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Seroprotection against tetanus in HIV-exposed and HIV-unexposed infants in Malawi in 2019–2020

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ABSTRACT

In Malawi, tetanus toxoid vaccination (TTV) is recommended in pregnancy, but few studies have assessed the prevalence of infant seroprotection against tetanus. Anti-TT levels from 84 6-week-old infants, born in 2019–2020 to mothers living with HIV (HEU: HIV-exposed-uninfected) infants and to HIV-negative women (HUU: HIV-unexposed-uninfected) infants were determined by ELISA assay. Although 94% of the infants (HEU=94.8%, HUU=92.3%) showed protective levels (>0.1 IU/mL), the mean titers observed (0.51 IU/mL) suggest an incomplete compliance with TT vaccination. The only factor positively correlated to anti-TT IgG levels was the duration of maternal antiretroviral therapy in HEU.

Tetanus toxoid-containing vaccines (TTV) are strongly recommended in pregnancy in countries striving to eliminate maternal and neonatal tetanus. In sub-Saharan countries, the proportion of women receiving two or more TTV doses during pregnancy varied from 28.6% to 78.4% in recent survey studies.[1] In a Ugandan study, the analysis of antibody titers performed on cord blood showed a high prevalence of protective TT IgG levels,[2] but cord blood does not exactly represent newborn status, and data on infants, reflecting the real rate of protection, are scarce. One of the few studies that assessed infant levels, performed in Mozambique in 6-week-old HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) infants, reported a seroprotection rate of 75% in HEU and 94% in HUU, in line with the notion that HIV infection can negatively affect maternal transplacental transfer.[3] A survey conducted in 2015 in Malawi, a sub-Saharan country with a high HIV prevalence, reported compliance with tetanus toxoid vaccination during pregnancy of 73%.[4]

In the present serological study—part of a larger clinical study on infant health conducted within the structures of the DREAM Programme of the Community of S. Egidio in the suburban/urban area of Blantyre, Malawi[5]—we aimed to determine the level of protection against tetanus in 6-week-old infants born between February 2019 and February 2020. We also explored potential differences between HEU and HUU infants.

Dried blood spot samples from 84 (58 HEU and 26 HUU) 6-week-old infants were analysed for anti-TT IgG levels. No differences in socio-demographic characteristics were observed between the two groups of mother/infant pairs. Among mothers living with HIV, 23/58 (39.7%) initiated antiretroviral therapy (ART) during pregnancy, with a median duration of therapy before delivery of 4.8 months (IQR: 3.1–5.1). The remaining 35 women had been on a stable ART regimen for at least 16 months (median: 108.1, IQR: 79.4–138.2) before delivery.

Overall, mean anti-TT IgG level in infants was 0.51 IU/mL. Most infants (94%) showed an anti-TT titre considered sufficient to protect against the pathogen (>0.1 IU/mL). Antitetanus IgG titers were over this threshold in all but five infants, 3 HEU (5.2%) and 2 HUU (7.7%) (p=0.773). HUU infants showed a higher level of protection, with 30.8% of them presenting high anti-TT titers (>1.0 IU/mL) compared with 15.5% of HEU infants (table 1). The infant's TT IgG titers did not correlate with maternal age, educational level, residency or gravidity (data not shown). Still, maternal ART duration significantly impacted on the TT IgG levels: the infants whose mothers started ART during pregnancy had significantly lower antitetanus IgG titers compared with HUU infants (p=0.031) and HEU infants born to mothers on long-term ART (p<0.023) (figure 1).

Our results showed that protection against tetanus was still maintained at sufficient levels

Table 1 IgG levels against tetanus toxoid (TT) in 6-week-old infants

	Overall	HUU	HEU	P values
Infants	84	26	58	
Tetanus toxoid IgG (IU/mL)	0.51 (0.42–0.63)	0.61 (0.41–0.90)	0.48 (0.38–0.61)	0.196
TT-IgG				
>0.1 (IU/mL)	79 (94.0%)	24 (92.3%)	55 (94.8%)	0.773
<0.1 (IU/mL)	5 (6.0%)	2 (7.7%)	3 (5.2%)	
>0.1≤1.0 (IU/mL)	62 (73.8%)	16 (61.5%)	46 (79.3%)	0.275
>1.0 (IU/mL)	17 (20.2%)	8 (30.8%)	9 (15.5%)	

The tetanus toxoid IgG levels were evaluated using a commercial ELISA kit specifically designed for DBS (Euroimmun, Lubeck, Germany). Following the manufacturer's instructions, the level of protection against tetanus was determined using the following ranges: <0.1 IU/mL insufficient; >0.10<1.0 minimum protective level; >1.0 IU/mL indicative of long-term protection.
Values are expressed as geometric mean and 95% CI for antibody levels and as number and percentage for infants with protective levels. Differences were assessed using the Mann-Whitney U test or the χ^2 test as appropriate.
HEU, HIV-exposed-uninfected infants; HUU, HIV-unexposed-uninfected infants; TT, tetanus toxoid.

in Malawian infants until 6 weeks of life, and support, although based on a limited sample size, previous reports on the high prevalence of protective TT IgG titers in cord blood of newborns in different sub-Saharan countries.[2] However, the antibody concentrations that we observed, although generally sufficient, were low and only in a limited proportion of infants reached levels indicative of full immune protection.

As already observed by others,[6] several factors can be responsible for the low anti-TT IgG levels in infants. One of the possible reasons could be the low attendance at early antenatal care. Full tetanus vaccination is defined as receiving at least two doses during pregnancy. Unfortunately, we do not have reliable documentation on maternal TT vaccination status, but late presentation for antenatal care could be a barrier to achieve complete vaccination coverage. Based on the timing of HIV screening, which in Malawi is recommended at the first antenatal visit, we found that most women (39 out of 49) with unknown HIV status received the test only during the second or third trimester (n=32, 65.3%, and n=7, 14.2%, respectively). Although in the centres involved in this study antenatal care was free of charge, our results suggest that most women do not begin antenatal care in the first trimester as recommended by the most recent Malawi guidelines (2014–2019), missing the opportunity to receive early health interventions. Additionally, in women with HIV diagnosis during pregnancy, the short duration of ART may have allowed only partial maternal immune reconstitution, potentially inhibiting vaccine responsiveness to tetanus toxoid and hindering the adequate transplacental transfer of anti-TT IgG to their neonates.

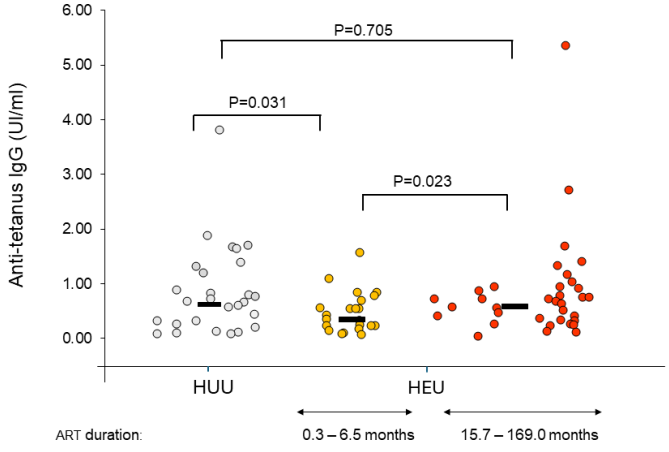

Figure 1 Antitetanus IgG levels in 84 Malawian infants at 6 weeks of life. This survey is part of a larger study including 235 infants.[5] The availability of blood samples was the inclusion criteria for this serological study. Values are expressed as geometric means. Grey spots: HUU infants (n=26 GM: 0.61 IU/mL, 95% CI: 0.41 to 0.90); yellow: HEU infants from mothers initiating ART during pregnancy (n=23, GM: 0.35 IU/mL, 95% CI: 0.24 to 0.50); red: HEU infants from mothers in stable ART (n=35, GM: 0.59 IU/mL, 95% CI: 0.44 to 0.80). Differences between groups were analysed by the Mann-Whitney U test using the SPSS software, V.29 (IBM, Somers, NY, USA). ART, antiretroviral therapy; HEU, HIV-exposed-uninfected infants; HUU, HIV-unexposed-uninfected infants.

Strategies to implement maternal preventive vaccination and encouraging early initiation of antenatal care should be promoted to improve maternal and child health.

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Contributors SB and MG were responsible for the design of the study, and wrote the manuscript. SB was responsible for statistical analysis. CMG designed and supervised the laboratory procedures. SO supervised the implementation of the project. RL, RM and TK were responsible for data and sample collection at the clinical sites, RA was involved in the laboratory assays. MF and MA contributed to the data acquisition and to the interpretation of data. FC and MCM contributed to the critical revision of the manuscript for important intellectual content. All coauthors reviewed and approved on the manuscript. SB is the guarantor of the manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and was approved by National Health Research Committee in Malawi (approval number 2085). Participants gave informed consent to participate in the study before taking part.

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