 and 2030 and eliminate mother-to-child transmission with robust testing, prevention, and treatment strategies needed for these goals to be achieved [3].

Globally, mother-to-child transmission (MTCT) accounts for approximately 50% of new hepatitis B infections [4]. The risk of developing chronic hepatitis B (defined as persistent detection of HBsAg for more than six months), is much higher the earlier in life a person is exposed. Approximately 90% of infants infected with hepatitis B at birth and 30% of children infected between ages 1–5 years will develop chronic hepatitis B, while the risk of chronic infection is around 5% for people infected as adults [5–7]. Administration of hepatitis B immune globulin (HBIG) within 12 h and hepatitis B birth dose (Hep-BD) within 24 h, as well as two additional doses of hepatitis B vaccine within 6–12 months can prevent 90–95% of cases of MTCT [8]. Even with HBIG and vaccination, up to 10% of HBsAg-positive mothers with high viral load may transmit hepatitis B to their infants [8]. Antiviral prophylaxis with tenofovir disoproxil fumarate (TDF) has been found to be safe during pregnancy and a meta-analysis found TDF to have a protective effect against MTCT (OR 0.16, 95% CI: 0.10–0.26) [9].

Hepatitis B is endemic in Vanuatu, a small island nation in the South Pacific, with an estimated 9% of the total population of just over 300,000 people living with chronic infection and ongoing evidence of transmission [10]. Currently, rates of co-infection with hepatitis delta virus in Vanuatu are not known, but co-infection contributes to a higher likelihood of severe liver outcomes [11]. Given the high prevalence of hepatitis B and the risk of vertical transmission, the Vanuatu Ministry of Health has prioritised the routine screening of all pregnant women for hepatitis B surface antigen (HBsAg). Pregnant women in Vanuatu found to be HBsAg-positive are recommended to give birth in a healthcare facility and are educated about the importance of completing infant vaccination. HBIG is not available in Vanuatu, but Hep-BD and three doses of hepatitis B vaccine have been on the vaccination schedule for several decades. Additionally, antiviral therapy for hepatitis B is available, with TDF listed on the Vanuatu Essential Medicines List since 2020.

WHO guidelines from 2020 recommended that HBsAg-positive pregnant women with a high HBV DNA viral load (defined as an HBV DNA ≥ 200,000 IU/mL) receive TDF antiviral prophylaxis (herein referred to as peripartum antiviral prophylaxis [PAP]) from week 28 of pregnancy until at least the time of giving birth [12]. Where viral load testing is not available, the 2020 guidelines recommended hepatitis B e antigen (HBeAg) testing as a proxy measure for determining PAP eligibility, as positive HBeAg is suggestive of high viral load [12, 13]. In 2024, WHO updated the guidelines for settings where neither HBV DNA viral load nor HBeAg testing are available, as is the case for much of Vanuatu, to consider universal PAP for all HBsAg-positive pregnant women [7]. At time of publishing, these updated 2024 recommendations are conditional and based on low certainty evidence and are based on programmatic realities to increase PAP and further reduce the risk of MTCT. Vanuatu's national guidelines are based on the high-DNA driven care recommendations, with TDF recommended for pregnant women with viral load ≥ 200,000 IU/mL in the third trimester of pregnancy to four weeks after birth [14].

Despite TDF being available in Vanuatu and shipped to provincial hospitals, there are several key barriers for pregnant women living with hepatitis B to access PAP. Firstly, the availability of HBV DNA viral load testing is limited. Cepheid GeneXpert® platforms are available nationally but are centralised to the one national and five provincial hospital laboratories, which are based on six of the 83 islands. Secondly, there is limited health workforce trained to prescribe and monitor hepatitis B treatment

and/or PAP. Thirdly, there is no availability of HBeAg testing in Vanuatu and the current point-of-care HBeAg tests available commercially have a wide range of sensitivity and specificity and none are currently prequalified by WHO [15, 16], there is no central laboratory capacity for HBeAg testing in Vanuatu, and shipment of samples to laboratories overseas is costly and time consuming. These delays mean results are not available in time to be used and increases loss to follow up. As such, it is not feasible to use HBeAg as a proxy for HBV viral load in Vanuatu.

The impact of the limited access to HBV DNA viral load and HBeAg testing is that currently, no pregnant women in Vanuatu have been offered PAP. The Protektem Pikinini Blong Yu Trial, a translation of "Protect Your Baby" Trial in Bislama, a national language of Vanuatu, will evaluate the effectiveness and safety of universal PAP to prevent MTCT. The trial will also provide updated prevalence estimates for HBsAg and hepatitis delta virus among pregnant women in Vanuatu through testing of participants, as well as provide a platform to assess acceptability and cost-effectiveness of universal PAP.

Methods

This clinical trial protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [17] and presents protocol version 2 (20 June 2024) (see supplementary file 1 for SPIRIT Outcomes 2022 Checklist and schematic). This study is a prospective, single-arm field trial which will assess the effectiveness of using universal PAP compared to a real-world external control group.

The aim is to evaluate whether a prophylaxis for all approach to managing pregnant women living with hepatitis B leads to a reduction in HBsAg-positive infants. Ultimately, the goal is to improve maternal and child health through expanded use of TDF PAP to prevent MTCT of hepatitis B and provide evidence for national, regional, and global guidelines.

Recruitment

Pregnant women presenting to designated antenatal care (ANC) clinics in SHEFA or SANMA Provinces for first ANC visits will undergo routine screening for HBsAg. Pregnant women with a positive rapid HBsAg test will be told about the study by the clinic midwife or nurse, and if they agree, will then be referred to participate in the trial by a research nurse employed by the project who will seek informed consent and formally enrol the participant. Recruitment started in July 2024 and it is anticipated that it will take approximately six months to recruit the required sample size. Active recruitment strategies include laboratory testing on-site at ANC clinics, active review of laboratory records, and advertisements about the field trial.

For the external control group, women attending the provincial hospitals in TAFEA and MALAMPA provinces for ANC care will also undergo routine screening for HBsAg. If they have a positive rapid test, the clinic midwife or nurse will inform them about the study and refer them to the research nurse for enrolment. Figure 1 shows a map of participating sites and other hospitals.

Eligibility criteria

Eligible participants include pregnant women aged 18 years or older, before 27 weeks gestation at their first

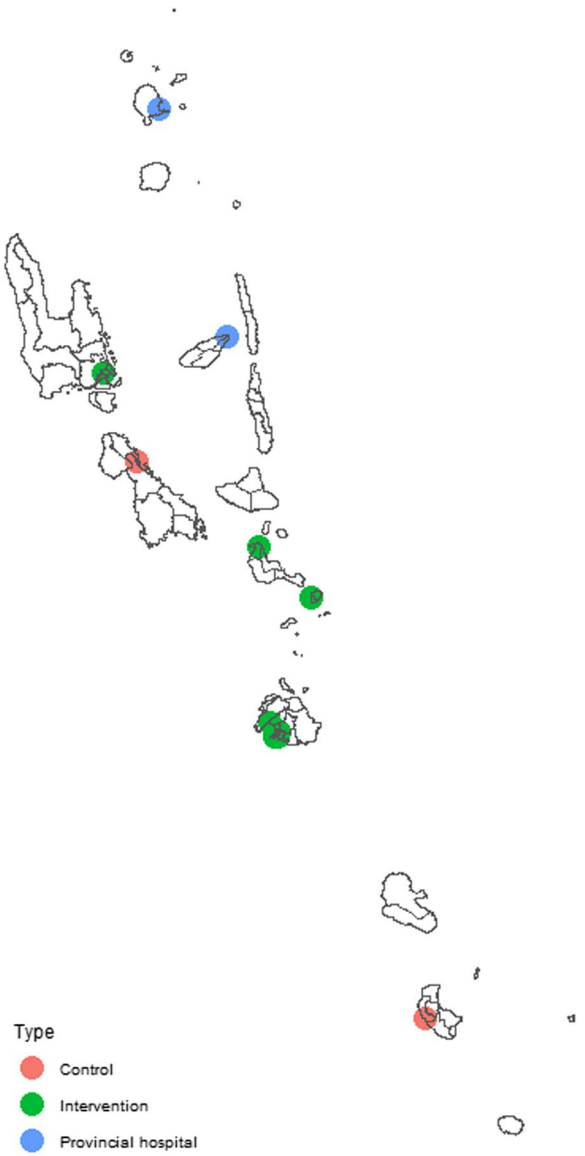

Fig. 1 Map of participating sites and provincial hospitals

ANC appointment at a study site, that have a positive HBsAg test result during routine ANC care, evidence of a negative HIV test during routine ANC testing and are able and willing to provide written informed consent prior to study-related procedures being performed. Infants born to eligible HBsAg-positive pregnant women are also considered participants.

Exclusion criteria include women coinfected with HIV, clinical evidence of cirrhosis such as jaundice or ascites, evidence of kidney disease, an aspartate aminotransferase ratio index (APRI) score over two which is suggestive of significant liver damage or are already receiving hepatitis B antiviral therapy prior to pregnancy. Women not planning on giving birth in Vanuatu or living in Vanuatu for the 12 months after birth will also be excluded.

Potential participants who decline to participate or are ineligible will be referred to the closest hospital for routine care.

Sample size

Sample size requirements were based on available data relating to hepatitis B birth dose (HepB-BD) coverage for Vanuatu and the rate of HBV MTCT with and without interventions. National Hep B-BD coverage in Vanuatu was 76% in 2023 [18]. Published studies suggested that the HBV MTCT rate was 5–10% when HepB-BD was administered within 24 h followed by two to three additional doses and negligible when PAP was administered, and 70% in the absence of any preventive interventions [8, 9]. The associated HBV positivity among infants in the control arm was 18% and 0.001% in the intervention arm. Assuming $\alpha = 0{\cdot}05$, $\beta = 0{\cdot}20$ (80% power), and intracluster correlation coefficient of 0.1, we would require a minimum of 52 women in each arm. To allow for anticipated loss-to-follow up of 20% and TDF compliance rate of 80%, we planned to enrol 61 women in the control arm and 74 women in the intervention arm.

There is limited data on the MTCT rate and PAP adherence rate in Vanuatu; as such, the sample size required will be reviewed three months after recruitment begins to ensure that the study is powered sufficiently to detect effect differences.

Real world control sites

The control sites will be at Norsup Hospital on Malekula in MALAMPA Province and Lenakel Hospital on Tanna, TAFEA Province. These sites will continue current routine care. While the national guidelines specify viral load screening and subsequent prophylaxis if HBV DNA viral load is high (> 200,000 IU/mL), this has not been implemented, due to challenges with viral load testing [14]. As such, routine care includes counselling on importance of timely hepatitis B birth dose and completion of the full childhood immunisation programme.

Intervention sites

Participants recruited at intervention sites will receive oral TDF (300 mg tablet once daily) regardless of HBV DNA viral load level also from the second trimester of pregnancy to at least 14 weeks after birth, when infants complete their hepatitis B vaccination series.

Laboratory testing

All HBsAg-positive pregnant women that consent to participate will undergo additional laboratory testing including routine testing (complete blood count) and testing for research purposes (HBV DNA viral load, hepatitis delta, liver function tests including alanine transaminase [ALT], aspartate aminotransferase [AST], and bilirubin, and creatinine). No additional testing will be conducted, but routine ANC screening for HIV and syphilis will have been offered prior to enrolment. Fourteen weeks following birth, bloods will be collected to test ALT to assess hepatitis B virus flare. If ALT is high at 14 weeks, participants will be referred to the hospital for specialist monitoring and care.

Once infants are born, they will be tested at 6–12 months using the qualitative Abbott "Determine HBsAg 2" rapid test (sensitivity: 100%, specificity: 99.72%) [19].

Outcomes

The domain of the primary outcome is infection in infants, specifically measurement is HBsAg positivity (or reactivity if this term has been used earlier in the paper). HBsAg reactivity will be assessed in infants at one time point (6–12 months after birth) using the qualitative Determine HBsAg test, measuring the presence or absence of HBsAg.

Secondary outcome measures include universal PAP adherence rates and predictors of adherence, post-delivery complications and infant outcomes. Additionally, the field trial will have several nested projects that will assess the feasibility and acceptability of midwife-delivered universal PAP, and cost-effectiveness.

Follow up

For the intervention sites, the study team will review ANC cards during routine ANC visits and contact the participants weekly to monitor TDF adherence. All participants will be encouraged to ensure their infants are fully immunised. At or near the time of birth, information on the birth and infant including Hep-BD administration, Hep-BD timeliness, and TDF adherence will be collected. Participants will be reviewed at fourteen weeks after birth by the research team. At

6–12 months of age, all infants from both the intervention arm and the real-world control sites will undergo testing for HBsAg. Hepatitis B surface antibody testing is not available in Vanuatu so will not be conducted.

Active and passive adverse event monitoring will be conducted, with participants counselled during enrolment to report any adverse events directly or during the weekly follow-up calls. In the event of significant adverse events, clinical experts will be consulted to determine any need to withdraw the participant. Adverse events following immunisation (AEFI) will be reported following National AEFI surveillance protocols. All participants will be referred to National pathways for ongoing monitoring and provision of care after their participation in the trial is completed.

Statistical analysis

Effect measures, comparing outcomes, will be estimated with 95% confidence intervals and *p*-values from the corresponding hypothesis tests. The effect measure for the primary outcome measure will be a risk ratio, defined as the ratio between the proportion recorded as having the outcome of interest in participants at the intervention sites, and the corresponding proportion in participants at control sites. Multilevel mixed effects regression will be used to compare time-varying and longitudinal outcomes over time. The mother-infant pair ID and any multiple births (twins, triplets) will be modelled as random effects. Co-primary endpoints will be otherwise adjusted for multiplicity using a Bonferroni adjustment of false discovery rate. Primary data analysis will be by intention to treat, meaning that all participants with a recorded outcome will be included in the analysis, and will be analysed according to the treatment group to which they were allocated. The volume of missing data will be reported, and additional statistical measures may be used to account for these missing data. If there appear to be any important imbalances between randomised groups, adjusted analyses will be performed and presented in addition to unadjusted comparisons.

Interim analysis will be conducted to determine the proportion of HBsAg-positive enrolled pregnant women that have high HBV DNA viral load to ensure that the sample size is sufficient. We anticipate that 35–40% of HBsAg-positive pregnant women will have high HBV DNA viral load (defined as HBV DNA level $\geq$ 200,000 IU/mL). If there are insufficient numbers of HBsAg-positive pregnant women with a high HBV DNA viral load recruited (measured after three months), the required sample size will be recalculated.

Data management, monitoring and auditing

A non-identifiable, unique study ID will be generated and used across all databases and for analysis. Personal information recorded for research purposes will be stored in a password protected database which will only be accessible to study investigators and coordinators. Research nurses will have access to identifying information, such as name and phone number, to facilitate follow-up but this database will not include any health or sensitive data. Paper-based forms will be used and then entered into the database on a regular basis. Data transfer from Vanuatu to Victoria, Australia, will be conducted in accordance with the Victorian Information Privacy Principles (IPP) Principal 9 (Transborder Data Flows) whereby data transfer including individual data has been approved by the individual (e.g. via the Participant Information and Consent Form – see Appendix 1). Data will be transferred through direct upload to the REDCap database.

Approved members from the study sponsor will have access to the final data set.

The Principal Investigator and two members of the study team will conduct regular monitoring visits, during which they will review and verify the signing of Informed Consent Forms and study data including personal and health-related data, laboratory results, and protocol deviations. The monitoring team will ensure compliance with Good Clinical Practice (GCP) and all aspects of the protocol. Source documents will be reviewed for consistency with data entered into in [enter name of EMR as per protocol] .

Dissemination

Information will be shared with participants via a one-page plain language summary of findings at the completion of the research. The summary of findings will also be provided to the Vanuatu Ministry of Health to share with the community via their Facebook page. Recruitment-based and interim and final findings will be presented to the PPBY Trial Advisory Committee at various time points (e.g. after 2, 6 and 10 months after recruitment) and after completion of the study (i.e. at the completion of follow-up for all infants). We anticipate the submission of several manuscripts to peer reviewed journals for consideration of publishing. All collaborators will have the opportunity to contribute to these scientific publications.

Ethical oversight

Ethical approval was granted by the Alfred Human Research Ethics Committee (HREC/105780-Alfred-2024. Additionally, approval has also been granted by the Vanuatu Health Research Ethics Committee.

Roles and responsibilities

The Principal Researcher is responsible for the design and conduct of the trial, preparation of protocol and revisions, preparation of data collection forms, oversight of data collection, data analysis and publication of study reports.

A trial management committee consists of the Principal Researcher, program manager and research coordinator, and meets fortnightly This committee has oversight for study planning, budget, audits, data verification and adherence to ethical requirements.

An international research steering committee has been established comprised of experts in infectious diseases, viral hepatitis, midwifery, obstetrical and gynaecology and global health. The role of the international research steering committee is to provide guidance to trial design, implementation, analysis and dissemination. The international research steering committee receives monthly updates and meets as required.

A local research steering committee of key members from Vanuatu Ministry of Health and civil society has been established. The committee provides guidance and oversight on design and implementation of the trial as well as support training, development of guidelines, and approval of information, education and communication resource development. The local research steering committee receives monthly updates and meets quarterly.

Discussion

This field trial will provide important evidence to the updated WHO recommendations and aims to provide high-quality evidence to the currently low-certainty recommendation for universal PAP. Additionally, while there are estimates for the efficacy of PAP during pregnancy to prevent MTCT of hepatitis B, there are some notable gaps. Key gaps include the use of TDF without HBIG, in settings of low- to moderate-vaccination coverage, settings of low ANC screening coverage, and in small island developing countries (SIDS).

Much of the evidence for efficacy of TDF prophylaxis to prevent MTCT is based on a meta-analysis of 129 studies, among which TDF prophylaxis was administered in addition to both Hep-BD and HBIG in 79% (15/19 studies). In all but one study, at least HBIG was administered at birth [9]. Additionally, there is a gap in understanding of the efficacy of antiviral prophylaxis in pregnancy in settings with low Hep-BD or Hep-B3 immunization coverage. There is evidence of the effectiveness of prevention of MTCT by using HBeAg and ALT levels to assess eligibility of treatment [20], but this has been done in study sites with infants receiving Hep-BD. In Vanuatu, the proportion of Hep-BD coverage decreased from 82% in 2019 to 69% in 2022, and the Hep-B3 coverage decreased from 90% in 2019 to 68% in 2022 [21]. In settings with low Hep-BD and Hep-B3 coverage, assessment of the effectiveness of universal PAP pregnancy is even more important.

The WHO Western Pacific Region has set a target for HBsAg ANC screening rates to be over 95% [22], but currently there is a paucity of data on ANC testing coverage in Pacific Island Countries [23]. Anecdotal evidence suggests that fewer than 50% of pregnant women are currently screened for HBsAg in Vanuatu, with significant disparity between islands. Therefore, there is a high proportion of undiagnosed hepatitis B infection in Vanuatu. The utility and sensitivity/specificity of point-of-care use of the Determine HBsAg 2 assay, the currently available point-of-care test in Vanuatu, has been demonstrated in Africa [24, 25] and Europe [26]. Currently there has been limited point-of-care use of these rapid tests in Vanuatu, instead relying on trained laboratory scientists to conduct these rapid diagnostic tests in hospital laboratories. In archipelago nations with limited health care infrastructure, such as Vanuatu, access to low-cost, reliable point-of-care testing that can be conducted by nurses or midwives and that allows for diagnosis and treatment in a single visit is critical to the control of hepatitis B. This field trial will support the initiation of this decentralised testing process, in line with the national decentralisation policy [27] as well as provide evidence for task shifting as an essential method to rapidly increase access to hepatitis B testing through ANC.

The TA-PROHM study in Cambodia used HBeAg and ALT to determine PAP eligibility and aimed to evaluate effectiveness of PAP with and without HBIG use [20] The results from this trial found that using HBeAg and ALT to determine eligibility for PAP for at least four week was effective at preventing MTCT of hepatitis B. Recently, a test-and-treat approach has been rolled out in Kiribati with treatment with tenofovir alafenamide offered to all HBsAg-positive women aged 15 years or above and men aged 18 years and above [28]. Neither of these studies reported on any safety signals from this scaled up treatment.

Studies have been conducted to determine cost-effectiveness of a treat-all approach for pregnant women and found this to be a cost-effective approach [29, 30]. These studies were, however, conducted in settings with lower HBsAg prevalence and large populations and in systems with integrated laboratory services and transportation systems. These circumstances are not reflective of Vanuatu and other Pacific Island Country settings where prevalence can be high, populations small, with limited laboratory capacity and transportation between islands and countries often limited and costly. These challenges all impact the timeliness of service delivery for pregnant

women, and further increase the risk of missing the window of opportunity to provide targeted TDF prophylaxis. Specific cost-effectiveness studies are recommended to reflect the Pacific context including potentially higher costs for service delivery, as well as potentially increased impact given challenges with access to health care services.

This trial will be the first to assess a universal PAP approach to prevent MTCT of hepatitis B in the Pacific. Most evidence available for the benefits of antiviral prophylaxis for MTCT is from larger settings, with more integrated laboratories, larger laboratory capacity and lower prevalence, and in conjunction with HBIG use. The WHO guidelines highlight several gaps in research, including the efficacy of TDF to prevent MTCT of HBV among women whose infants did not receive HBIG and women whose infants did not receive timely vaccination after birth [12]. The trial will address several important evidence gaps on the management of pregnant women living with hepatitis B, particularly in the setting of small island developing states.

Abbreviations

ANC	Antenatal care
HBIG	Hepatitis B immune globulin
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hep-BD	Hepatitis B birth dose
MTCT	Mother-to-child transmission
PAP	Peripartum antiviral prophylaxis
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1.

Additional file 1: Appendix 1.

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Authors' contributions

LB drafted the manuscript and provided input into the methodology of the trial. CvG is the principal investigator on this trial and was a major contributor in writing the manuscript. AK and KA are core members of the research team. SN, AT, KK, LD, LO, FT, HO, BT, PG, JI, JGP, MP, HS, JS, SV sit on the PPBY Trial Advisory Committee and provide oversight and guidance into project implementation. NA, ZD, CH, KJ, NK, ED, JH, and MH provided technical expertise into the protocol and sit on the technical steering committee. TS provided statistical expertise. All authors input into, read, and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical approval was granted by the Alfred Human Research Ethics Committee (HREC/105780-Alfred-2024 and from the Vanuatu Health Research Ethics Committee. All participants will only be enrolled following written consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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